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REVIEW

Therapeutic Targeting of Signaling Pathways in Abdominal Aortic Aneurysm: From Pathogenesis to Precision Medicine

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Abstract: Abdominal aortic aneurysms (AAAs) are life-threatening cardiovascular disorders with limited treatment options, largely due to an incomplete understanding of their molecular and cellular pathogenesis. A comprehensive elucidation of the mechanisms driving AAA initiation, progression, and rupture is critical for developing novel therapeutic interventions. Emerging research has highlighted the central role of inflammatory processes in AAA pathophysiology, including dysregulated extracellular matrix (ECM) remodeling, chronic vascular inflammation, immune cell infiltration, and vascular smooth muscle cell (VSMC) dysfunction. These pathological processes are regulated by complex signaling pathways with divergent roles in AAA progression: while NF-κB, MAPK, STAT, and Notch signaling exacerbate disease pathogenesis, AMPK, PPAR-γ, and Nrf2 pathways exert protective effects. Notably, the PI3K/Akt and TGF-β signaling cascades demonstrate context-dependent dual roles, capable of either promoting or inhibiting AAA development. This comprehensive review synthesizes current knowledge of AAA pathophysiology with emphasis on druggable targets within these signaling networks. We critically evaluate emerging therapeutic strategies including miRNA-based interventions, nanoparticle-mediated drug delivery systems, and stem cell therapies that offer promising approaches for precision modulation of disease-specific pathways. By integrating current mechanistic understanding with therapeutic development, this review aims to provide a framework for designing effective pharmacological strategies that could transform AAA management from surgical intervention to medical prevention, addressing a critical unmet clinical need.

Keywords: abdominal aortic aneurysm, extracellular matrix remodeling, inflammation, vascular smooth muscle cell dysfunction, cellular signaling, therapeutic targets

Background

Abdominal aortic aneurysm (AAA) represents a significant vascular disorder characterized by permanent, localized dilation of the abdominal aorta, typically defined as a diameter exceeding 3.0 cm or measuring 1.5 times the normal adjacent aortic segment[1,2] (Figure 1). Anatomically, approximately 80% of AAAs occur inferior to the renal arteries (infrarenal), with remaining cases classified as suprarenal or pararenal based on their relationship to renal vessels.[3,4] True aneurysms, the most common form, involve dilation of all three arterial wall layers, while pseudoaneurysms result from arterial injury leading to blood extravasation between wall layers. Morphologically, AAAs typically demonstrate

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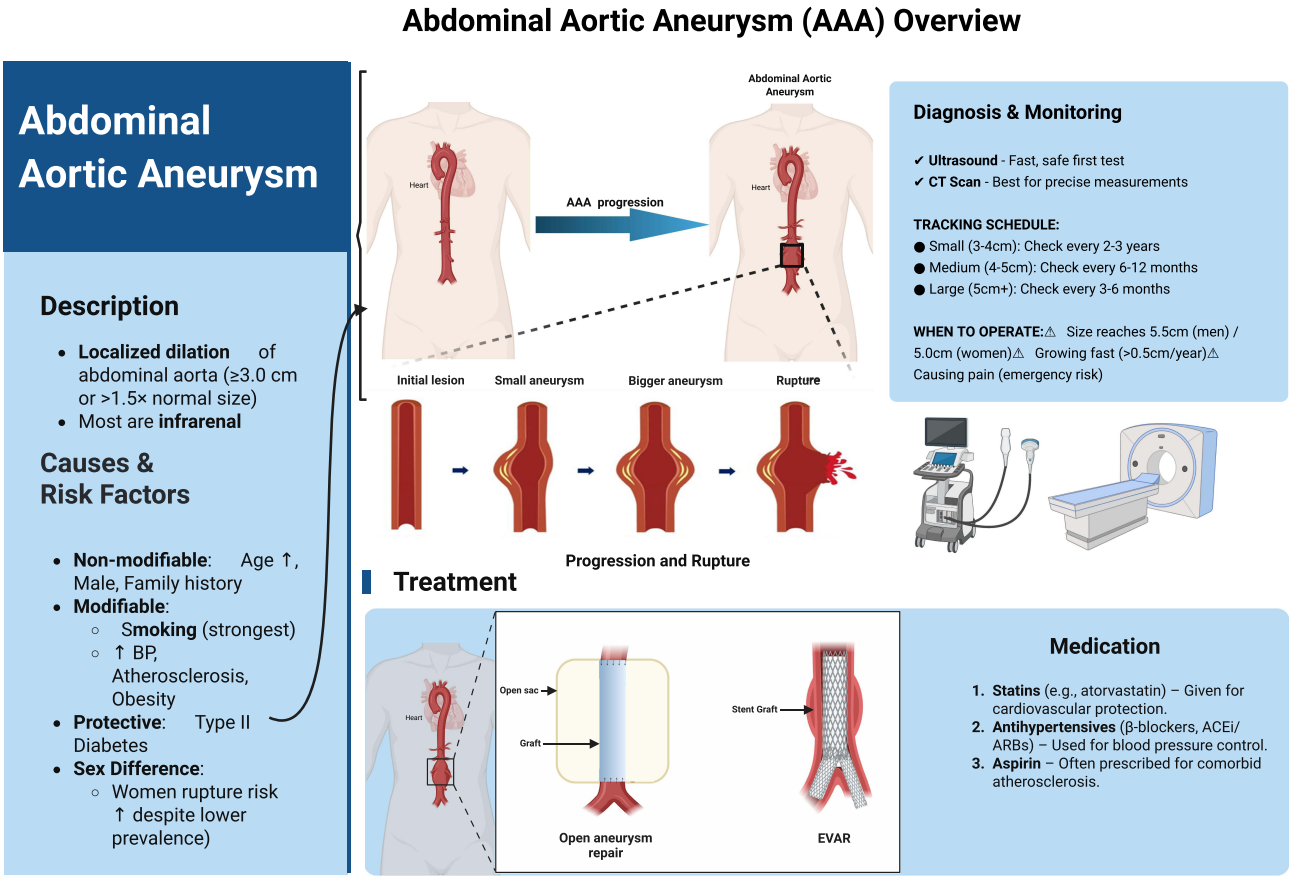

Figure 1 Overview of abdominal aortic aneurysm (AAA). This figure summarizes the definition, risk factors, progression, diagnosis, and treatment of AAA. It shows how aneurysms develop and may rupture, highlights key risk factors (eg, age, male sex, smoking), and outlines diagnostic tools (ultrasound, CT) and monitoring intervals. Treatment includes surgical options (open repair, EVAR) and medications like statins, antihypertensives, and aspirin for cardiovascular protection. (↑ indicates increase). This figure is generated using https://BioRender.com.

fusiform (circumferential) expansion, though saccular (asymmetric) variants occasionally occur.[5] The clinical significance of AAA lies in its propensity for progressive, often asymptomatic expansion until the catastrophic complication of rupture occurs, carrying mortality rates exceeding 80%.[6]

Contemporary epidemiological data reveal a substantial decline in AAA prevalence compared to historical estimates, reflecting significant public health achievements in risk factor modification. Recent large-scale screening programs demonstrate that AAA prevalence among 65-year-old men has decreased from 1.32% to 0.69% between 2010 and 2023 in population-based cohorts.[7] General population imaging studies using CT angiography report current prevalence rates of 4.0% in men versus 0.7% in women, maintaining the well-established male predominance with approximately 5-6-fold higher disease burden in males.[8,9] Meta-analyses of contemporary screening data demonstrate pooled odds ratios of 3.78 (95% CI 2.80–5.10) for male sex as a risk factor for AAA.[10] These figures represent a remarkable reduction from the historical 4–8% prevalence range reported in earlier screening programs, primarily attributed to declining smoking rates and enhanced cardiovascular risk management in high-income countries.[7,11] Global mortality patterns reflect similar improvements, with age-standardized mortality rates declining from 2.57 to 1.86 per 100,000 between 1992 and 2021 (estimated annual percentage change −1.36%), though absolute deaths have increased due to population aging.[12] Significant regional disparities persist, with age-adjusted mortality in US adults aged 65+ declining dramatically from 32.6 to 13.2 per 100,000 between 1999 and 2020, while high-income Asia Pacific regions maintain among the highest age-standardized death rates at 4.38 per 100,000.[13,14] These favorable trends contrast with stable or increasing AAA burdens reported in some Eastern European and lower Socio-demographic Index (SDI) regions, highlighting substantial

geographic heterogeneity in AAA epidemiology and underscoring ongoing healthcare disparities that require targeted intervention strategies.[12,14]

The natural history of AAA progression demonstrates substantial heterogeneity that complicates clinical management. Contemporary studies report means expansion rates of 2.16–2.6 mm/year with considerable individual variability.[15,16] While baseline diameter independently predicts growth velocity, it explains only minimal interpatient variability (R^2 = 0.054), highlighting the limitation of size-based monitoring alone.[17] This variability is particularly evident in sex-specific analyses, where size-stratified analyses in women reveal mean annual growth rates of 0.91 mm/year for aneurysms <3.0 cm, 2.34 mm/year for 3.0–3.9 cm, 2.49 mm/year for 4.0–4.9 cm, and 6.16 mm/year for aneurysms ≥5.0 cm, demonstrating accelerating expansion with increasing diameter.[18] Imaging characteristics provide crucial prognostic information beyond simple diameter measurements. The presence of intraluminal thrombus (ILT) doubles expansion rates (median 2.0 vs 1.0 mm/year), especially in smaller aneurysms.[19] Growth patterns further stratify risk, with "peak growth" trajectories conferring a 5.24-fold higher hazard (95% CI 1.68–16.38) of requiring surgical intervention within one year compared to "edge growth" patterns.[20] Contemporary surveillance data reveal that baseline diameter strongly influences intervention timing, with no patients measuring <4.25 cm requiring repair within two years, compared to 26% of those with baseline diameters ≥4.25 cm.[21] The limitations of diameter-based risk assessment become particularly evident in rupture prediction. Recent biomechanical studies demonstrate that peak wall stress and rupture index independently predict rupture risk after adjusting for diameter. Among patients who experienced rupture, the median maximum diameter was 56 mm at last imaging, with median time to rupture of 2.13 years (IQR 0.64–4.72), confirming that catastrophic events occur near conventional intervention thresholds.[22] Rupture continues to carry devastating consequences, with overall fatality exceeding 80% and 30-day hospital mortality ranging from 16–36% in contemporary series.[23,24] These observations collectively underscore the critical need for advanced biomarkers and personalized risk prediction tools that integrate biomechanical parameters, growth patterns, and molecular signatures to improve patient outcomes beyond current diameter-dependent paradigms.

The pathophysiology of AAA involves a complex interplay of chronic inflammation, extracellular matrix degradation, vascular smooth muscle cell apoptosis, and oxidative stress.[25,26] These processes are orchestrated by intricate signaling networks that remain incompletely understood. Current management remains predominantly reactive, relying on serial monitoring until aneurysms reach intervention thresholds, with surgical or endovascular repair reserved for high-risk cases. This "watchful waiting" approach fails to address the underlying molecular drivers of disease progression and creates substantial physical and psychological burdens for patients.[27] This comprehensive review aims to systematically evaluate the molecular pathogenesis of AAA, with particular focus on identifying and characterizing druggable targets within key signaling pathways governing disease progression. We will critically assess the pathological roles of pro-aneurysmal pathways (NF-κB, MAPK, STAT, Notch) versus protective signaling cascades (AMPK, PPAR-γ, Nrf2), and elucidate the context-dependent functions of PI3K/Akt and TGF-β pathways. Furthermore, we will examine emerging therapeutic strategies including miRNA-based interventions and nanoparticle-mediated drug delivery systems for their potential to modulate critical pathological processes. By integrating mechanistic insights with therapeutic development, this review aims to establish a conceptual framework for advancing targeted pharmacotherapies that could transform AAA management from surgical intervention to medical prevention, addressing a crucial unmet need in cardiovascular medicine.

Risk Factors

Male sex and advanced age remain well-established non-modifiable risk factors for AAA. Contemporary population-based imaging studies demonstrate AAA prevalence of 4.0% in men versus 0.7% in women, representing an approximately 5-6-fold higher burden in males.[8,9] Recent screening cohorts report even more pronounced disparities, with multivariable-adjusted odds ratios of 8.04 (95% CI 4.87–13.28) for male sex in ultrasound screening studies.[28] Global Burden of Disease analyses indicate that males experience approximately 2.25-fold higher age-standardized death rates from aortic aneurysm compared to females.[14] Age substantially stratifies AAA risk, with peak mortality occurring in men aged 70–74 years and disability-adjusted life years peaking in the 65–69 age group.[29] While women develop AAAs at significantly lower absolute rates, they experience disproportionately worse outcomes: in large US inpatient cohorts,

women comprised 22.8% of AAA admissions but rupture accounted for 18.4% of female admissions versus 12.6% of male admissions.[30] Smoking stands as the most potent modifiable risk factor for AAA, profoundly influencing aneurysm formation, progression, and rupture. Large prospective cohorts demonstrate that current smoking confers hazard ratios of 4.32–4.81 for incident AAA compared to never-smokers, with meta-analyses yielding pooled odds ratios of 3.39 (95% CI 2.57–4.48).[10,31,32] The association exhibits pronounced anatomic specificity: UK Biobank analyses report hazard ratios of 8.90 for abdominal aortic aneurysms and 10.47 for ruptured aortic aneurysms in current versus never-smokers, while thoracic aneurysms show no clear association. Dose-response relationships are evident, with smoking ≥20 versus <10 cigarettes daily associated with HR 5.67 for aortic aneurysm incidence.[31] Pack-year analyses reveal monotonic risk increases: Japanese cohort data show aortic mortality hazard ratios versus never-smokers of 2.39 for <20 pack-years, 3.57 for 20–39 pack-years, and 3.92 for ≥40 pack-years.[33] The smoking effect demonstrates marked sex specificity, with women experiencing disproportionately greater relative risk increases; meta-analyses report a pooled women-to-men relative risk ratio of 1.78 (95% CI 1.32–2.38), indicating current smoking confers 78% greater relative increase in AAA risk in women compared to men.[32] Additionally, factors associated with AAA development include hypertension,[34] atherosclerosis,[35] coronary artery disease,[36] dyslipidemia,[37] cerebrovascular disease,[38] obesity,[39] and a positive family history.[40] Emerging research highlights genetic/epigenetic contributors like microRNAs and lncRNAs.[41] Although diabetes mellitus typically promotes atherosclerosis, type 2 diabetes appears to confer protection against AAA formation.[42] Comprehensive meta-analyses of population and clinical studies demonstrate that diabetic patients have approximately 50% lower AAA risk compared to non-diabetic individuals.[43] Additionally, diabetes is associated with reduced aneurysm expansion rates and markedly decreased rupture risk.[44,45]

Symptoms

Most AAAs typically remain asymptomatic until they rupture, often discovered during routine physical examinations or diagnostic investigations for other health concerns. Patients with unruptured AAAs may occasionally present with vague symptoms, including abdominal discomfort or radiating pain extending to the lumbar region or groin.[46] Larger AAAs can compress nearby structures, such as the ureters, inferior vena cava, or duodenum, potentially leading to symptoms, although this is uncommon. Ischemic symptoms in the lower limbs due to acute thrombosis or embolization of peripheral circulation may occur but are infrequent in AAA patients. Clinical examination may detect a pulsatile epigastric mass on deep abdominal palpation, though this finding has limited diagnostic sensitivity for AAA.[47] Alarmingly, 50% of AAA cases first present with rupture, typically into the retroperitoneal space. This rupture can cause symptoms such as back pain, with or without abdominal pain, hypotension, lightheadedness, and a pulsatile epigastric mass.[48]

Diagnosis

Imaging is crucial in identifying AAA, monitoring its growth rate, diagnosing rupture, guiding therapeutic decisions, planning treatment, and assessing post-surgical outcomes. Ultrasonography (US) and computed tomography angiography (CTA) are essential for AAA management. Despite advancements in aortic imaging technologies, ultrasonography remains the preferred method for AAA screening and surveillance due to its wide availability, non-invasive nature, cost-effectiveness, and high diagnostic accuracy.[49] US, including colour and duplex imaging, is indicated for AAA screening and diagnosis in asymptomatic patients and offers rapid emergency assessment for symptomatic cases. For comprehensive characterization and procedural planning, CTA is the cornerstone modality. It provides high-resolution, three-dimensional visualization of the aneurysm's morphology, including precise measurements of maximum diameter, proximal and distal extension (neck), and involvement of visceral branches. Furthermore, CTA is indispensable for detecting critical features such as the presence of an intraluminal thrombus, penetrating atherosclerotic ulcers, and dissection flaps. This detailed anatomical information is vital for determining eligibility and planning both endovascular (EVAR) and open surgical repair. Consequently, CTA is the definitive test for confirming rupture and for pre-procedural assessment and post-operative surveillance.[50] Magnetic resonance angiography (MRA) serves as an alternative to CTA, offering advantages such as avoiding radiation exposure and needing iodinated contrast agents. However, MRA is comparatively more expensive, less widely available, and has longer imaging times.[51] Although not part of routine AAA management, positron emission tomography–computed tomography (PET–CT) molecular imaging offers unique

diagnostic value for characterizing inflammatory aneurysms, mycotic AAAs, and infected endovascular grafts.[52] Nevertheless, this technique has limitations, including limited spatiotemporal resolution, radiation exposure, high cost, and restricted availability.[53]

Treatment

Pharmacological Treatment

Numerous pharmacological approaches have been explored for potential benefits in the treatment of AAA (Table 1). However, to date, no medical therapy has proven sufficiently effective in reducing AAA growth or preventing rupture to be incorporated into treatment guidelines. Antihypertensive drugs such as beta-blockers and angiotensin-converting enzyme (ACE) inhibitors have shown no impact on AAA expansion.[54,55] While antibiotics such as doxycycline significantly lowered plasma markers of proteolytic activity, recent studies found no attenuation of AAA expansion.[56] Macrolides (roxithromycin, azithromycin) likewise showed no therapeutic benefit in slowing aneurysm progression.[57,58] Although observational data suggest statins may reduce AAA growth rates, larger nonrandomized trials failed to confirm this effect.[59] Other pharmacologic agents including NSAIDs, mast cell inhibitors, calcium channel blockers, diuretics, and angiotensin II receptor blockers demonstrated preclinical potential but ultimately showed no efficacy in curbing AAA enlargement in clinical studies. Current randomized clinical trials are examining the impact of ticagrelor, a platelet aggregation inhibitor; telmisartan/valsartan, an angiotensin II receptor blocker (ARB); cyclosporine A, an immunosuppressive agent; and eplerenone, an aldosterone antagonist, on the growth rate of small AAAs. However, there is presently no definitive recommendation for pharmacological intervention to mitigate the risk of AAA progression and rupture.[60]

Surgical Treatment

Currently, surgical intervention remains the only definitively proven treatment to prevent abdominal aortic aneurysm (AAA) rupture and associated mortality. The established indications for repair include AAAs reaching 5.5 cm in diameter

Table 1 Evidence Summary for Pharmacological Therapies in AAA Management

	Agent/Class	Mechanism of Action	Highest Evidence Tier & Key Finding	Status of Human Efficacy & Clinical Guidance
1	**Doxycycline**[56]	Broad-spectrum matrix metalloproteinase (MMP) inhibitor.	RCT - Multiple RCTs show no significant attenuation of AAA expansion despite reducing plasma proteolytic markers.	No clinical efficacy demonstrated. Recommended only in the context of clinical trials, not for standard care.
2	**Beta-Blockers**[54]	Reduce hemodynamic stress and heart rate.	RCT - Multiple RCTs (eg, Propranolol, Atenolol) show no impact on AAA expansion rates.	No clinical efficacy demonstrated. Not recommended for the purpose of slowing AAA growth.
3	**ACE Inhibitors/ARBs**[55]	Block the renin-angiotensin system; reduce inflammation and proteolysis.	Mixed Evidence (RCT vs Observational) - RCTs for ACE inhibitors show no effect. Observational data for some ARBs is conflicting, but definitive RCT evidence is lacking.	No conclusive RCT evidence for efficacy. Not recommended for AAA-specific treatment outside of hypertension management.
4	**Statins**[59]	Pleiotropic effects including reduced inflammation and protease activity.	Observational Human Data - Retrospective studies suggest reduced growth, but larger non-randomized trials and RCT subgroup analyses have failed to confirm a significant effect.	No proven efficacy for AAA growth. Recommended for co-morbid cardiovascular disease, but not specifically for AAA.
5	**Macrolides (Roxithromycin, Azithromycin)**[57,58]	Immunomodulatory and anti-inflammatory effects.	RCT - Clinical trials demonstrated no therapeutic benefit in slowing aneurysm progression.	No clinical efficacy demonstrated. Not recommended for AAA treatment.
6	**Mast Cell Inhibitors, NSAIDs**[60]	Various anti-inflammatory and immunomodulatory mechanisms.	Animal Model - Demonstrated preclinical potential in reducing AAA formation and progression in rodent models.	No human efficacy data. Promising animal data has not been translated to successful clinical studies.
7	**Ticagrelor, Telmisartan, Cyclosporine A, Eplerenone**[60]	Platelet inhibition, angiotensin blockade, immunosuppression, aldosterone antagonism.	Ongoing RCTs - These agents are currently being evaluated in clinical trials for their impact on the growth rate of small AAAs.	Evidence is pending. There is currently no recommendation for their use. Represents the current frontier of clinical translation.

for male patients or 5.0 cm for female patients, as well as any symptomatic aneurysm regardless of size.[61] For cases where the risks of elective surgery outweigh the potential rupture risk, a conservative approach is recommended. This involves regular monitoring with imaging intervals tailored to aneurysm size: every three years for 3.0–3.9 cm AAAs, annually for 4.0–4.9 cm AAAs, and every 3–6 months for aneurysms ≥5.0 cm, with adjustments made for rapid growth (>1 cm/year) or other high-risk features like elevated wall stress.[62] For smaller AAAs below the surgical threshold, a strategy of surveillance combined with optimal medical management has been shown to be safer and more effective than early elective repair. This comprehensive conservative approach emphasizes rigorous cardiovascular risk factor control, including mandatory smoking cessation, dietary modifications, and regular physical activity. Such lifestyle interventions have demonstrated greater efficacy in reducing cardiovascular events and improving overall outcomes compared to early surgical intervention, while also being cost-effective. The combination of size-appropriate monitoring and aggressive medical therapy represents the standard of care for small AAAs.[63] Currently, two main surgical interventions are employed for AAA repair: open surgical repair (OSR) and endovascular aneurysm repair (EVAR). OSR involves a midline laparotomy with replacement of the aneurysmal aortic segment using either a tube or bifurcated synthetic graft, followed by closure of the aneurysm sac around the prosthesis.[64] This approach carries significant perioperative risks, including cardiac (myocardial infarction), pulmonary (pneumonia), and renal (insufficiency) complications.[65] Postoperative wound complications, particularly incisional hernias following midline laparotomy, significantly impair patient recovery after AAA repair.[66] Potential long-term complications following AAA repair include graft infections, graft limb occlusion, secondary aortoenteric fistulae, and para-anastomotic aneurysm formation.[67] In contrast, EVAR offers a minimally invasive alternative involving percutaneous or open femoral artery access for stent-graft deployment under fluoroscopic guidance after precise angiographic measurements.[68] While EVAR reduces immediate surgical risks, it introduces unique complications, particularly endoleaks[69] and access site issues, especially in patients with challenging iliac anatomy (small, calcified, or tortuous vessels). The choice between these approaches depends on patient anatomy, comorbidities, and surgical expertise. Both surgical interventions are associated with high risk, cost, longer procedural time, severe complications, high mortality rates in unsuccessful procedures, and poor long-term survival.[70] Given the elevated mortality rates associated with rupture and post-surgery, there is a pressing need for alternative pharmacological therapies.

Pathogenesis of AAA

While the precise pathophysiology of AAA remains incompletely understood, emerging evidence highlights four interconnected pathological processes driving disease progression: (1) dysregulated ECM remodeling, (2) chronic vascular inflammation, (3) immune cell infiltration, and (4) VSMC dysfunction (Figure 2). These processes collectively contribute to structural and biomechanical weakening of the aortic wall in response to hemodynamic stress, aging, and other risk factors. Earlier studies established that AAA development involves both molecular alterations (eg, protease activation, cytokine dysregulation) and mechanical degradation (eg, loss of elastin, collagen disruption). To develop targeted therapies, a deeper investigation of the cellular and molecular mechanisms underlying these pathological changes—particularly their role in aortic wall remodeling and rupture risk is critical.

Aortic Wall

In its normal state, the aorta functions to efficiently transmit pulsatile arterial blood pressure and adapt continually to maintain a consistent diameter in response to changing hemodynamic conditions.[71] This functionality is contingent upon the elastic properties and material composition of the aortic wall.[72] The structural composition of the aortic wall comprises three distinct layers: the tunica intima, tunica media, and tunica adventitia, encompassing the lumen through which blood flow circulates. Each layer serves a specific function and possesses unique mechanical properties. The innermost layer, the intima, directly interfaces with the blood flow. It serves as a selective barrier formed by endothelial cells, preventing blood product infiltration into the wall and facilitating the delivery of oxygen and nutrients from the blood to the inner wall. The middle layer, referred to as the tunica media, represents the thickest vascular layer, measuring ~2 μm distal to the renal arteries. Bounded internally by a prominent internal elastic lamina and externally by a thinner, age-sensitive external elastic lamina, this middle layer consists of concentric elastic lamellae alternating

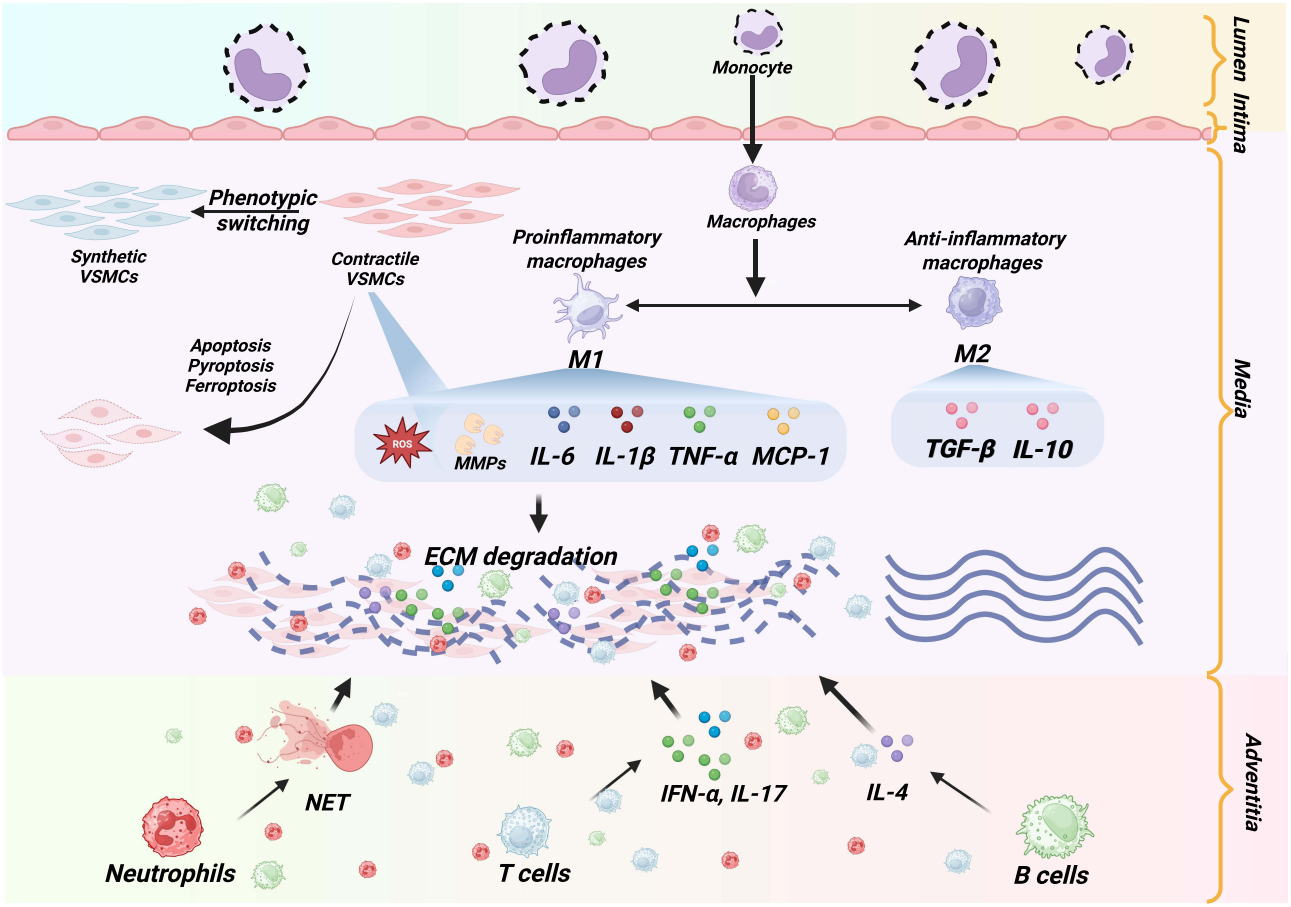

Figure 2 Pathological hallmarks of abdominal aortic aneurysm. AAA lesions are characterized by infiltration of immune cells, inflammation, oxidative stress, extracellular matrix (ECM) degradation, and loss of vascular smooth muscle cells (VSMCs). This figure is generated using https://BioRender.com.
Abbreviations: IL, interleukin; MMP, matrix metalloproteinase; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; MCP-1, monocyte chemoattractant protein-1; NET, neutrophil extracellular traps; IFN-γ, interferon-γ; ROS, reactive oxygen species.

with vascular SMCs. These structural "lamellar units" provide critical circumferential elasticity, protecting against hemodynamic deformation.[73] The media's extracellular matrix contains sparse fibroblasts within a network of elastin, collagen fibers, proteoglycans, and glycosaminoglycans. The outermost tunica adventitia comprises loose collagen fibers, fibroblasts, neural elements, and vasa vasorum micro vessels, with its collagen framework maintaining structural integrity.

ECM

The primary component of the blood vessel wall is the ECM, offering structural support to the cells. This dynamic structure is pivotal in governing vascular function, functioning critically under both physiological and pathological circumstances. Maintaining proper ECM function is essential for preserving aortic homeostasis and mechanical properties. The key macromolecules comprising the ECM in large arteries include elastin, collagens, glycoproteins, and proteoglycans, all of which are vital for the function and integrity of the vessel wall. In the middle layer of the aorta, smooth muscle cells are responsible for producing proteins such as elastin and collagen, contributing to the ECM in this part of the aorta. In the adventitia layer, fibroblasts produce collagen, osteopontin, and fibronectin, which are specific to this segment of the aortic wall.[74] Elastin and collagens are the most significant fibrillar proteins in the ECM of the aortic wall, influencing the passive mechanical properties of the aorta. Although vascular smooth muscle cells (VSMCs) retain contractile responsiveness to physiological stimuli and can thereby modulate aortic wall dynamics, this functional capacity appears to have minimal physiological significance in the abdominal aorta's overall mechanical behavior.[75]

Elastin

Elastin, constituting 50% of the dry weight of the aorta, is a hydrophobic and insoluble protein, serving as the predominant protein in the vascular wall. The ELN gene encodes elastin, and its soluble precursor, tropoelastin, is produced and released into the extracellular space. Tropoelastin monomers undergo polymerization to generate insoluble mature elastin, which then forms a highly cross-linked, rubber-like network through the action of lysyl oxidase, resulting in the development of elastin fibers.[76] Within the middle layer of the aortic wall, elastin fibers are particularly abundant and are peripherally associated with SMCs and collagen fibers, creating lamellar units. Under low tension, the laminae exhibit a wavy configuration, while increased tension causes them to stretch and straighten. Upon tension reduction, the laminae can revert to their original dimensions. Thus, elastin is the primary protein conferring structure to the vascular wall and contributes to elastic recoil in the aorta.[77]

Collagen

Collagen fibers, the second major structural protein in the aortic wall, constitute approximately 20% of the total protein in the normal aorta. The aortic wall contains various types of collagen, with types I and III being the most abundant, comprising 80–90% of the total collagen. The collagen molecule is composed of three polypeptides twisted together to create a triple helix, and covalent cross-linking between these collagen helices forms large, highly organized fibrillar bundles. Lysyl oxidase (LOX) catalyzes the formation of covalent cross-links between collagen molecules, enabling the assembly of mature collagen fibrils the dominant structural elements of the extracellular matrix.[78] Within the aortic adventitia, this cross-linked collagen network confers critical tensile strength, both protecting against elastin over-distension and providing mechanical resistance to wall deformation.[79] Collagen, being 100–1000 times stiffer than elastin, serves as the load-bearing component at higher pressures, while under normal blood pressure, the stretchy elastic fibers in the middle aortic wall handle the pressure changes. Consequently, elastin fibers and collagen fibrils together create a robust scaffold for the aorta, offering protection against mechanical damage.

ECM Remodeling

In the vascular wall, remodeling of the ECM is a physiological process essential for maintaining tissue homeostasis and functionality. However, when ECM remodeling becomes excessive or uncontrolled, it can lead to several life-threatening pathological conditions. Abnormal remodeling of the vessel wall diminishes the strength of the aortic wall, and if the forces acting on the aortic wall surpass its strength, it contributes to the development of AAA or leads to rupture. It has been proposed that the rapid fragmentation of elastin fibers may serve as the triggering event in AAA, initiating wall weakening and ultimately causing AAA expansion.[80] Under normal conditions, collagen fibers in the aortic wall remain relaxed. However, as an aneurysm forms and expands, these fibers gradually straighten and align until they approach their maximum stretching capacity. Studies have reported that collagen synthesis increases during the early stages of aneurysm formation, suggesting that collagen turnover is important for vessel wall repair and regeneration and maintaining the strength of the aortic wall and its structural integrity during AAA progression.[81] This suggests that increased collagen synthesis might occur as a response to increased wall tension as a consequence of increased elastin degradation together with an expanding aorta. But in later stages of the disease, collagen degradation exceeds its synthesis, and thus increased degradation of collagen fibers might reduce the mechanical strength of the aortic wall, which in turn becomes the responsible factor for AAA rupture. Thus, as the disease advances, the remodeling of the ECM leads to gradual deterioration and weakening of the aortic wall. This process culminates in dilation and eventual rupture when the aortic wall can no longer endure the hemodynamic forces. Several cellular and molecular mechanisms contribute to ECM remodeling in the progression of AAAs. Among these, proteolysis and inflammation play crucial roles.

Matrix Metalloproteinases (MMPs)

Numerous studies propose that the specific degradation of medial elastin is a key factor leading to the weakening and dilation of the aortic wall in AAAs.[82] Various works have concentrated on proteinases exhibiting elastolytic activity, with substantial evidence indicating that elastin degradation in AAA formation and progression is predominantly mediated by matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9.[83] Normally, MMPs play diverse roles in biological

processes, including tissue remodeling, cell growth, proliferation, migration, angiogenesis, vascularization, apoptosis, tissue repair, wound healing, and immune response.[84] All matrix metalloproteinases (MMPs) exhibit similar fundamental structural characteristics, consisting of five key domains: a signal peptide that directs protein secretion, an inhibitory propeptide domain that maintains enzyme latency, a catalytic domain responsible for substrate cleavage, a flexible hinge region, and a hemopexin-like domain that contributes to substrate specificity. MMPs are initially secreted in an inactive form known as pro-MMPs, requiring activation for proteolytic activity. The propeptide domain contains a cysteine residue (Cys73), stabilizing the inactive proenzyme. The catalytic domain features an active Zn2+ site bonded to the cysteine residue. The intact Cys73-Zn2+ bond maintains pro-MMP inactivity by preventing water molecules from reacting with the zinc molecule. MMP activation involves disrupting the bond between the active Zn2+ site and the cysteine residue, known as the "cysteine switch", a conserved mechanism in the MMP family.[85] The elevated activity of these enzymes results in excessive ECM degradation, which contributes to the formation of multiple pathological disease conditions, including the development of AAA.[86] So, it is crucial to control the MMPs' concentrations in order to regulate the correct level of the proteolytic activity of active MMPs, and One regulatory system involves the endogenous family of tissue inhibitors of metalloproteinases (TIMPs).[87] Physiologically, MMP activation is tightly regulated by TIMPs. Aneurysmal tissues often exhibit an imbalance between MMP and TIMP activities, as indicated by messenger RNA level studies.[88]

MMP-9, also known as gelatinase B, plays a significant role in elastin, collagen, laminin, gelatin, and fibrinogen degradation. It has been observed that MMP-9 levels and proteolytic activities are upregulated in AAA aortic tissues compared to healthy aortae,[89] and highly correlates with aneurysm size. MMP-9 are highly elevated at the site of aneurysmal rupture, showing AAA rupture is associated with higher levels of MMP-9 in the AAA wall.[90] Furthermore, higher plasma levels of MMP-9 are observed in AAA and aortic dissection patients.[91] Several population-based studies showed that plasma levels of MMP-9 dropped significantly in patients after AAA surgical repair.[92] Moreover, several animal models have been employed to investigate the role of MMP-9 in AAA, and MMP-9-deficient mice exhibit protection against aortic dilation and destruction in experimental aneurysms.[93] In human AAA, histological analysis confirmed that macrophages are the primary source for MMP-9 in the aortic wall, and it is reported that MMP-9 colocalizes with infiltrating macrophages present in the AAA wall mainly in the media and media-adventitia junction.[94] Similar findings are also reported in animal model studies. MMP-9 deficient mice receiving wildtype bone marrow post-nonlethal irradiation showed marked development of AAA, while the converse experiment in which wildtype mice received MMP-9 deficient marrow did not induce aneurysm formation, suggesting macrophage-derived MMP-9 is crucial for AAA formation.[95] Overall, the current opinion regarding MMP-9 is that it is positively related to AAA size, more specifically AAA rupture, and that its causality in AAA is independent of its cellular source and mainly due to inflammatory infiltrate macrophages. MMP-2 is a key protease implicated in the early pathogenesis of abdominal aortic aneurysm, playing a central role in the extracellular matrix (ECM) remodeling that drives aneurysm expansion. Primarily produced by vascular smooth muscle cells (VSMCs), MMP-2 exhibits potent elastolytic and gelatinolytic activity, specifically targeting elastin and type IV collagen in the aortic media. While its overall activity levels are generally lower than the inflammation-associated MMP-9 in established aneurysms, increased MMP-2 activity represents an early pathogenic event that precedes significant inflammatory cell infiltration.[96,97] Multiple studies in human tissues and animal models consistently demonstrate that elevated MMP-2 activity correlates with characteristic histopathological features of AAA, including elastin fragmentation, collagen disorganization, and progressive aortic dilation.[98,99] This evidence positions MMP-2 as a critical initiator of the proteolytic cascade that weakens the aortic wall and facilitates aneurysm development. Although MMPs play a pivotal role in AAA pathogenesis, broad-spectrum MMP inhibition (eg, with doxycycline) has failed to demonstrate clinically meaningful suppression of aneurysm progression in human trials,[100] highlighting the complex interactions and multiple mechanisms involved.

Inflammatory and Immune Response

Cytokines

The pivotal role of inflammation in the initiation and progression of AAAs has long been established. Numerous studies indicate that the upregulation of cytokines and chemokines is associated with AAA development. Several key

inflammatory mediators, including interleukin-6 (IL-6), interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and monocyte chemoattractant protein-1 (MCP-1), have been identified with elevated levels in both the plasma of AAA patients and AAA tissues.[101]

Interleukin-1β

Interleukin (IL) is recognized as a crucial regulator of inflammation and cellular apoptosis in chronic inflammatory diseases. Studies have demonstrated a significant elevation in IL-1β concentration in tissue samples from AAA compared to healthy aortas.[102] Moreover, plasma concentrations of IL-1 in male AAA patients were found to be nearly ten times higher than those in the control group.[103] Experiments also revealed a substantial increase in IL-1 secretion in AAA.[104] Animal studies, particularly using elastase-induced AAA mouse models, showed significantly higher aortic IL-1 protein levels compared to control mice and both genetic depletion of IL-1 and pharmacological inhibition of the IL-1 receptor successfully prevented elastase-induced AAA formation.[105] Similarly, in an Angiotensin II (AngII) induced AAA model, inhibiting IL-1 with an antibody effectively inhibited AAA formation.[106] Several other animal studies consistently demonstrated that targeting IL-1 protects against aneurysm development.[107] In a model of β-aminopropionitrile (BAPN) induced dissecting AA, elevated IL-1 levels were observed in aortic samples, suggesting a local contribution of IL-1 to AAA formation. This involvement was linked to the activation of MMP-2 and MMP-9 and the degradation of elastin fibers, ultimately compromising the biomechanical properties of the aortic wall.[108]

Interleukin-6

The pro-inflammatory cytokine IL-6 plays a pivotal role in driving the systemic inflammatory response involved in the pathogenesis of various cardiovascular diseases. Specifically, patients with AAA exhibit a high concentration of IL-6 compared to donor aortas, suggesting a potential significance of this cytokine in aneurysm formation.[109] Numerous studies have consistently demonstrated an elevated level of circulating IL-6 in AAA patients, which correlates with the diameter of the aorta.[110,111] Additionally, IL-6 production was found to be increased in AAA compared to normal aortas.[112] Notably, a study presented evidence associating a single nucleotide polymorphism (SNP) that reduces the function of the IL-6 receptor with a decreased risk of developing AAA, reinforcing a potential causative role for IL-6 in human AAA.[113] It has been demonstrated that selectively blocking the IL-6 trans-signaling pathway can prevent AAA progression and aortic rupture.[114] Several studies have reported associations between IL-6 and its receptor with the risk of AAA.[115] Animal research has also revealed that IL-6 is related to aneurysmal disease.[116] Animal research, including studies by Nishihara et al, revealed that inhibition of the IL-6 receptor using a monoclonal antibody reduces the diameter of the aorta in a murine model of CaCl2-induced AAA.[117] Tamsulosin was also found to attenuate the formation of AAAs by reducing the production of pro-inflammatory cytokines and promoting the preservation of elastin.[118]

Tumor Necrosis Factor

Tumor necrosis factor (TNF) stands out as a pivotal cytokine in numerous inflammatory responses. Extensive clinical evidence collected from numerous studies indicates an elevation of TNF-α in the plasma and serum of patients with AAAs.[119] Systematic reviews emphasize that TNF-α is consistently among the most upregulated cytokines in AAAs.[120] Furthermore, the expression of TNF-α and TNF-converting enzyme (TACE) is notably heightened in human AAA tissues, particularly in the media and adventitia, compared to the normal aorta.[121] This increase is also observed in both human AAA and mouse CaCl2-induced AAA samples in comparison to the normal aorta and temporal depletion of TACE in mice results in reduced AAAs induced by calcium chloride, accompanied by mitigation of ECM disruption and inflammation in the aortic wall.[122] Studies by Xiong et al demonstrate that genetic deficiency or pharmacological inhibition of TNF-α using infliximab attenuates calcium chloride-induced AAAs in mice by reducing MMP-2 and MMP-9 expression, along with decreased macrophage infiltration into the aortic tissue.[123] Another study revealed that agents such as tumor necrosis factor binding protein (TNF-BP) effectively prevent post-elastase dilation of the aorta in a rat model of elastase-induced AAA.[124] Hence, TNF-α, an inflammatory cytokine that induces the release of proteases, plays a substantial role in breaking down structural proteins in the aortic wall, potentially contributing to the development of AAA.

Chemokines

Chemokines, a family of small secreted peptide cytokines regulating diverse cell functions, primarily immune-cell recruitment, play crucial roles in various pathological conditions such as inflammation, atherosclerosis, altered hematopoiesis, and cancer. Numerous studies have highlighted the prominence of chemokine (C-C motif) ligand 2 (CCL2), also known as MCP-1, within AAA tissue, demonstrating higher expression in aneurysm tissue compared to controls.[125] In a particular study, aortic explants from aneurysmal tissue were found to release MCP-1 to a greater extent than occlusive or normal aortic tissue.[126] MCP-1, a C-C chemokine, regulates monocyte recruitment to the site of inflammation through its receptor, C-C chemokine receptor-2 (CCR-2). Studies have demonstrated that genetic deletion of CCR-2 substantially attenuated Ang II–induced lumen dilatation in the ascending aorta.[127] Beyond the CC chemokine family, G protein-coupled receptor Chemokine (CXC) chemokines and their receptors, CXCR are equally instrumental. The CXCL12/CXCR4 axis, in particular, has been identified as a significant contributor to AAA pathogenesis.[128] CXCL12 (SDF-1) promotes the recruitment of pro-inflammatory cells to the aortic wall, and inhibition of the CXCR4 receptor has been shown to limit experimental AAA formation and progression.[129] Similarly, CXCR2, activated by CXC chemokines, serves as a significant receptor for macrophage-mediated inflammatory responses. In animal models, pharmacological inhibition of CXCR2 significantly reduced Ang II–induced AAA formation, evident in reduced collagen deposition, elastin degradation, metal matrix metalloprotease expression, and diminished accumulation of macrophage cells in the aortic wall.[130] Collectively, these findings underscore that multiple chemokine pathways including CCL2/CCR2, CXCL12/CXCR4, and the CXCR2 axis are coordinately involved in recruiting inflammatory cells and driving the proteolytic cascade in AAA. This highlights their collective potential as therapeutic targets for suppressing aneurysm development.

Immune Cells

Macrophages

Macrophages represent the predominant immune population in abdominal aortic aneurysm tissues, demonstrating complex temporal and spatial distribution patterns throughout disease progression.[131–135] While surgical specimens often show diminished macrophage presence likely reflecting late-stage diseaseanimal models demonstrate crucial early infiltration, particularly in the adventitial-medial junction.[134,136–142] The macrophage population in AAA originates from two distinct lineages: tissue-resident macrophages derived from embryonic precursors that maintain local vascular homeostasis, and monocyte-derived macrophages recruited from circulation during inflammatory responses.[137,143,144]

The traditional classification of macrophages, two distinct phenotypes, M1 (classically activated) and M2 (alternatively activated) macrophages, exhibit divergent functions in regulating inflammatory processes.[145–150] Both M1 and M2 macrophages are present in AAA, and their polarization during AAA development determines the progression.[151] Maintaining a balance between M1 and M2 is crucial for AAA regulation, as an imbalance in the M1/M2 ratio can promote AAA development.[152,153] Recent advances in single-cell transcriptomics have fundamentally transformed our understanding of macrophage heterogeneity, identifying at least five functionally distinct subsets that transcend the conventional M1/M2 classification system.[154] These include: (1) Tissue-resident macrophages characterized by expression of *Cd200, Pla2g2d, Timd4, Il4i1, and Mif*, which help maintain local environmental homeostasis; (2) Tissue-repairing macrophages characterized by high expression of *Cd163 and Mrc1 (Cd206)*, along with extracellular matrix organization genes that facilitate vascular remodeling; (3) Anti-inflammatory macrophages, marked by *Arg1, Mmp19, and Fn1*, which exhibit immunosuppressive properties and may attempt to limit disease progression; (4) Pro-inflammatory macrophages, display a classical inflammatory phenotype characterized by elevated expression of *Ccl5, Stat1, Il1b, and Nlrp3*, driving the inflammatory cascade through cytokine production and matrix degradation; and (5) IRF7+ macrophages, representing a unique transitional state identified by co-expression of both M1 (*Cd52*) and M2 (*Cd72 and MS4A4A*) markers alongside interferon regulatory factor 7 (IRF7), potentially coordinating immune responses through interferon-related pathways.

While the field agrees that macrophage polarization significantly influences AAA progression, substantial controversy exists regarding therapeutic targeting strategies. Some studies suggest promoting M2 polarization may attenuate AAA,[153] while others argue that specific macrophage subpopulations—particularly GPNMB+ macrophages localized to areas of

elastic degradation represent more promising targets.[155] The relative contributions of tissue-resident versus monocyte-derived macrophages also remain debated, with emerging evidence suggesting they may drive distinct aspects of pathogenesis. Furthermore, the functional significance of macrophage phenotypic switching during AAA development remains incompletely understood, particularly regarding whether certain transitional states might be harnessed for therapeutic benefit.

Neutrophil

Some studies suggest circulating neutrophils may be an important contributor to AAA formation in the early phase.[156,157] Neutrophils play a significant role in the progression of AAA through various mechanisms, including the formation of neutrophil extracellular traps (NETs), oxidative stress, and inflammatory responses. NETs are implicated in the pathogenesis of AAA, particularly in the adventitia and intraluminal thrombus. Inhibition of NET formation has been shown to prevent the progression of AAA in certain models, such as those induced by angiotensin II, which resemble human disease with thrombus development.[158] NETs contribute to tissue injury and inflammation, promoting AAA progression. Inhibition of NET formation through specific pathways, such as PAD4-dependent mechanisms, has been shown to reduce AAA rupture and progression in experimental models.[159] Elevated levels of hydrogen peroxide and myeloperoxidase in neutrophils from AAA patients indicate heightened oxidative activity, which is associated with aneurysm development and progression.[160] Neutrophils release leukotriene B4, a major chemotactic factor, from the intraluminal thrombus, which recruits additional neutrophils and perpetuates inflammation within the aneurysm site.[161] Neutrophil activation and recruitment are also linked to external factors such as periodontal disease, where bacterial DNA from pathogens like *Porphyromonas gingivalis* has been found in AAA samples, suggesting a role in neutrophil-driven inflammation and aneurysm growth.[162] Targeting neutrophil-mediated inflammation and NET formation presents a potential therapeutic strategy for AAA. Nanotherapies designed to inhibit neutrophilic inflammation have shown promise in reducing AAA progression by attenuating NET formation and associated inflammatory responses.[163] The use of noninvasive imaging techniques to monitor neutrophil activity and NET formation in AAA patients could aid in early diagnosis and intervention, potentially improving patient outcomes.[164] Moreover, neutrophils are the main source of MMPs in AAA.[165] While neutrophils are central to AAA progression, it is important to consider the broader inflammatory milieu and the interplay of various immune cells and mediators. The precise temporal window for neutrophil-targeted interventions and the optimal strategy for selective NET inhibition without impairing host defense remain active investigation areas.

T Cells

T cells play a crucial role in the progression of AAA through their involvement in the chronic inflammatory response within the aortic wall.[166,167] The infiltration of different subsets of T cells contributes to the complex inflammatory environment that leads to aortic wall degradation, matrix remodeling, and eventual aneurysm expansion.[168] Mainly CD4+T cells are the most abundant T cells infiltrating AAA and When CD4+T cells are not present; the development of AAA is significantly inhibited.[169] Research have indicated that all the CD4+T cells subsets (Th1 cells, Th2 cells, Th17 cells, regulatory T (Treg) cells and T follicular helper (Tfh) cells) are involved in the formation of AAA.[170] CD8+ T cells, also known as cytotoxic T cells, can directly kill infected or damaged cells. CD8+ T cells contribute to the inflammatory milieu in AAA by secreting IFN-γ, which enhances the activity of MMPs such as MMP-2 and MMP-9. These enzymes degrade the extracellular matrix, weakening the aortic wall and promoting aneurysm formation.[171] The study further demonstrated that experimental depletion of CD8+ T cells correlates with attenuated AAA progression, mediated through reduced smooth muscle cell apoptosis and consequent limitation of vascular wall degeneration. These findings implicate CD8+ T cells as key contributors to SMC loss and aneurysmal pathogenesis. While CD8+ T cells are implicated in promoting SMC apoptosis and AAA progression, other immune cells and pathways also contribute to the disease's complexity. For instance, Vδ2+ T cells are significantly increased in AAA tissues and are major producers of IL-17A, a pro-inflammatory cytokine that may exacerbate inflammation and tissue damage in AAA.[172] This highlights the need for comprehensive strategies that address multiple aspects of the immune response in AAA. The relative importance of specific lymphocyte subsets varies considerably across different experimental models, suggesting context-dependent

roles that may reflect the heterogeneous nature of human AAA. Furthermore, the antigenic drivers of adaptive immune responses in AAA remain largely unidentified, representing a critical knowledge gap in our understanding of disease mechanisms.

B Cells

B cells play a significant role in the progression of AAA through various mechanisms, including the production of specific antibodies and interaction with other immune cells.[173] B cells organized in tertiary lymphoid organs (TLOs) within the aortic wall are implicated in AAA progression through the production of IgE antibodies. IgE antibodies produced by TLO B cells activate mast cells (MCs), which are enriched at sites of unhealed hematomas in the aortic wall. This activation leads to the production of IL-4, a cytokine that promotes further IgE class-switching and production by B cells, creating an amplification loop that exacerbates aneurysmal progression.[174] Overactivated B cells secrete pathological antibodies, such as anti-beta 2 glycoprotein I (anti-β2GPI) IgG, which contribute to AAA formation, particularly in the context of hyper-homocysteinemia (HHcy). HHcy induces the secretion of these antibodies, which polarize inflammatory macrophages in a TLR4-dependent manner, leading to increased elastin degradation and matrix metalloproteinase (MMP) expression, thereby aggravating AAA progression.[175] Studies have shown that targeting the B cell-mediated pathways may help reduce inflammation and tissue degradation, potentially slowing or preventing the progression of AAA.[176] While T-cell and B-cell depletion strategies show consistent efficacy across multiple animal models, their translational potential remains uncertain given the risks associated with systemic immunosuppression.

Vascular Smooth Muscle Cell

VSMCs play a vital role in the structure and function of blood vessels, including the aorta. SMCs exhibit functional plasticity in AAA pathogenesis, contributing to both extracellular matrix maintenance and disease-propagating inflammatory responses. SMC dysfunction, apoptosis (cell death), and phenotypic changes are key processes in the development and expansion of AAA. One of the primary mechanisms underlying AAA formation is the phenotypic switching of VSMCs. In healthy aortic walls, VSMCs primarily exhibit a contractile phenotype, maintaining vascular tone and structural integrity. However, in the context of AAA, these cells undergo a phenotypic switch to a synthetic state. This switch is characterized by decreased expression of contractile markers such as calponin and myosin heavy chain, and increased production of extracellular matrix components, inflammatory cytokines, and proteases.[177–179] This transition is influenced by various factors, including cytokines, mechanical forces, oxidative stress, and specific signaling pathways. Increased levels of TNF-α in the aortic wall activate the PERK/eIF2α/ATF4 pathway, leading to VSMC apoptosis and promoting a synthetic phenotype.[180] Mechanical stress and oxidative stress are known to influence VSMC behavior, which can trigger changes in their contractile properties and promote a synthetic state. Elevated oxidative stress contributes to VSMC dysfunction, impacting their ability to maintain a contractile phenotype.[181] Key regulators include SLC44A2, which, when overexpressed, promotes a contractile phenotype through TGF-β/SMAD signaling, while its silencing leads to a synthetic phenotype, exacerbating AAA susceptibility.[182,183] Additionally, CCN2 deficiency in smooth muscle cells triggers reprogramming towards a pro-AAA phenotype, indicating its critical role in maintaining VSMC identity and function.[184] The phenotypic landscape of VSMCs in AAA is diverse, with single-cell RNA sequencing revealing multiple phenotypes, including contractile, fibroblast-like, and macrophage-like VSMCs, each contributing differently to aneurysm formation.[185] These findings underscore the multifaceted regulation of VSMC phenotypic switching, involving genetic, molecular, and mechanical factors, which collectively contribute to the pathophysiology of AAA.

SMC apoptosis is indeed a critical factor in the progression of AAA, contributing to the thinning of the aortic wall and compromising its structural integrity, which increases susceptibility to aneurysm expansion and rupture. The upregulation of phosphodiesterase 4D (PDE4D) in SMCs has been shown to promote apoptosis through the cAMP-PKA-pBad axis, suggesting that PDE4D plays a causative role in AAA development, and its inhibition could be a potential therapeutic strategy.[186] Single-cell RNA sequencing has revealed that during AAA progression, there is a proportional decrease in major SMC subpopulations, accompanied by down-regulation of contractile markers and up-regulation of pro-inflammatory genes, highlighting the role of SMCs in AAA pathogenesis.[135] Mitochondrial dysfunction

and oxidative stress in SMCs are also implicated in AAA, with increased reactive oxygen species production and DNA damage observed in AAA-derived SMCs.[187] The loss of cysteine-rich protein 2 (CRP2) in SMCs has been shown to attenuate AAA formation by maintaining ECM homeostasis and reducing apoptosis through the Erk1/2-Col III and MMP2 axis.[188] Additionally, the long non-coding RNA SENCR has been identified as a suppressor of AAA formation by inhibiting SMC apoptosis and ECM degradation, suggesting its potential as a therapeutic target.[189] Collectively, these studies describe that in AAA, SMCs undergo apoptosis, phenotypic switching, and contribute to ECM degradation, all of which weaken the aorta and promote aneurysm expansion. This underscore the importance of preserving SMC integrity and function to limit AAA progression.

Endothelial Cells

Endothelial cells maintain vascular homeostasis by regulating blood vessel tone, permeability, and anti-inflammatory, anti-thrombotic surface in aorta. Endothelial dysfunction serves as a critical initiating factor in abdominal aortic aneurysm development, transforming the intimal layer from a protective barrier into a active contributor to disease progression. The dysfunctional endothelium exhibits impaired nitric oxide (NO) bioavailability due to eNOS uncoupling, creating a state of oxidative stress through NADPH oxidase overexpression that promotes vascular inflammation and matrix degradation[190] This is accompanied by a shift toward pro-inflammatory activation, characterized by increased expression of adhesion molecules (VCAM-1, ICAM-1) and chemokines (CCL2) that facilitate monocyte/macrophage recruitment into the aortic wall.[191] Mechanosensitive pathways play a crucial role, as spatially heterogeneous wall shear stress in the infrarenal aorta induces endothelial damage and inflammatory signaling that correlates with preferential aneurysm formation.[192] The activated endothelium also demonstrates a pro-coagulant shift through tissue factor induction and von Willebrand factor release, promoting intraluminal thrombus formation that further alters the local proteolytic environment.[193] Additional mechanisms include aberrant angiogenic signaling and endothelial-to-mesenchymal transition (EndMT), which contribute to neovessel formation and inflammation amplification within the aneurysmal wall.[194] These endothelial changes collectively drive medial degeneration through increased protease induction (particularly MMP-2 and MMP-9), elastin fragmentation, and vascular smooth muscle cell apoptosis. Emerging preclinical evidence suggests that targeting specific endothelial pathways—including eNOS signaling, Kruppel-like factor 11 (KLF11), C-type natriuretic peptide (CNP), VEGF signaling, and ROS generation—may represent promising therapeutic strategies to mitigate aneurysm progression by restoring endothelial homeostasis.[193]

Signaling Pathways in AAA Pathogenesis: Mechanisms and Therapeutic Implications

Several signaling pathways have been implicated in the development of AAA. As illustrated in Figures 3 and 4, some signaling pathways promote AAA progression when activated, while others exert protective effects. Understanding these distinct pathways has been crucial for developing targeted therapeutic approaches, including specific inhibitors for pathogenic pathways and activators for protective signaling molecules.

Nuclear Factor Kappa B (NF-κB) Pathway

A prominent player in both acute and chronic inflammatory responses associated with AAA is the nuclear factor-kappa B (NF-κB) signaling pathway. The NF-κB signaling pathway primarily consists of five key protein subunits from the NF-κB/Rel family: RelA (p65), RelB, c-Rel, p50/p105 (NF-κB1), and p52/p100 (NF-κB2). These proteins act as inducible transcription factors that regulate gene expression by binding to specific DNA sequences known as κB elements by forming various homo- and heterodimers. In most cell types, NF-κB complexes are retained in the cytoplasm by a family of inhibitory proteins known as inhibitors of NF-κB (IκBs), mainly IB. Activation of NF-κB typically involves the phosphorylation of IκB by the IκB kinase (IKK) complex, which results in IκB ubiquitination and subsequent degradation. This releases NF-κB and allows it to translocate freely to the nucleus. In the nucleus, NF-κB binds to the κB sequence of various genes, thereby activating their transcription. NF-κB directly regulates numerous cytokines and

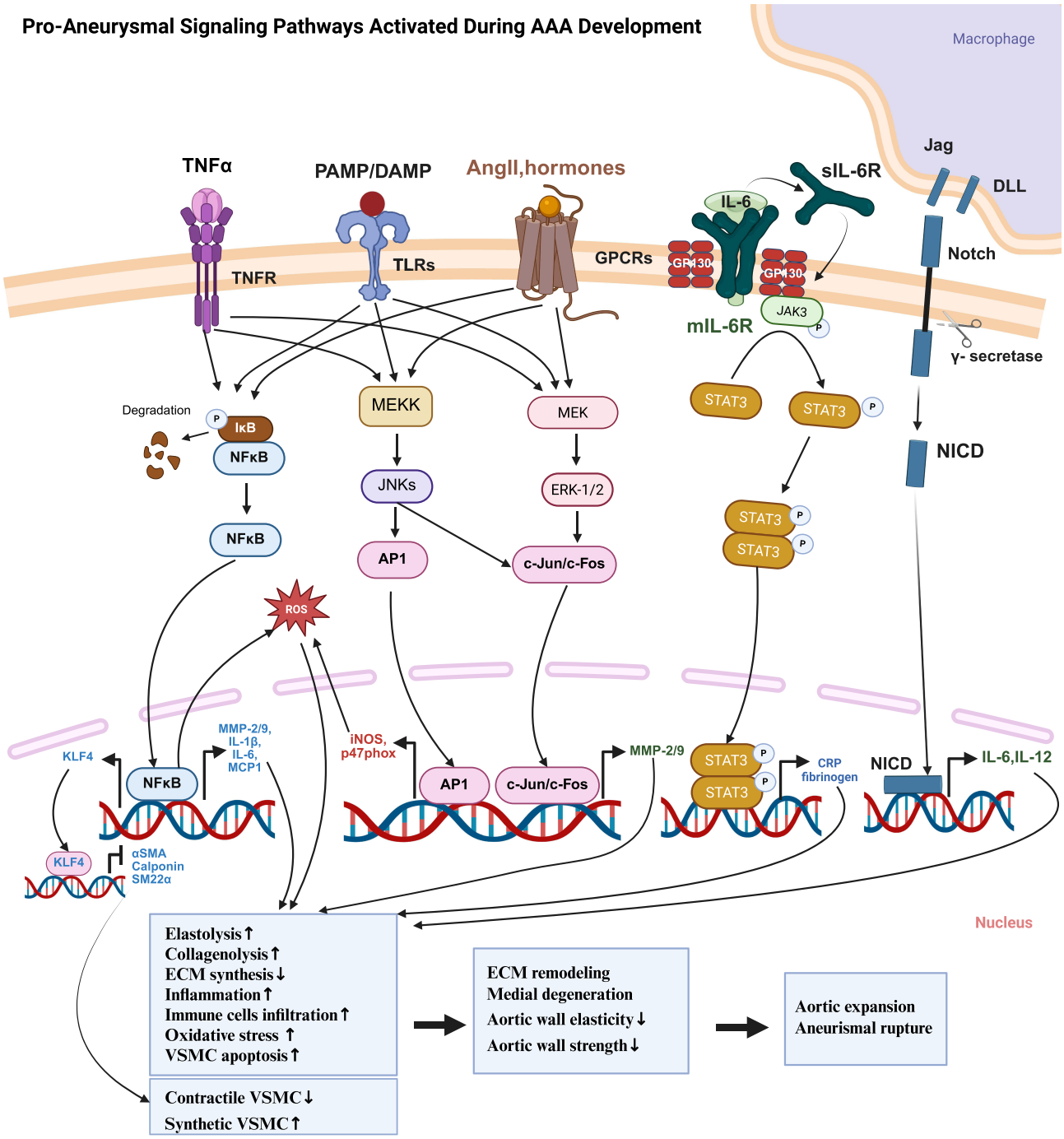

Figure 3 Pro-Aneurysmal Signaling pathways during abdominal aortic aneurysm formation. (↑ indicates increase and ↓ indicates decrease).This figure is generated using https://BioRender.com.

Abbreviations: TNFα, tumor necrosis factor α; TNFR, TNF receptor; PAMP, pathogen-associated molecular pattern; DAMP, damage-associated molecular pattern; TLRs, toll-like receptors; AngII, angiotensin II; GPCRs, G protein-coupled receptors; IL-6, interleukin-6; mIL-6R, membrane interleukin-6 receptor; sIL-6R, soluble interleukin-6 receptor; GP130, glycoprotein 130; JAK3, Janus kinase 3; NF-κb, nuclear factor κB; IκB, inhibitor of NF-κB; P, phosphorylation; MEKK, mitogen-activated protein kinase kinase; JNKs, c-Jun N-terminal kinases; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinases; MEK, MAPK/ERK kinase; STAT3, Signal transducer and activator of transcription3; MMP, matrix metalloproteinase; IL-1β, interleukin-1β; MCP-1, monocyte chemoattractant protein-1; ECM, extracellular matrix; CRP, C reactive protein; DLL, delta like canonical Notch ligand; JAG, jagged; NICD, Notch intracellular domain; IL-12, interleukin-12; AP1, activator protein 1; iNOS, inducible nitric oxide synthase; ROS, reactive oxygen species; KLF4, Kruppel-like factor 4; α-SMA, α- smooth muscle actin; SM22α, smooth muscle 22α.

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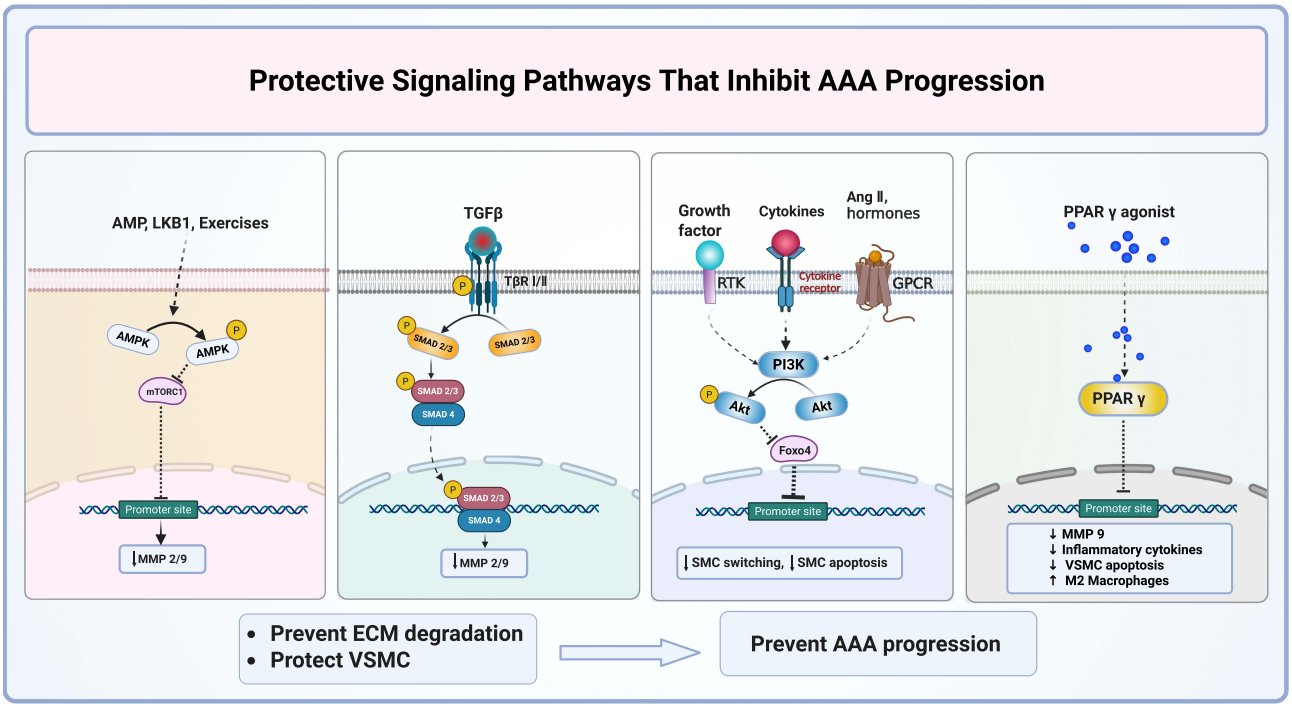

Figure 4 Protective Signaling pathways that inhibit abdominal aortic aneurysm progression. (↑ indicates increase and ↓ indicates decrease). This figure is generated using https://BioRender.com.

Abbreviations: AMPK, AMP-activated protein kinase; LKB1, Liver kinase B1; TGFβ, transforming growth factor β; AMP, adenosine monophosphate; mTORC1, mammalian target of rapamycin complex 1; TβRI/II, transforming growth factor β receptor 1/2; RTK, receptor tyrosine kinase; Ang-II, angiotensin II; GPCRs, G protein-coupled receptors; PI3K, phosphatidylinositol 3-kinase; P, phosphorylation; FoxO4, Forkhead box protein O 4; VSMC, vascular smooth muscle cell; PPAR-γ, Peroxisome proliferator-activated receptors γ; MMP, matrix metalloproteinase; ECM, extracellular matrix.

proteases, such as IL-1β, IL-6, TNF-α, and MMPs. NF-κB also regulates the expression of adhesion molecules and chemokines, which induce the migration of inflammatory cells. Multiple factors can trigger NF-κB signaling in AAA diseases, such as Ang-II, MMP9, ROS and hypertension.[195–198] Gene enrichment and positive immunostaining of NF-κB p65 and p50 have been observed in AAA tissues.[199] In addition, recent studies have demonstrated that NF-κB inhibits transcription of the elastin and collagen genes, leading to suppression of their synthesis.[200] Studies have shown that suppression of NF-κB inhibits the formation and progression of AAA by reducing MMP and inflammatory cytokine expression.[201] Ijaz et al demonstrated that genetic ablation of Rela (p65) in mesenchymal cells markedly attenuated Ang-II -induced AAA formation. This NF-κB suppression correlated with diminished IL-6 and IL-1β production and reduced infiltration of inflammatory monocytes, highlighting the pathway's critical role in AAA pathogenesis.[202] Qi et al also found that 17-dimethyl-aminoethylamino-17-demethoxy-geldanamycin (17-DMAG) attenuates Ang-II -induced AAA in mice by blocking p65 nuclear translocation.[203] Wang et al showed that 3-hydroxyanthranilic acid (3-HAA) promotes Ang-II -induced AAA formation in mice by upregulating mmp2 via a transcription factor NF-κB.[204] Thus, these findings show NF-κB is critical in AAA pathogenesis.

MAPK Pathways (ERK, JNK, p38 MAPK)

The mitogen-activated protein kinase (MAPK) signaling pathway plays a pivotal role in coordinating cellular responses to diverse extracellular signals. This family comprises three core kinase subgroups: Jun N-terminal kinases (JNK1-3), extracellular signal-regulated kinases (ERK1/2), and p38 isoforms (p38α/β/γ/δ). In AAA pathogenesis, both human and rodent studies demonstrate significant upregulation of total and phosphorylated JNK.[205] Pharmacological JNK inhibition attenuates experimental AAA progression,[206] with multiple JNK-targeting compounds showing comparable protective effects.[207–210] Notably, cigarette smoke/nicotine exacerbates AAA via JNK-mediated MMP2/9 induction in Ang-II models.[211] Another member, The ERK cascade involves sequential activation of MAPKKK (Raf), MAPKK (MEK1/2), and MAPK (ERK1/2), ultimately phosphorylating transcriptional regulators (eg, STAT1/3, ELK-1, c-FOS, PPAR-γ). ERK-1/-2 activation, has been

shown to play critical roles in the pathogenesis of AAA.[212,213] In human AAA tissues, as well as in the elastase perfusion and Ang-II infusion models of AAA, the levels of phospho-MEK-1/2 (pMEK-1/2) and pERK are markedly increased.[214,215] Consistent with its pathogenic role, ERK inhibition (via CI1040) reduces MMP activity and aneurysm formation in mice.[216]

JAK/STAT Pathway

Signal transducer and activator of transcription (STAT) regulates the transcription of several genes associated with inflammatory and immune responses. The pathway was investigated by Liao et al, who suggest STAT may also be involved in the process of AAA pathogenesis.[217] In another set of experimental studies, pharmacological inhibition of STAT3 reduced the incidence and severity of Ang II–induced AAA formation.[218] A key mediator in these pathways is IL-6 signaling. IL-6 activates signaling through two distinct pathways one IL-6 bound to the membrane-bound IL-6 receptor (mIL-6R) and another IL-6 also binds to the soluble IL-6 receptor (sIL-6R) that forms a dimer with the coreceptor glycoprotein-130 (gp-130). This dimerization activates Janus kinase (JAK) and leads to the phosphorylation of STATs, which translocate into the nucleus and regulate the expression of target gene that are involved in immune system development, autoimmunity, acute-phase reactions and chronic inflammation. Elevated IL-6 and downstream STAT3 activation have been consistently documented in both aortic tissue and plasma from AAA patients compared to healthy controls.[219] Recent mechanistic studies demonstrate that selective inhibition of IL-6 trans-signaling using sgp130Fc significantly enhances survival in experimental AAA models (Ang-II infusion and elastase+TGF-β neutralization), implicating the IL-6/sIL-6R/gp130 axis as a key driver of aneurysmal pathogenesis.[114] Thus, this data shows that these signaling pathways play an important role in AAA formation.

PI3K/Akt Signaling Pathway

The PI3K/Akt signaling pathway plays a dual role in AAA pathogenesis, with effects critically dependent on cellular context and specific isoforms. This pathway regulates multiple processes central to AAA progression, including vascular smooth muscle cell (VSMC) behavior, inflammatory responses, and extracellular matrix integrity. The pathway's complexity is exemplified by its cell-specific effects: in inflammatory cells such as neutrophils, PI3Kγ activation promotes neutrophil extracellular trap (NET) formation and enhances inflammatory cytokine production, thereby accelerating AAA development. Accordingly, inhibition of PI3Kγ reduces NET formation and inflammation, ameliorating AAA in experimental models.[220] Similarly, in macrophages, PI3K inhibition suppresses AAA progression by reducing inflammatory cell infiltration and ECM degradation.[221] Conversely, in vascular smooth muscle cells (VSMC), PI3K/Akt activation promotes cell survival and maintains contractile phenotypes, exerting protective effects against aneurysm progression.[222] This protective role is further supported by evidence that Akt2 activation in VSMCs contributes to the beneficial effects observed with rapamycin treatment.[220] These opposing cell-type-specific effects underscore the necessity for precisely targeted therapeutic strategies. Future approaches should aim to selectively inhibit pathogenic PI3Kγ signaling in inflammatory cells while preserving or enhancing protective Akt signaling in VSMCs, potentially through cell-specific delivery systems that can achieve this sophisticated modulation.

TGF-β Signaling

Transforming Growth Factor-Beta (TGF-β) signaling exhibits complex, context-dependent roles in abdominal aortic aneurysm pathogenesis, demonstrating both protective and pathogenic functions.[222,223] Elevated TGF-β1 levels detected in human AAA tissue and experimental models suggest its involvement in disease progression, though whether this represents a causative pathogenic factor or a compensatory homeostatic response remains unclear.[224,225] Evidence supporting TGF-β's protective role includes studies demonstrating that localized TGF-β1 overexpression in the aortic wall limits aneurysm expansion in rodent models,[226,227] while systemic TGF-β neutralization significantly exacerbates AAA prevalence and severity in angiotensin II–infused mice.[228] The cellular specificity of TGF-β signaling critically determines its functional outcomes. Research by Angelov et al[229] revealed that systemic but not SMC-specific TGF-β signaling blockade significantly increased AAA prevalence and promoted adventitial expansion with macrophage accumulation, whereas SMC-specific inhibition caused medial thinning without substantial effects on inflammation or

adventitial expansion. These findings indicate that TGF-β's protective effects in AAA are mediated primarily through non-SMC populations, likely including immune cells and adventitial fibroblasts, rather than through direct actions on vascular smooth muscle cells. This cellular compartmentalization of TGF-β signaling underscores the therapeutic challenge in targeting this pathway. Future therapeutic strategies should aim for precise cellular and signaling modulation, potentially through cell-type-specific delivery systems or receptor-subtype-selective approaches that enhance protective ECM-stabilizing effects while avoiding disruption of anti-inflammatory signaling in critical protective cell populations.

Notch Signaling

The Notch signaling pathway plays a significant role in the development and progression of AAA, a serious vascular condition. The pathway is involved in various cellular processes, including cell fate determination, proliferation, and apoptosis, which are crucial in the pathogenesis of AAA. Recent studies have highlighted the potential of targeting the Notch pathway as a therapeutic strategy for AAA. Notch1 signaling is activated in AAA tissues, as evidenced by increased expression of the Notch intracellular domain (NICD) and its target gene Hes1 in both animal models and human AAA samples. The use of γ-secretase inhibitors like dibenzazepine (DBZ) has shown promise in preventing AAA formation by blocking Notch activation. DBZ effectively reduces the incidence and severity of AAA in animal models by inhibiting inflammatory cell accumulation and reversing Th2 immune responses.[230] Inhibition of Notch1-mediated inflammation by intermedin (IMD) has been shown to protect against AAA development. IMD reduces the expression of inflammatory factors and macrophage infiltration, which are critical in AAA pathogenesis.[231] Pharmacological inhibition of Notch signaling, specifically using DAPT, has been demonstrated to regress pre-established AAA by reducing inflammation and proteolytic activity in the aortic tissue.[232] Notch3 activation is linked to aortic aneurysm development by influencing VSMC differentiation. In marfan syndrome, increased Notch3 activation correlates with a contractile phenotypic change in VSMCs, contributing to aneurysm formation. Inhibition of Notch3 can attenuate aortic enlargement and improve survival, suggesting a role in AAA as well.[233] Notch1 haploinsufficiency in VSMCs maintains a contractile phenotype and prevents matrix remodeling, which limits aortic dilation in AAA. This highlights the importance of Notch signaling in maintaining VSMC function and preventing aneurysm progression.[234] The Notch pathway is a highly conserved signaling mechanism involved in numerous developmental and pathological processes beyond AAA, such as cancer, hematopoiesis, and tissue regeneration. This complexity underscores the need for further research to refine Notch-targeted therapies for AAA and other conditions.

AMPK Signaling

AMP-activated protein kinase (AMPK) signaling plays a crucial role in the pathogenesis of AAA. AMPK is a key regulator of cellular energy homeostasis and has been implicated in various cellular processes, including inflammation and angiogenesis, which are critical in AAA development. Activation of AMPK has been shown to have protective effects against AAA progression, suggesting its potential as a therapeutic target. AMPK activation has been found to reduce the incidence and severity of AAA in experimental models. In a study using ApoE -/- mice, the AMPK activator AICAR significantly decreased aneurysm formation and associated mortality.[235] In this study, Metformin, a common anti-diabetic drug known to activate AMPK, also demonstrated a retardation of AAA progression, highlighting the therapeutic potential of AMPK activation in AAA management. In endothelial cells, AMPK regulates processes like fatty acid oxidation and nitric oxide production, which are relevant to vascular health and may contribute to its protective role in AAA.[236] While AMPK activation shows promise in mitigating AAA progression, it is essential to consider the complexity of AMP signaling networks and their broader physiological roles. Further research is needed to fully elucidate the mechanisms by which AMPK influences AAA and to explore its potential in clinical applications.

PPAR-γ Pathway

Peroxisome proliferator-activated receptors (PPARs), particularly PPAR-γ, serves as a critical modulator in AAA, with emerging evidence supporting its therapeutic potential. PPAR-γ is involved in maintaining the structural integrity of

the aorta by regulating elastogenesis and inflammation, which are critical in AAA development. The research highlights the multifaceted role of PPAR-γ in AAA, focusing on its impact on elastic fiber integrity, inflammation modulation, and potential therapeutic applications. PPAR-γ is crucial for the structural integrity of elastic fibers in the aorta. Reduced expression of PPAR-γ leads to fragmentation of elastic fibers and decreased production of essential components like elastin and fibulin-5, which are vital for maintaining aortic wall integrity.[237] PPAR-γ agonists, such as rosiglitazone, have been shown to alter the distribution of inflammatory cytokines during AAA formation, reducing pro-inflammatory cytokines like TNF-α and increasing anti-inflammatory cytokines like IL-10.[238] n human studies, PPAR-γ agonists decreased macrophage infiltration and expression of inflammatory markers such as TNF-α and MMP-9 in the aortic wall, suggesting a potential therapeutic role in reducing AAA progression.[239] Deletion of PPAR-γ in SMCs promotes AAA development by increasing aortic dilatation and elastin degradation. This suggests that PPAR-γ in SMCs is protective against AAA.[240] The broad spectrum of PPAR-γ activation effects, including improved endothelial function and reduced oxidative stress, may offer therapeutic benefits in managing AAA and other cardiovascular conditions.[241]

Nrf2 Pathways

The Nrf2 pathways play significant roles in the pathophysiology of AAA through their involvement in oxidative stress and vascular remodeling. Nrf2, a transcription factor, is crucial for regulating antioxidant responses, while NOX enzymes contribute to ROS production, influencing vascular health. The interplay between these pathways affects the progression of AAA by modulating oxidative stress and inflammation. Nrf2 is a key regulator of antioxidant responses, mitigating oxidative stress by upregulating genes involved in redox homeostasis. In AAA, Nrf2 activation is linked to the protection of VSMCs and the prevention of phenotypic switching, which is crucial for maintaining vascular integrity.[242] Nrf2 expression is influenced by hemodynamic shear stress, which affects endothelial cell function. Disturbed hemodynamics can lead to endothelial dysfunction, a precursor to AAA, by altering Nrf2 activity.[243] Nrf2 can suppress inflammatory responses by regulating the expression of pro-inflammatory cytokines and enzymes, thereby potentially slowing AAA progression.[244] NOX enzymes, particularly NOX1 and NOX4, are major sources of ROS in vascular tissues. These enzymes contribute to oxidative stress, which is a critical factor in AAA development. NOX4 has been shown to activate Nrf2, suggesting a feedback mechanism where increased ROS production by NOX enzymes can trigger antioxidant defenses via Nrf2. This interaction may help balance oxidative stress in AAA.[245–247]

Signaling Network Integration and Stage-Specific Therapeutic Targeting

While the individual roles of NF-κB, MAPK, STAT, Notch, AMPK, PPAR-γ, Nrf2, PI3K/Akt, and TGF-β signaling in AAA pathogenesis have been extensively characterized, their functional crosstalk represents a critical layer of complexity that has received insufficient attention. These pathways form an intricate regulatory network where perturbations in one signaling cascade frequently produce compensatory or opposing effects in others. The inflammatory axes demonstrate particularly robust interconnectivity, with NF-κB and MAPK pathways engaging in bidirectional reinforcement while STAT3 activation amplifies NF-κB-mediated cytokine production, establishing a potent inflammatory positive feedback loop.[248] The PI3K/Akt pathway serves as a crucial signaling hub, integrating inputs from multiple pathways and influencing both inflammatory and survival responses through its connections to Notch signaling and inflammatory regulation.[231] Protective pathways likewise demonstrate significant interdependence. Pharmacologic AMPK activation decreased NF-κB and STAT-3 activation in Ang-II models and reduced inflammatory cell infiltration and MMP activity, identifying AMPK as an anti-inflammatory brake.[235] NRF2 activation increases antioxidant gene expression (eg, GCLM) and suppresses ferroptosis in VSMCs; this attenuates structural degeneration that otherwise would be exacerbated by NF-κB driven inflammation and ROS.[249] PPAR-γ exerts its beneficial effects through cross-inhibition of inflammatory pathways, with PPAR-γ agonists demonstrating potent suppression of both NF-κB and STAT signaling in vascular cells.[239]

The therapeutic implications of this network crosstalk are substantial and stage-dependent. During AAA initiation, therapeutic strategies should prioritize enhancement of protective signaling through AMPK activators and Nrf2 inducers while implementing early NF-κB and MAPK inhibition to prevent inflammatory cascade establishment. In the

progression phase, multi-target approaches become essential to simultaneously inhibit NF-κB/MAPK/STAT inflammatory hubs while selectively modulating PI3K isoforms and implementing PPAR-γ agonists to restore metabolic homeostasis. The pre-rupture phase demands even more sophisticated combination therapies targeting multiple pathways concurrently, including MMP inhibitors coupled with potent antioxidants and selective TGF-β pathway modulators. This stage-specific understanding of signaling network dynamics enables the development of precisely timed therapeutic interventions that account for the evolving dominance of different pathways throughout AAA progression, moving beyond single-pathway targeting toward integrated network modulation strategies.

The recognition that pathway dominance shifts throughout AAA progression with protective pathways predominating in early stages and inflammatory pathways dominating later phases—provides a crucial framework for designing stage-appropriate therapeutic interventions. Future therapeutic development should focus on multi-target approaches that simultaneously modulate several interconnected pathways, with timing of intervention becoming as important as target selection. This network perspective and temporal understanding of signaling dynamics will be essential for developing effective therapeutic strategies that can adapt to the evolving pathological landscape of AAA progression.

Emerging Therapeutic Platforms: Precision Medicine and Translational Challenges

Recent advances in AAA research have yielded significant progress in identifying several promising therapeutic targets within key signaling pathways involved in disease progression. Preclinical studies using various animal models have demonstrated that targeted modulation of these pathways can influence AAA development (Table 2). These findings provide a strong foundation for developing novel pharmacological interventions aimed at halting aneurysm growth and preventing rupture. While, recent research has yielded significant progress in developing precision medicine approaches, primarily focusing on miRNA-based therapies, nanoparticle-mediated delivery systems, and stem cell therapies. While these innovative strategies show promising results in preclinical models, substantial translational barriers must be addressed before clinical implementation.

miRNA-Based Therapeutics: Promise and Practical Hurdles

MicroRNAs (miRNAs) have emerged as a promising focus in AAA research due to their regulatory roles in key pathological processes. These small non-coding RNAs modulate gene expression involved in inflammation, ECM remodeling, and VSMC dysfunction - all critical mechanisms in AAA pathogenesis. Specific miRNAs such as miR-29 and miR-27b-3p are involved in extracellular matrix degradation and inflammatory processes, making them potential targets for therapeutic intervention.[272] miR-24 has been identified as a potential biomarker for AAA, with studies showing its differential expression in small and large AAAs compared to controls.[273] miR-122-5p is significantly downregulated in AAA patients, suggesting its potential as a diagnostic biomarker.[274] miR-193a-5p regulates vascular smooth muscle cell proliferation and migration, with its downregulation linked to AAA progression.[275] Single nucleotide polymorphisms (SNPs) in miRNAs, such as miR-145, are associated with AAA susceptibility, indicating a genetic component in miRNA regulation and AAA risk.[276]

However, therapeutic miRNA applications face considerable challenges related to stability and delivery, as naked oligonucleotides are rapidly degraded by serum nucleases and exhibit poor cellular uptake. Additional concerns include off-target effects from unintended gene regulation due to partial sequence complementarity, immunogenicity triggered by synthetic nucleic acids activating pattern recognition receptors, and the fundamental difficulty of achieving targeted delivery to the aortic wall while minimizing systemic exposure.

Nanotechnology Approaches: Engineering Solutions and Limitations

Recently, the development of nano-therapies has emerged as a promising strategy for treating various vascular diseases, including AAA. Nano micelles, a type of nanoscale drug delivery system along with other nanoparticle-based therapies, offer novel approaches for targeted drug delivery, enhancing therapeutic efficacy while minimizing systemic side effects. These nanotherapeutics hold great potential for addressing the complex molecular and cellular mechanisms underlying

Table 2 Therapeutic Targeting of Signaling Pathways in AAA

Signaling Pathway	Target/Action	Intervention	AAA Model	Effect on AAA	Reference
NFkB	NFκB inhibition	Oligodeoxynucleotides (ODNs)	Elastase induced	• Decreased AAA progression • Preserved elastic fibers • Reduced MMP-2 and −9 • Suppressed VCAM-1 and MCP-1 • Inhibited macrophage infiltration	[250,251]
	NFκB inhibition	Apigenin (API)	Cacl2 induced	• Attenuated AAA progression • Preserved elastic fiber • Inhibited MMP activation • Modulated vascular smooth muscle cell contractile phenotypic transition	[252]
	NFκB inhibition	Andrographolide (Andro)	Elastase induced	• Attenuated AAA growth • Decreased infiltration of monocytes/macrophages and T cells • Reduced the production of proinflammatory cytokines [CCL2, CXCL10, tumor necrosis factor α, and interferon-γ] • Suppressed α4 integrin expression and attenuated the ability of monocytes/macrophages to adhere to activated endothelial cells	[253]
	NFκB inhibition	Protein phosphatase 2A (PP2A) activators	Angiotensin II–induced	• Reduced AAA incidence along with the corresponding pathologies	[254]
	NFκB inhibition	Sol TNF inhibitor, XPro1595	Elastase induced, Angiotensin II–induced	• Improved elastin integrity scores • Attenuated AAA progression	[255]

(*Continued*)

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Table 2 (Continued).

Signaling Pathway	Target/Action	Intervention	AAA Model	Effect on AAA	Reference
MAPKs	JNK inhibition	SP600125	Angiotensin II–induced, CacI2 induced	• Reduction in aneurysmal diameter • Reduced MMP activity	[206,256,257]
	JNK inhibition	Zoledronate	Angiotensin II–induced	• Attenuated the expansion of the suprarenal aorta • Reduced elastin degradation in the media layer of the aorta, and significantly diminished vascular inflammation by reduction in vascular cell adhesion molecule expression and macrophage accumulation, • Decreased MMP-2	[209]
	JNK inhibition	Quercetin	CacI2 induced	• Decreased AAA incidence and inhibited the reactive oxygen species generation • Nitro-tyrosine formation and lipid peroxidation production in the aortic tissue during AAA development. • Lower expression of the p47phox subunit of nicotinamide adenine dinucleotide phosphate oxidase and inducible nitric oxide synthase, as well as coordinated downregulation of manganese-superoxide dismutase activities and glutathione peroxidase (GPx)-1 and GPx-3 expression	[210]
	JNK inhibition	Rosiglitazone (RGZ)	Angiotensin II–induced	• Inhibited the occurrence of fatal rupture • Reduced maximal dilatation of the aorta • Reducing Ang II–induced expression of E-selectin, tumor necrosis factor-alpha, and interleukin-6	[208,258]
	JNK inhibition	Ginsenoside Rb1	Angiotensin II–induced	• Suppressed Ang II–induced diameter enlargement • Extracellular matrix degradation • Matrix metalloproteinase (MMP) production • Inflammatory cell infiltration • Vascular smooth muscle cell (VSMC) dysfunction.	[207]
	ERK inhibition	Alpha-ketoglutarate	Elastase induced	• Prevented aneurysmal dilation, reduced aortic rupture • Attenuating the macrophage infiltration • Elastin degradation and collagen fibers remodeling • Inhibiting oxidative stress and the inflammatory response	[259]
	ERK inhibition	Simvastatin	Angiotensin II–induced	• Reversed Ang-II-stimulated angiogenesis and MMP secretion by human umbilical vein endothelial cells	[216]
	ERK inhibition	Curcumin	Angiotensin II–induced	• Decreased the occurrence of AAA • Decreased macrophage infiltration and cytokines (MCP-1, and TNF-α) • Increased level of superoxide dismutase (SOD)	[260]
	p38 MAPK inhibition	Daidzein	Angiotensin II–induced	Attenuated incidence of AAA, inhibited cytokines (TNF-α, IL-1β), suppressed COX-2, MMP-2, TIMP-1, TGF-β1, and iNOS expression	[261]
JAK/STAT	JAK inhibition	Suppressor of cytokine signalling-1 (SOCS1)	Elastase induced	Incidence of AAA reduced, decreased the maximal aortic dilation, preservation of medial VSMC, decreased the accumulation of CD68+ macrophages, Ly6G+ neutrophils, CD3+ T-cells and CD45R+ B-cells in AAA lesions, reduced gene expression of chemokines (Ccl2 and Ccl5) and cytokines (Ifnγ, Tnfα), Lower gene expression of elastolysis enzymes (Mmp2 and Mmp9)	[262]
	STAT3 inhibition	Ursolic acid (UA)	Angiotensin II–induced	• Alleviated the degradation of elastin fibers and inflammation • Decreased the expression of MMP2, MMP9	[263]
	STAT3 inhibition	S3I-201	Angiotensin II–induced	• Decreased MMP activity and the ratio of M1/M2 macrophages, wall thickness was markedly increased, decreased elastin degradation	[218]

PI3K/Akt/mTOR	PI3K, AKT and mTOR inhibition	Metformin	Angiotensin II–induced	• Preserved the elastin structure of the aorta • Inhibited the loss of collagen • Decreased cell proliferation, apoptosis, migration and autophagy of vascular smooth muscle cells (VSMCs)	[264]
	PI3K inhibition	Wortmannin	Elastase induced	• Decreased elastin destruction score and SMC destruction score • Reduced infiltration of inflammatory cells	[221]
	PI3K and Akt inhibition	IPI-549	Elastase induced	Reduced aortic macrophages, T cells and neo-angiogenesis, CD45+ leukocytes and CD45+ F4/80+ macrophages	[265]
	mTOR inhibition	Rapamycin	Cacl2 induced	• Decreased cytokines (TNF-α, IL-6 and IL-1β) • Decreased CD68 macrophages • Increased α-actin and calponin contractile proteins • Reduced MMP-2 and MMP-9	[266]
TGF-β	TGF-β1 inhibition	Daxx	Angiotensin II–induced	• Reduced the damage to elastin, up-regulated the expression levels of α-SMA and SM22α	[267]
Notch	γ-secretase inhibition	DAPT	Angiotensin II–induced	• Reduced inflammatory response and elastin fragmentation, • Decrease in the proteolytic activity • Preserved vascular smooth muscle cells	[232,268,269]
	γ-secretase inhibition	Dibenzoazepine (DBZ)	Angiotensin II–induced	• Prevented AAA formation • Prevented accumulation of macrophages and CD4+ T cells • Reversal of Th2 immune responses	[230]
	ADAM10 inhibition	Intermedin	Angiotensin II–induced, Cacl2 induced	• Reduced inflammatory factors expression • Decreased infiltration of CD68 positive macrophages	[231]
AMPK	AMPK activation	AICAR (5-aminoimidazole-4-carboxamide-1-β-d-ribofuranoside) and metformin	Angiotensin II–induced	• Reduced the incidence, severity and mortality of aneurysm. • Alleviated macrophage infiltration and neovascularity. • Alleviated the expression of pro-inflammatory factors. • Angiogenic factors and the activity of MMPs.	[235]
PPAR-γ	PPAR-γ activation	Rosiglitazone (RGZ)	Angiotensin II–induced	Reduce the expression of TNF-α in the late stage and increase the expression level of IL-10	[238]
Nrf2	Nrf2 activation	Cryptotanshinone (CTS)	Angiotensin II–induced	Prevented the activation of NLRP3 and GSDMD-initiated pyroptosis in VSMCs, thereby mitigating VSMC inflammation and maintaining the VSMC contractile phenotype.	[270]
	Nrf2 activation	Itaconate	Angiotensin II–induced	Inhibited vascular inflammation	[271]

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AAA, such as inflammation, ECM degradation, and oxidative stress. Nanoparticles engineered to inhibit neutrophilic inflammation, such as LaCD NP, have shown to alleviate AAA progression by targeting neutrophil-mediated inflammatory responses and reducing NETs formation.[163] These nanoparticles release rapamycin in response to reactive oxygen species, effectively reducing AAA expansion by inhibiting calcification, oxidative stress, and apoptosis.[277] These nanoparticles demonstrate protective effects against AAA development by inactivating Notch1 signaling, reducing elastin degradation, and decreasing pro-inflammatory cytokines.[278] A study demonstrated the use of nanomicelles derived from bioactive conjugates, which effectively inhibit inflammatory cell migration and protect VSMCs from oxidative stress and apoptosis. These nanomicelles, particularly TPTN, accumulate in aneurysmal tissues and normalize the pro-inflammatory microenvironment, significantly delaying AAA expansion in rat models.[279] Another approach involves statin-loaded micelles that prevent AAA expansion by reducing macrophage infiltration and matrix metalloproteinase-9 activity, showcasing dose-dependent efficacy in rat models.[280]

Despite these advances, nanotherapies confront significant translational barriers including biocompatibility and toxicity concerns regarding long-term tissue accumulation and clearance pathways. The manufacturing scalability of complex nanoparticles under Good Manufacturing Practice standards presents substantial engineering challenges, while combination products face complex regulatory pathways and potential cost-effectiveness limitations that may restrict accessibility compared to conventional therapies.

Stem Cell Therapy: Emerging Opportunities and Translational Challenges

Stem cell therapy has emerged as a promising regenerative approach for abdominal aortic aneurysm, primarily leveraging the potent paracrine and immunomodulatory properties of various stem cell population. Derived from bone marrow (BM-MSCs), adipose tissue (AD-MSCs), or umbilical cord sources, these cells mediate therapeutic effects through multiple mechanisms: secretion of trophic factors promoting vascular smooth muscle cell viability and function; release of extracellular vesicles containing regulatory microRNAs and proteins; modulation of macrophage polarization from pro-inflammatory M1 toward anti-inflammatory M2 phenotypes; and suppression of T-cell and B-cell activation that sustains chronic aortic wall inflammation.[281] Additionally, MSCs facilitate tissue repair through stimulation of constructive angiogenesis and production of extracellular matrix components that contribute to aneurysmal wall stabilization. There have been a number of experimental and preclinical studies that indicate their promise as a potential AAA treatment. Hashizume et al demonstrated that BM-MSC administration attenuates angiotensin II–induced aortic aneurysm growth in apolipoprotein E-deficient mice, establishing foundational proof-of-concept for cellular therapy in AAA.[282] Moreover, based on the work of Li et al, mesenchymal stem cell (MSC) therapy demonstrates efficacy in abdominal aortic aneurysm by attenuating aortic expansion, preserving elastic fiber integrity, and regulating the local immuno-inflammatory microenvironment.[283] Subsequent investigation by Schneider et al revealed that BM-MSCs stabilize established aortic aneurysms more effectively than vascular smooth muscle cells in a rat xenograft model, associated with enhanced extracellular matrix preservation.[284] Further studies by Tian et al utilizing adipose-derived mesenchymal stem cells (AD-MSCs) in a rat calcium chloride model documented improved elastin content and reduced matrix metalloproteinase activity, suggesting direct modulation of key pathological processes.[285] Consistent with these findings, Zilberman et al demonstrated that stem cell-based intervention effectively attenuated aortic dilatation in a porcine aneurysm model.[286] Delivery optimization studies have yielded significant insights, with Blose et al demonstrating that periadventitial AD-MSC delivery via sponge-based systems effectively halts elastase-induced AAA progression while preserving elastic lamellar structure.[287] Complementary research by Xie et al revealed that intravenous AD-MSC administration exerts potent anti-inflammatory effects, reducing macrophage infiltration, promoting M2 polarization, and expanding regulatory T-cell populations mechanisms associated with attenuated aneurysm expansion.[288] The development of advanced delivery platforms, exemplified by Parvizi et al's perivascular recombinant collagen peptide scaffolds for adventitial AD-MSC transplantation, demonstrates successful prevention of AAA development and progression in combined elastase/calcium chloride models.[289] Several studies have shown that intravenous administration of human umbilical cord-derived mesenchymal stem cells.[290,291]

Despite these promising findings, stem cell translation faces substantial challenges. Significant heterogeneity in cell sourcing and preparation methods complicates standardization, while the inflammatory, proteolytic microenvironment of

AAA compromises engraftment efficiency and cellular survival. Safety concerns regarding potential aberrant differentiation and ectopic tissue formation necessitate careful evaluation, alongside optimization of delivery strategies to maximize therapeutic efficacy. Furthermore, the precise molecular mechanisms underlying MSC-mediated protection remain incompletely elucidated, particularly regarding the relative contributions of paracrine signaling versus direct cellular interactions. Addressing these limitations through rigorous mechanistic investigation, standardized production protocols, and advanced delivery system development will be essential for clinical translation of stem cell-based therapies for abdominal aortic aneurysm.

Integrated Perspectives and Future Directions

The successful translation of these precision medicine approaches will require integrated strategies that combine miRNA, nanoparticle, and cell-based therapies to address the multifactorial nature of AAA pathogenesis. Future success depends on developing robust biomarker systems for patient stratification, creating advanced tissue-specific delivery modalities, establishing comprehensive long-term safety profiles, and advancing regulatory science frameworks for these complex therapeutic platforms. While precision medicine approaches hold tremendous potential for transforming AAA management, acknowledging and systematically addressing these translational challenges through interdisciplinary collaboration is essential for bridging the gap between preclinical promise and clinical reality.

Conclusions

AAA remains a formidable clinical challenge characterized by asymptomatic progression and catastrophic complications. Despite diagnostic advances enabling earlier detection, current management strategies remain predominantly reactive, limited to surveillance for small AAAs and surgical intervention for high-risk cases. This paradigm fails to address the fundamental pathophysiology driving aneurysm progression while imposing significant physical and psychological burdens on patients. Our review elucidates the complex molecular mechanisms underlying AAA pathogenesis, particularly highlighting the central roles of dysregulated extracellular matrix remodeling, chronic inflammation, immune dysregulation, and vascular smooth muscle cell dysfunction. The opposing influences of key signaling pathways - with NF-κB, MAPK, and STAT promoting disease progression versus the protective effects of AMPK, PPAR-γ, and Nrf2 - present multiple therapeutic opportunities. Particularly noteworthy are the context-dependent dual roles of PI3K/Akt and TGF-β signaling, which require precise therapeutic modulation.

Looking ahead, strategic research priorities must focus on translating mechanistic insights into clinical advances. First, comprehensive biomarker development is crucial integrating circulating miRNAs, proteomic signatures, and imaging-based markers to enable early detection, risk stratification, and treatment monitoring. Second, personalized therapeutic approaches should be prioritized, leveraging multi-omics profiling to identify patient-specific signaling vulnerabilities and guide targeted interventions. Third, rational combination strategies demand systematic investigation, particularly targeting complementary pathways (eg, AMPK activation with NF-κB inhibition) while accounting for temporal variations in pathway dominance across AAA stages. Fourth, advanced delivery platforms require optimization, including cell-specific nanoparticle systems and engineered stem cell therapies to achieve spatial precision while minimizing systemic exposure. The clinical translation of emerging interventions particularly miRNA regulators, nanotherapeutics, and cell-based approaches must address key challenges: standardizing manufacturing protocols, establishing long-term safety profiles, and validating efficacy in relevant disease models. Future success will depend on interdisciplinary collaboration integrating computational modeling of signaling networks with functional validation in sophisticated animal models and human tissue systems.

Ultimately, these advances promise to transform AAA management from surgical rescue to precision medicine, enabling mechanism-based therapies that prevent progression and rupture. By focusing on these strategic priorities, the field can move toward personalized therapeutic regimens that significantly improve patient outcomes and quality of life —a fundamental shift from the current watchful-waiting paradigm to active, targeted intervention.

Abbreviations

AAA, Abdominal aortic aneurysm; VSMCs, vascular smooth muscle cells; ECM, Extracellular matrix; PAMP, Pathogen-associated molecular pattern; GPCRs, G protein-coupled receptors; TNF- α, Tumor necrosis factor α; DAMP, damage-associated molecular pattern; TLRs, Toll-like receptors; Ang-II, Angiotensin II; GPCRs, G protein-coupled receptors; IL-6, Interleukin-6; mIL-6R, Membrane interleukin-6 receptor; sIL-6R, Soluble interleukin-6 receptor; GP130, Glycoprotein 130; JAK3, Janus kinase 3; NF-κB, nuclear factor κB; IκB, Inhibitor of NF-κB; P, Phosphorylation; MEKK, Mitogen-activated protein kinase kinase; JNKs- c, Jun N-terminal kinases; MAPK, Mitogen-activated protein kinase; ERK, Extracellular signal-regulated kinases; STAT3, Signal transducer and activator of transcription3; MMP, Matrix metalloproteinase; IL-1β, Interleukin-1β; MCP-1, monocyte chemoattractant protein-1; ECM, Extracellular matrix; CRP, C reactive protein.

Declaration of Generative AI in Scientific Writing

The authors declare that no generative AI was used in scientific writing upon preparation of the article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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References

1. Benson RA, Meecham L, Fisher O, Loftus IM. Ultrasound screening for abdominal aortic aneurysm: current practice, challenges and controversies. *Brit J Radiol*. 2018;91(1090):20170306. doi:10.1259/bjr.20170306
2. Al-Saadi N, Bown JM. Abdominal aortic aneurysm: epidemiology, screening and work-up for repair. *Surgery*. 2021;39(5):283–288.
3. Matsumoto T. Anatomy and physiology for the abdominal aortic aneurysm repair. *Ann Vascular Dis*. 2019;12(3):329–333. doi:10.3400/avd.ra.19-00077
4. Takayama T, Yamanouchi D. Aneurysmal disease: the abdominal aorta. *Surg Clin North Am*. 2013;93(4):877–891. doi:10.1016/j.suc.2013.05.005
5. Danzer D, Becquemin JP. *Abdominal Aortic Aneurysm. Vascular Surgery: Cases, Questions and Commentaries*. 2018;19–28.
6. Reimerink JJ, van der Laan MJ, Koelemay MJ, Balm R, Legemate DA. Systematic review and meta-analysis of population-based mortality from ruptured abdominal aortic aneurysm. *Br J Surg*. 2013;100(11):1405–1413. doi:10.1002/bjs.9235
7. Siika A, Axelsson A, Fattahi N, et al. Decreasing aortic diameter and decreasing prevalence of infrarenal aortic aneurysms in a population-based screening programme. *Br J Surg*. 2025;112(8). doi:10.1093/bjs/znaf156
8. Pham MHC, Sigvardsen PE, Fuchs A, et al. Aortic aneurysms in a general population cohort: prevalence and risk factors in men and women. *Eur Heart J Cardiovasc Imaging*. 2024;25(9):1235–1243. doi:10.1093/ehjci/jeae103
9. Song P, He Y, Adeloye D, et al. The global and regional prevalence of abdominal aortic aneurysms: a systematic review and modeling analysis. *Ann Surg*. 2023;277(6):912–919. doi:10.1097/SLA.0000000000005716
10. Zhang P, Liu C, Li J, et al. Risk factors for abdominal aortic aneurysm in general populations: a systematic review and meta-analysis. *PLoS One*. 2025;20(9):e0329500. doi:10.1371/journal.pone.0329500
11. Ngetich E, Ward J, Cassimjee I, Lee R, Handa A, Aneurysm. Prevalence and epidemiological pattern of abdominal aortic aneurysms in Africa: a systematic review. *J West Afr Coll Surg*. 2020;10(1):3–14. doi:10.4103/jwas.jwas_15_21
12. Tang J, Cheng XE, He YS, et al. Global, regional, and national perspectives on aortic aneurysm burden from 1992 to 2021: temporal patterns and age-period-cohort analyses. *Eur J Prev Cardiol*. 2025. doi:10.1093/eurjpc/zwaf266
13. Goyal A, Saeed H, Shahnoor S, et al. Mortality trends, sex, and racial disparities in older adults due to abdominal aortic aneurysm: a nationwide cross-sectional analysis. *Int J Surg*. 2024;110(12):8241–8245. doi:10.1097/JS9.0000000000002114

14. Zhuo Y, Zhao D, Luo M, Zhou Z, Shu C. Global, regional, and national burden of aortic aneurysm disease and its attributable risk factor, 1990-2021: a systematic analysis for the global burden of disease study 2021. *Intern Emerg Med*. 2025;20(7):2089–2101. doi:10.1007/s11739-025-04061-8
15. Prendes CF, Gouveia EMR, Caldeira D, et al. Editor's choice - systematic review and meta-analysis of contemporary abdominal aortic aneurysm growth rates. *Eur J Vasc Endovasc Surg*. 2024;67(1):132–145. doi:10.1016/j.ejvs.2023.09.039
16. Siika A, Bogdanovic M, Liljeqvist ML, Gasser TC, Hultgren R, Roy J. Three-dimensional growth and biomechanical risk progression of abdominal aortic aneurysms under serial computed tomography assessment. *Sci Rep*. 2023;13(1):9283. doi:10.1038/s41598-023-36204-2
17. Olson SL, Wijesinha MA, Panthofer AM, et al. Evaluating growth patterns of abdominal aortic aneurysm diameter with serial computed tomography surveillance. *JAMA Surg*. 2021;156(4):363–370. doi:10.1001/jamasurg.2020.7190
18. DiLosa K, Brittenham G, Pozolo C, et al. Evaluating growth patterns of abdominal aortic aneurysms among women. *J Vasc Surg*. 2024;80(1):107–113. doi:10.1016/j.jvs.2024.02.042
19. Zhu C, Leach JR, Wang Y, Gasper W, Saloner D, Hope MD. Intraluminal thrombus predicts rapid growth of abdominal aortic aneurysms. *Radiology*. 2020;294(3):707–713. doi:10.1148/radiol.2020191723
20. Vanmaele A, Karamanidou M, Branidis P, et al. Abdominal aortic aneurysm growth profiles over time: prognostic implications and biological insights. *J Vasc Surg*. 2025;2025:1.
21. Kim GY, Corriere MA. Balancing watching vs waiting during imaging surveillance of small abdominal aortic aneurysms. *JAMA Surg*. 2021;156(4):370–371. doi:10.1001/jamasurg.2020.7258
22. Siika A, Talvitie M, Lindquist Liljeqvist M, et al. Peak wall rupture index is associated with risk of rupture of abdominal aortic aneurysms, independent of size and sex. *Br J Surg*. 2024;111(5):znae125.
23. Dansey KD, de Guerre L, Swerdlow NJ, et al. A comparison of administrative data and quality improvement registries for abdominal aortic aneurysm repair. *J Vasc Surg*. 2021;73(3):874–888. doi:10.1016/j.jvs.2020.06.105
24. Velickovic VM, Carradice D, Boyle JR, et al. Umbrella review and meta-analysis of reconstructed individual patient data of mortality following conventional endovascular and open surgical repair of infrarenal abdominal aortic aneurysm. *Expert Rev Cardiovasc Ther*. 2023;21(5):347–356. doi:10.1080/14779072.2023.2207009
25. Domagala D, Data K, Szyller H, et al. Cellular, molecular and clinical aspects of aortic aneurysm-vascular physiology and pathophysiology. *Cells*. 2024;13(3):274. doi:10.3390/cells13030274
26. Kuivaniemi H, Ryer EJ, Elmore JR, Tromp G. Understanding the pathogenesis of abdominal aortic aneurysms. *Expert Rev Cardiovasc Ther*. 2015;13(9):975–987. doi:10.1586/14779072.2015.1074861
27. de Bruin JL, Verhagen HJM. The 2024 European Society for Vascular Surgery (ESVS) clinical practice guidelines on the management of abdominal aorto-iliac artery aneurysms: cutting edge or just another update? *Eur J Vasc Endovasc Surg*. 2024;67(2):190–191. doi:10.1016/j.ejvs.2023.12.026
28. Koncar IB, Jovanovic A, Kostic O, et al. Screening men and women above the age of 50 years for abdominal aortic aneurysm: a pilot study in an upper middle income country. *Eur J Vasc Endovasc Surg*. 2024;68(1):10–15. doi:10.1016/j.ejvs.2024.03.003
29. Wang H, Li Y, Fan K, et al. global epidemiology of early-onset aortic aneurysm: temporal trends, risk factors, and future burden projections. *J Epidemiol Glob Health*. 2025;15(1):25.
30. Sciria CT, Osorio B, Wang J, et al. Sex-based disparities in outcomes with abdominal aortic aneurysms. *Am J Cardiol*. 2021;155:135–148. doi:10.1016/j.amjcard.2021.06.023
31. Zheng L, Baroom G, Naqvi REZ, et al. Tobacco smoking and the risk of aortic aneurysm in the UK biobank. *Sci Rep*. 2025;15(1):32191. doi:10.1038/s41598-025-18013-x
32. Welsh P, Pouncey AL, Sattar N, Powell JT. Sex-specific risk of smoking for abdominal aortic aneurysm and exploration of potential mechanism: meta-analysis and prospective cohort study. *Arterioscler Thromb Vasc Biol*. 2025;45(7):1316–1325. doi:10.1161/ATVBAHA.125.322601
33. Yang Y, Yamagishi K, Kihara T, et al. Smoking cessation and mortality from aortic dissection and aneurysm: findings from the Japan Collaborative Cohort (JACC) study. *J Atheroscler Thromb*. 2023;30(4):348–363. doi:10.5551/jat.63258
34. Kobeissi E, Hibino M, Pan H, Aune D. Blood pressure, hypertension and the risk of abdominal aortic aneurysms: a systematic review and meta-analysis of cohort studies. *Eur J Epidemiol*. 2019;34(6):547–555. doi:10.1007/s10654-019-00510-9
35. Toghill BJ, Saratzis A, Bown MJ. Abdominal aortic aneurysm—an independent disease to atherosclerosis? *Cardiovasc Pathol*. 2017;27:71–75. doi:10.1016/j.carpath.2017.01.008
36. Elkalioubie A, Haulon S, Duhamel A, et al. Meta-analysis of abdominal aortic aneurysm in patients with coronary artery disease. *Am J Cardiol*. 2015;116(9):1451–1456. doi:10.1016/j.amjcard.2015.07.074
37. Stather PW, Sidloff DA, Dattani N, et al. Meta-analysis and meta-regression analysis of biomarkers for abdominal aortic aneurysm. *Br J Surg*. 2014;101(11):1358–1372. doi:10.1002/bjs.9593
38. MacSweeney STR, O'Meara M, Alexander C, O'Malley MK, Powell JT, Greenhalgh RM. High prevalence of unsuspected abdominal aortic aneurysm in patients with confirmed symptomatic peripheral or cerebral arterial disease. *Surgery*. 1993;113(6):582–584.
39. Apoloni RC, Zerati AE, Wolosker N, et al. Analysis of the correlation between central obesity and abdominal aortic diseases. *Ann Vasc Surg*. 2019;54:176–184. doi:10.1016/j.avsg.2018.06.016
40. Sakalihasan N, Defraigne JO, Kerstenne MA, et al. Family members of patients with abdominal aortic aneurysms are at increased risk for aneurysms: analysis of 618 probands and their families from the liège AAA family study. *Ann Vasc Surg*. 2014;28(4):787–797. doi:10.1016/j.avsg.2013.11.005
41. Mangum KD, Farber MA. Genetic and epigenetic regulation of abdominal aortic aneurysms. *Clin Genet*. 2020;97(6):815–826. doi:10.1111/cge.13705
42. Climent E, Benaiges D, Chillarón JJ, Flores-Le Roux JA, Pedro-Botet J. Diabetes mellitus as a protective factor of abdominal aortic aneurysm: possible mechanisms. *Clínica e Investigación en Arteriosclerosis*. 2018;30(4):181–187. doi:10.1016/j.arteri.2018.01.002
43. Xiong J, Wu Z, Chen C, Wei Y, Guo W. Association between diabetes and prevalence and growth rate of abdominal aortic aneurysms: a meta-analysis. *Int J Cardiol*. 2016;221:484–495. doi:10.1016/j.ijcard.2016.07.016
44. Takagi H, Umemoto T. Negative association of diabetes with rupture of abdominal aortic aneurysm. *Diabetes Vasc Dis Res*. 2016;13(5):341–347. doi:10.1177/1479164116651389

45. Takagi H, Umemoto T. Diabetes and abdominal aortic aneurysm growth. *Angiology*. 2016;67(6):513–525. doi:10.1177/0003319715602414
46. Karkos CD, Mukhopadhyay U, Papakostas I, Ghosh J, Thomson GJL, Hughes R. Abdominal aortic aneurysm: the role of clinical examination and opportunistic detection. *Eur J Vasc Endovascular Surg*. 2000;19(3):299–303. doi:10.1053/ejvs.1999.1002
47. Fink HA, Lederle FA, Roth CS, Bowles CA, Nelson DB, Haas MA. The accuracy of physical examination to detect abdominal aortic aneurysm. *Arch Internal Med*. 2002;160(6):833–836. doi:10.1001/archinte.160.6.833
48. Assar AN, Zarins CK. Ruptured abdominal aortic aneurysm: a surgical emergency with many clinical presentations. *Postgraduate Med J*. 2009;85(1003):268–273. doi:10.1136/pgmj.2008.074666
49. Rudarakanchana N, Powell JT. Advances in imaging and surveillance of AAA: when, how, how often? *Prog Cardiovasc Dis*. 2013;56(1):7–12. doi:10.1016/j.pcad.2013.05.006
50. Hallett RL, Ullery BW, Fleischmann D. Abdominal aortic aneurysms: pre- and post-procedural imaging. *Abdom Radiol*. 2018;43(5):1044–1066. doi:10.1007/s00261-018-1520-5
51. Kumar Y, Hooda K, Li S, Goyal P, Gupta N, Adeb M. Abdominal aortic aneurysm: pictorial review of common appearances and complications. *Ann Translat Med*. 2017;5(12):1–7. doi:10.21037/atm.2017.04.32
52. Husmann L, Huellner MW, Ledergerber B, et al. Diagnostic accuracy of PET/CT and contrast enhanced CT in patients with suspected infected aortic aneurysms. *Eur J Vasc Endovascular Surg*. 2020;59(6):972–981. doi:10.1016/j.ejvs.2020.01.032
53. Brangsch J, Reimann C, Collettini F, Buchert R, Botnar RM, Makowski MR. Molecular imaging of abdominal aortic aneurysms. *Trends Mol Med*. 2017;23(2):150–164. doi:10.1016/j.molmed.2016.12.002
54. Wilmink ABM, Vardulaki KA, Hubbard CSF, et al. Are antihypertensive drugs associated with abdominal aortic aneurysms? *J Vascular Surg*. 2002;36(4):751–757. doi:10.1016/S0741-5214(02)00129-5
55. Salata K, Syed M, Hussain MA, et al. Renin-angiotensin system blockade does not attenuate abdominal aortic aneurysm growth, rupture rate, or perioperative mortality after elective repair. *J Vascular Surg*. 2018;67(2):629–36.e2. doi:10.1016/j.jvs.2017.09.007
56. Baxter BT, Matsumura J, Curci JA, et al. Effect of doxycycline on aneurysm growth among patients with small infrarenal abdominal aortic aneurysms: a randomized clinical trial. *JAMA*. 2020;323(20):2029–2038. doi:10.1001/jama.2020.5230
57. Høgh A, Vammen S, Ostergaard L, Joensen JB, Henneberg EW, Lindholt JS. Intermittent roxithromycin for preventing progression of small abdominal aortic aneurysms: long-term results of a small clinical trial. *Vascular Endovascu Surg*. 2009;43(5):452–456. doi:10.1177/1538574409335037
58. Karlsson L, Gnarpe J, Bergqvist D, Lindbäck J, Pärsson H. The effect of azithromycin and Chlamydophilia pneumonia infection on expansion of small abdominal aortic aneurysms - A prospective randomized double-blind trial. *J Vascular Surg*. 2009;50(1):23–29. doi:10.1016/j.jvs.2008.12.048
59. Ferguson CD, Clancy P, Bourke B, et al. Association of statin prescription with small abdominal aortic aneurysm progression. *Am Heart J*. 2010;159(2):307–313. doi:10.1016/j.ahj.2009.11.016
60. Yoshimura K, Morikage N, Nishino-Fujimoto S, Furutani A, Shirasawa B, Hamano K. Current status and perspectives on pharmacologic therapy for abdominal aortic aneurysm. *Current Drug Targets*. 2017;19(11):1265–1275. doi:10.2174/1389450119666171227223331
61. Powell JT, Wanhainen A. Analysis of the differences between the ESVS 2019 and NICE 2020 guidelines for abdominal aortic aneurysm. *Eur J Vasc Endovascular Surg*. 2020;60(1):7–15. doi:10.1016/j.ejvs.2020.04.038
62. Leemans EL, Willems TP, Van Der Laan MJ, Slump CH, Zeebregts CJ. Biomechanical indices for rupture risk estimation in abdominal aortic aneurysms. *J Endovascular Ther*. 2017;24(2):254–261. doi:10.1177/1526602816680088
63. Arinze N, Farber A, Levin SR, et al. The effect of the duration of preoperative smoking cessation timing on outcomes after elective open abdominal aortic aneurysm repair and lower extremity bypass. *J Vascular Surg*. 2019;70(6):1851–1861. doi:10.1016/j.jvs.2019.02.028
64. Mei F, Hu K, Zhao B, et al. Retroperitoneal versus transperitoneal approach for elective open abdominal aortic aneurysm repair. *Cochrane Database Syst Rev*. 2021;2021(6):1.
65. Salata K, Hussain MA, De Mestral C, et al. Comparison of outcomes in elective endovascular aortic repair vs open surgical repair of abdominal aortic aneurysms. *JAMA Network Open*. 2019;2(7):1–14. doi:10.1001/jamanetworkopen.2019.6578
66. Nicolajsen CW, Eldrup N. Abdominal closure and the risk of incisional hernia in aneurysm surgery – a systematic review and meta-analysis. *Eur J Vasc Endovascular Surg*. 2020;59(2):227–236. doi:10.1016/j.ejvs.2019.07.041
67. Conrad MF, Crawford RS, Pedraza JD, et al. Long-term durability of open abdominal aortic aneurysm repair. *J Vascular Surg*. 2007;46(4):669–675. doi:10.1016/j.jvs.2007.05.046
68. Khoynezhad A, Rao R, Lee WA. Endovascular repair of abdominal aortic aneurysm. Catheter-based cardiovascular interventions: a knowledge-based approach. *Catheter Based Cardiovasc Intervent*. 2013;2013(1):971–983.
69. Antoniou GA, Antoniou SA. Editor's choice – Percutaneous access does not confer superior clinical outcomes over cutdown access for endovascular aneurysm repair: meta-analysis and trial sequential analysis of randomised controlled trials. *Eur J Vasc Endovascular Surg*. 2021;61(3):383–394. doi:10.1016/j.ejvs.2020.11.008
70. Moll FL, Powell JT, Fraedrich G, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. *Eur J Vasc Endovascular Surg*. 2011;41(SUPPL. 1):S1–58.
71. Pejcic S, Ali Hassan SM, Rival DE, Bisleri G. Characterizing the mechanical properties of the aortic wall. *Vessel Plus*. 2019;3:1–12.
72. van 't Veer M, Buth J, Merkx M, et al. Biomechanical properties of abdominal aortic aneurysms assessed by simultaneously measured pressure and volume changes in humans. *J Vascular Surg*. 2008;48(6):1401–1407. doi:10.1016/j.jvs.2008.06.060
73. Wolinsky H, Glagov S. A lamellar unit of aortic medial structure and function in mammals. *Circul Res*. 1967;20(1):99–111. doi:10.1161/01.RES.20.1.99
74. Xu J, Shi GP. Vascular wall extracellular matrix proteins and vascular diseases. *Biochim Biophys Acta Mol Basis Dis*. 2014;1842(11):2106–2119. doi:10.1016/j.bbadis.2014.07.008
75. Thompson RW, Geraghty PJ, Lee JK. Abdominal aortic aneurysms: basic mechanisms and clinical implications. *Curr Prob Surg*. 2002;39(2):110–230. doi:10.1067/msg.2002.121421
76. Rosenbloom J, Abrams WR, Mecham R. Extracellular matrix 4: the elastic fiber. *FASEB J*. 1993;7(13):1208–1218. doi:10.1096/fasebj.7.13.8405806

77. Wagenseil JE, Mecham RP. Elastin in large artery stiffness and hypertension. *J Cardiovascu Transl Res*. 2012;5(3):264–273. doi:10.1007/s12265-012-9349-8
78. Prockop DJ, Kivirikko KI. Collagens: molecular biology, diseases, and potentials for therapy. *Annu Rev Biochem*. 1995;64:403–434. doi:10.1146/annurev.bi.64.070195.002155
79. Berillis P. The role of collagen in the aorta's structure. *Open Circul Vascur J*. 2013;6(1):1–8. doi:10.2174/1877382601306010001
80. Tsamis A, Krawiec JT, Vorp DA. Elastin and collagen fibre microstructure of the human aorta in ageing and disease: a review. *J Royal Soc Interface*. 2013;10(83). doi:10.1098/rsif.2012.1004
81. Tanios F, Gee MW, Pelisek J, et al. Interaction of biomechanics with extracellular matrix components in abdominal aortic aneurysm wall. *Eur J Vasc Endovascular Surg*. 2015;50(2):167–174. doi:10.1016/j.ejvs.2015.03.021
82. Carmo M, Colombo L, Bruno A, et al. Alteration of elastin, collagen and their cross-links in abdominal aortic aneurysms. *Eur J Vasc Endovasc Surg*. 2002;23(6):543–549. doi:10.1053/ejvs.2002.1620
83. Maguire EM, Pearce SWA, Xiao R, Oo AY, Xiao Q. Matrix metalloproteinase in abdominal aortic aneurysm and aortic dissection. *Pharmaceuticals*. 2019;12(3):1–18. doi:10.3390/ph12030118
84. Wang X, Khalil RA. Matrix metalloproteinases, vascular remodeling, and vascular disease. *Adv Pharmacol*. 2018;81(617):241–330. doi:10.1016/bs.apha.2017.08.002
85. Snoek-van Beurden PAM, Von den Hoff JW. Zymographic techniques for the analysis of matrix metalloproteinases and their inhibitors. *BioTechniques*. 2005;38(1):73–83. doi:10.2144/05381RV01
86. Rabkin SW. The role matrix metalloproteinases in the production of aortic aneurysm. *Prog Mol Biol Transl Sci*. 2017;147:239–265.
87. Arpino V, Brock M, Gill SE. The role of TIMPs in regulation of extracellular matrix proteolysis. *Matrix Biol*. 2015;44-46:247–254. doi:10.1016/j.matbio.2015.03.005
88. Augusciak-Duma A, Stepien KL, Lesiak M, et al. Expression gradient of metalloproteinases and their inhibitors from proximal to distal segments of abdominal aortic aneurysm. *J Appl Genet*. 2021;62(3):499–506. doi:10.1007/s13353-021-00642-3
89. Annabi B, Shédid D, Ghosn P, et al. Differential regulation of matrix metalloproteinase activities in abdominal aortic aneurysms. *J Vasc Surg*. 2002;35(3):539–546. doi:10.1067/mva.2002.121124
90. Wilson WRW, Anderton M, Schwalbe EC, et al. Matrix metalloproteinase-8 and −9 are increased at the site of abdominal aortic aneurysm rupture. *Circulation*. 2006;113(3):438–445. doi:10.1161/CIRCULATIONAHA.105.551572
91. Takagi H, Manabe H, Kawai N, Goto SN, Umemoto T. Circulating matrix metalloproteinase-9 concentrations and abdominal aortic aneurysm presence: a meta-analysis. *Interact Cardiovasc Thoracic Surg*. 2009;9(3):437–440. doi:10.1510/icvts.2009.208835
92. Watanabe T, Sato A, Sawai T, et al. The elevated level of circulating matrix metalloproteinase-9 in patients with abdominal aortic aneurysms decreased to levels equal to those of healthy controls after an aortic repair. *Ann Vasc Surg*. 2006;20(3):317–321. doi:10.1007/s10016-006-9038-7
93. Pyo R, Lee JK, Shipley JM, et al. Targeted gene disruption of matrix metalloproteinase-9 (gelatinase B) suppresses development of experimental abdominal aortic aneurysms. *J Clin Investig*. 2000;105(11):1641–1649. doi:10.1172/JCI8931
94. Thompson RW, Holmes DR, Mertens RA, et al. Production and localization of 92-kilodalton gelatinase in abdominal aortic aneurysms. *Ame Soc Clin Invest*. 1995;96(July):318–326. doi:10.1172/JCI118037
95. Matthew Longo G, Xiong W, Greiner TC, Zhao Y, Fiotti N, Timothy Baxter B. Matrix metalloproteinases 2 and 9 work in concert to produce aortic aneurysms. *J Clin Investig*. 2002;110(5):625–632. doi:10.1172/JCI0215334
96. Atkinson G, Bianco R, Di Gregoli K, Johnson JL. The contribution of matrix metalloproteinases and their inhibitors to the development, progression, and rupture of abdominal aortic aneurysms. *Front Cardiovasc Med*. 2023;10:1248561. doi:10.3389/fcvm.2023.1248561
97. Wang S, Liu D, Zhang X, Tian X. Regulation of matrix metalloproteinase-2 and matrix metalloproteinase-9 in abdominal aortic aneurysm. *Cardiol Disc*. 2023;3(3):212–220. doi:10.1097/CD9.0000000000000097
98. Klaus V, Tanios-Schmies F, Reeps C, et al. Association of matrix metalloproteinase levels with collagen degradation in the context of abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg*. 2017;53(4):549–558. doi:10.1016/j.ejvs.2016.12.030
99. Dale MA, Suh MK, Zhao S, et al. Background differences in baseline and stimulated MMP levels influence abdominal aortic aneurysm susceptibility. *Atherosclerosis*. 2015;243(2):621–629. doi:10.1016/j.atherosclerosis.2015.10.006
100. Mosorin M, Juvonen J, Biancari F, et al. Use of doxycycline to decrease the growth rate of abdominal aortic aneurysms: a randomized, double-blind, placebo-controlled pilot study. *J Vasc Surg*. 2001;34(4):606–610. doi:10.1067/mva.2001.117891
101. Puchenkova OA, Soldatov VO, Belykh AE, et al. Cytokines in abdominal aortic aneurysm: master regulators with clinical application. *Biomarker Insights*. 2022;17:11772719221095676.
102. Davis FM, Rateri DL, Daugherty A. Mechanisms of aortic aneurysm formation: translating preclinical studies into clinical therapies. *Heart*. 2014;100(19):1498–1505. doi:10.1136/heartjnl-2014-305648
103. Wu X, Cakmak S, Wortmann M, et al. Sex-and disease-specific inflammasome signatures in circulating blood leukocytes of patients with abdominal aortic aneurysm. *Mol Med*. 2016;22(7):508–518. doi:10.2119/molmed.2016.00035
104. Pearce WH, Sweis I, Yao JST, McCarthy WJ, Koch AE. Interleukin-1β and tumor necrosis factor-α release in normal and diseased human infrarenal aortas. *J Vasc Surg*. 1992;16(5):784–789. doi:10.1016/0741-5214(92)90234-Y
105. Johnston WF, Salmon M, Su G, et al. Genetic and pharmacologic disruption of interleukin-1β signaling inhibits experimental aortic aneurysm formation. *Arteriosclerosis Thrombosis Vasc Biol*. 2013;33(2):294–304. doi:10.1161/ATVBAHA.112.300432
106. Isoda K, Akita K, Kitamura K, et al. Inhibition of interleukin-1 suppresses angiotensin II-induced aortic inflammation and aneurysm formation. *Int J Cardiol*. 2018;270(2017):2217. doi:10.1016/j.ijcard.2018.05.072
107. Da Ros F, Carnevale R, Cifelli G, et al. Targeting interleukin-1β protects from aortic aneurysms induced by disrupted transforming growth factor β signaling. *Immunity*. 2017;47(5):959–73.e9. doi:10.1016/j.immuni.2017.10.016
108. Jiang YF, Guo LL, Zhang LW, et al. Local upregulation of interleukin-1 beta in aortic dissecting aneurysm: correlation with matrix metalloproteinase-2, 9 expression and biomechanical decrease. *Interactive Cardiovasc Thoracic Surg*. 2019;28(3):344–352. doi:10.1093/icvts/ivy256
109. Treska V, Kocova J, Boudova L, et al. Inflammation in the wall of abdominal aortic aneurysm and its role in the symptomatology of aneurysm. *Cytokines Cell Mol Ther*. 2002;7(3):91–97. doi:10.1080/13684730310001652

110. Dawson J, Cockerill GW, Choke E, Belli AM, Loftus I, Thompson MM. Aortic aneurysms secrete interleukin-6 into the circulation. *J Vasc Surg*. 2007;45(2):350–356. doi:10.1016/j.jvs.2006.09.049
111. Flondell-Sité D, Lindblad B, Kölbel T, Gottsäter A. Cytokines and systemic biomarkers are related to the size of abdominal aortic aneurysms. *Cytokine*. 2009;46(2):211–215. doi:10.1016/j.cyto.2009.01.007
112. Ohno T, Aoki H, Ohno S, et al. Cytokine profile of human abdominal aortic aneurysm: involvement of JAK/STAT pathway. *Ann Vasc Dis*. 2018;11(1):84–90. doi:10.3400/avd.oa.17-00086
113. Harrison SC, Smith AJP, Jones GT, et al. Interleukin-6 receptor pathways in abdominal aortic aneurysm. *Eur Heart J*. 2013;34(48):3707–3716. doi:10.1093/eurheartj/ehs354
114. Paige E, Clément M, Lareyre F, et al. Interleukin-6 receptor signaling and abdominal aortic aneurysm growth rates. *Circ Genomic Precis Med*. 2019;12(2):84–93.
115. Smallwood L, Allcock R, van Bockxmeer F, et al. Polymorphisms of the interleukin-6 gene promoter and abdominal aortic aneurysm. *Eur J Vasc Endovasc Surg*. 2008;35(1):31–36. doi:10.1016/j.ejvs.2007.08.021
116. Kokje VBC, Gäbel G, Koole D, et al. IL-6: a Janus-like factor in abdominal aortic aneurysm disease. *Atherosclerosis*. 2016;251:139–146. doi:10.1016/j.atherosclerosis.2016.06.021
117. Nishihara M, Aoki H, Ohno S, et al. The role of IL-6 in pathogenesis of abdominal aortic aneurysm in mice. *PLoS One*. 2017;12(10):1–19. doi:10.1371/journal.pone.0185923
118. Montgomery WG, Spinosa MD, Cullen JM, et al. Tamsulosin attenuates abdominal aortic aneurysm growth. *Surgery*. 2018;164(5):1087–1092. doi:10.1016/j.surg.2018.06.036
119. Witkowska AM, Borawska MH, Gacko M. Relationship among TNF-α, sICAM-1, and selenium in presurgical patients with abdominal aortic aneurysms. *Biol Trace Elem Res*. 2006;114(1–3):31–40. doi:10.1385/BTER:114:1:31
120. Golledge ALV, Walker P, Norman PE, Golledge J. A systematic review of studies examining inflammation associated cytokines in human abdominal aortic aneurysm samples. *Dis Markers*. 2009;26(4):181–188. doi:10.1155/2009/352319
121. Nakamura H, Satoh H, Satoh M, et al. Expression and localization of tumour necrosis factor-α and its converting enzyme in human abdominal aortic aneurysm. *Clin Sci*. 2004;106(3):301–306. doi:10.1042/CS20030189
122. Kaneko H, Anzai T, Horiuchi K, et al. Tumor necrosis factor-α converting enzyme is a key mediator of abdominal aortic aneurysm development. *Atherosclerosis*. 2011;218(2):470–478. doi:10.1016/j.atherosclerosis.2011.06.008
123. Xiong W, MacTaggart J, Knispel R, Worth J, Persidsky Y, Baxter BT. Blocking TNF-α attenuates aneurysm formation in a murine model. *J Immunol*. 2009;183(4):2741–2746. doi:10.4049/jimmunol.0803164
124. Hingorani A, Ascher E, Scheinman M, et al. The effect of tumor necrosis factor binding protein and interleukin-1 receptor antagonist on the development of abdominal aortic aneurysms in a rat model. *J Vasc Surg*. 1998;28(3):522–526. doi:10.1016/S0741-5214(98)70139-9
125. Yuwen L, Ciqiu Y, Yi S, Ruilei L, Weiming L, Jie L. A pilot study of protein microarray for simultaneous analysis of 274 cytokines between abdominal aortic aneurysm and normal aorta. *Angiology*. 2019;70(9):830–837. doi:10.1177/0003319719844678
126. Koch AE, Kunkel SL, Pearce WH, et al. Enhanced production of the chemotactic cytokines interleukin-8 and monocyte chemoattractant protein-1 in human abdominal aortic aneurysms. *Am J Pathol*. 1993;142(5):1423–1431.
127. Daugherty A, Rateri DL, Charo IF, Iii APO, Howatt DA, Cassis LA. Angiotensin II infusion promotes ascending aortic aneurysms: attenuation by CCR2 deficiency in apoE−/− mice. *Clin Sci*. 2010;689:681–689.
128. Xuan X, Li Y, Cao G, et al. Inhibition of abdominal aortic aneurysm progression through the CXCL12/CXCR4 axis via MiR206-3p sponge. *J Cell Mol Med*. 2025;29(1):e70328. doi:10.1111/jcmm.70328
129. Michineau S, Franck G, Wagner-Ballon O, Dai J, Allaire E, Gervais M. Chemokine (C-X-C motif) receptor 4 blockade by AMD3100 inhibits experimental abdominal aortic aneurysm expansion through anti-inflammatory effects. *Arterioscler Thromb Vasc Biol*. 2014;34(8):1747–1755. doi:10.1161/ATVBAHA.114.303913
130. Zhang X. Inhibition of CXCR2 alleviates the development of abdominal aortic aneurysm in ApoE−/− mice. *Acta Cirúrgica Brasileira*. 2021;36(10):1–8.
131. Blomkalns AL, Gavrila D, Thomas M, et al. CD14 directs adventitial macrophage precursor recruitment: role in early abdominal aortic aneurysm formation. *J Ame Heart Assoc*. 2013;2(2):1–11. doi:10.1161/JAHA.112.000065
132. Boytard L, Spear R, Chinetti-Gbaguidi G, et al. Role of proinflammatory CD68+ mannose receptor-macrophages in peroxiredoxin-1 expression and in abdominal aortic aneurysms in humans. *Arteriosclerosis Thrombosis Vasc Biol*. 2013;33(2):431–438. doi:10.1161/ATVBAHA.112.300663
133. Xiong W, Knispel R, MacTaggart J, Greiner TC, Weiss SJ, Baxter BT. Membrane-type 1 matrix metalloproteinase regulates macrophage-dependent elastolytic activity and aneurysm formation in vivo. *J Biol Chem*. 2009;284(3):1765–1771. doi:10.1074/jbc.M806239200
134. Forester ND, Cruickshank SM, Scott DJA, Carding SR. Functional characterization of T cells in abdominal aortic aneurysms. *Immunology*. 2005;115(2):262–270. doi:10.1111/j.1365-2567.2005.02157.x
135. Zhao G, Lu H, Chang Z, et al. Single-cell RNA sequencing reveals the cellular heterogeneity of aneurysmal infrarenal abdominal aorta. *Cardiovasc Res*. 2021;117(5):1402–1416. doi:10.1093/cvr/cvaa214
136. Saraff K, Babamusta F, Cassis LA, Daugherty A. Aortic dissection precedes formation of aneurysms and atherosclerosis in angiotensin II-infused, apolipoprotein E-deficient mice. *Arteriosclerosis Thrombosis Vasc Biol*. 2003;23(9):1621–1626. doi:10.1161/01.ATV.0000085631.76095.64
137. Yuan Z, Lu Y, Wei J, Wu J, Yang J, Cai Z. Abdominal aortic aneurysm: roles of inflammatory cells. *Front Immunol*. 2021;11(February):1–12. doi:10.3389/fimmu.2020.609161
138. Emeto TI, Moxon JV, Au M, Golledge J. Oxidative stress and abdominal aortic aneurysm: potential treatment targets. *Clin Sci*. 2016;130(5):301–315. doi:10.1042/CS20150547
139. Ijaz T, Tilton RG, Brasier AR. Cytokine amplification and macrophage effector functions in aortic inflammation and abdominal aortic aneurysm formation. *J Thoracic Dis*. 2016;8(8):E746–E54. doi:10.21037/jtd.2016.06.37
140. Dutertre CA, Clement M, Morvan M, et al. Deciphering the stromal and hematopoietic cell network of the adventitia from non-aneurysmal and aneurysmal human aorta. *PLoS One*. 2014;9(2). doi:10.1371/journal.pone.0089983

141. Harada T, Yoshimura K, Yamashita O, et al. Focal adhesion kinase promotes the progression of aortic aneurysm by modulating macrophage behavior. *Arteriosclerosis Thrombosis Vasc Biol*. 2017;37(1):156–165. doi:10.1161/ATVBAHA.116.308542
142. Blassova T, Tonar Z, Tomasek P, et al. Inflammatory cell infiltrates, hypoxia, vascularization, pentraxin 3 and osteoprotegerin in abdominal aortic aneurysms – a quantitative histological study. *PLoS One*. 2019;14(11):1–14. doi:10.1371/journal.pone.0224818
143. Ginhoux F, Guilliams M. Tissue-resident macrophage ontogeny and homeostasis. *Immunity*. 2016;44(3):439–449. doi:10.1016/j.immuni.2016.02.024
144. Raffort J, Lareyre F, Clément M, Hassen-Khodja R, Chinetti G, Mallat Z. Monocytes and macrophages in abdominal aortic aneurysm. *Nat Rev Cardiol*. 2017;14(8):457–471. doi:10.1038/nrcardio.2017.52
145. Li H, Bai S, Ao Q, et al. Modulation of immune-inflammatory responses in abdominal aortic aneurysm: emerging molecular targets. *J Immunol Res*. 2018;2018:1–15. doi:10.1155/2018/7213760
146. Wang N, Liang H, Zen K. Molecular mechanisms that influence the macrophage M1-M2 polarization balance. *Front Immunol*. 2014;5:1–10. doi:10.3389/fimmu.2014.00614
147. Duque GA, Descoteaux A, Sacre S. Macrophage cytokines: involvement in immunity and infectious diseases. *Front Immunol*. 2014;5:1–12. doi:10.3389/fimmu.2014.00001
148. Gao JP, Guo W. Mechanisms of abdominal aortic aneurysm progression: a review. *Vasc Med*. 2022;27(1):88–96. doi:10.1177/1358863X211021170
149. Mantovani A, Sica A, Locati M. Macrophage polarization comes of age. *Immunity*. 2005;23(4):344–346. doi:10.1016/j.immuni.2005.10.001
150. Murray PJ, Wynn TA. Protective and pathogenic functions of macrophage subsets. *Nat Rev Immunol*. 2011;11(11):723–737. doi:10.1038/nri3073
151. Knappich C, Spin JM, Eckstein HH, Tsao PS, Maegdefessel L. Involvement of myeloid cells and noncoding RNA in abdominal aortic aneurysm disease. *Antioxid. Redox Signaling*. 2020;33(9):602–620. doi:10.1089/ars.2020.8035
152. Dale MA, Ruhlman MK, Baxter BT. Inflammatory cell phenotypes in AAAs: their role and potential as targets for therapy. *Arteriosclerosis Thrombosis Vasc Biol*. 2015;35(8):1746–1755. doi:10.1161/ATVBAHA.115.305269
153. Zhang Z, Xu J, Liu Y, et al. Mouse macrophage specific knockout of SIRT1 influences macrophage polarization and promotes angiotensin II-induced abdominal aortic aneurysm formation. *J Genet Genome*. 2018;45(1):25–32. doi:10.1016/j.jgg.2018.01.002
154. Yuan Z, Shu L, Fu J, et al. Single-cell RNA sequencing deconstructs the distribution of immune cells within abdominal aortic aneurysms in mice. *Arterioscler Thromb Vasc Biol*. 2024;44(9):1986–2003. doi:10.1161/ATVBAHA.124.321129
155. Zhao G, Cho CS, Liu H, et al. Single-cell spatial transcriptomics unravels the cellular landscape of abdominal aortic aneurysm. *JCI Insight*. 2025;10(16). doi:10.1172/jci.insight.190534
156. He L, Fu Y, Deng J, et al. Deficiency of FAM3D (Family With Sequence Similarity 3, Member D), A novel chemokine, attenuates neutrophil recruitment and ameliorates abdominal aortic aneurysm development. *Arterioscler Thromb Vasc Biol*. 2018;38(7):1616–1631. doi:10.1161/ATVBAHA.118.311289
157. Eliason JL, Hannawa KK, Ailawadi G, et al. Neutrophil depletion inhibits experimental abdominal aortic aneurysm formation. *Circulation*. 2005;112(2):232–240. doi:10.1161/CIRCULATIONAHA.104.517391
158. Ibrahim N, Bleichert S, Klopf J, et al. Reducing abdominal aortic aneurysm progression by blocking neutrophil extracellular traps depends on thrombus formation. *JACC Basic Transl Sci*. 2024;9(3):342–360. doi:10.1016/j.jacbts.2023.11.003
159. Wei M, Wang X, Song Y, et al. Inhibition of peptidyl arginine deiminase 4-dependent neutrophil extracellular trap formation reduces angiotensin II-induced abdominal aortic aneurysm rupture in mice. *Front Cardiovasc Med*. 2021;8:676612. doi:10.3389/fcvm.2021.676612
160. Ramos-Mozo P, Madrigal-Matute J, Martinez-Pinna R, et al. Proteomic analysis of polymorphonuclear neutrophils identifies catalase as a novel biomarker of abdominal aortic aneurysm: potential implication of oxidative stress in abdominal aortic aneurysm progression. *Arterioscler Thromb Vasc Biol*. 2011;31(12):3011–3019. doi:10.1161/ATVBAHA.111.237537
161. Houard X, Ollivier V, Louedec L, Michel JB, Back M. Differential inflammatory activity across human abdominal aortic aneurysms reveals neutrophil-derived leukotriene B4 as a major chemotactic factor released from the intraluminal thrombus. *FASEB J*. 2009;23(5):1376–1383. doi:10.1096/fj.08-116202
162. Delbosc S, Alsac JM, Journe C, et al. Porphyromonas gingivalis participates in pathogenesis of human abdominal aortic aneurysm by neutrophil activation. Proof of concept in rats. *PLoS One*. 2011;6(4):e18679. doi:10.1371/journal.pone.0018679
163. Hu K, Zhong L, Lin W, et al. Pathogenesis-guided rational engineering of nanotherapies for the targeted treatment of abdominal aortic aneurysm by inhibiting neutrophilic inflammation. *ACS Nano*. 2024;18(8):6650–6672. doi:10.1021/acsnano.4c00120
164. Wang H, Zhang R, Jia X, et al. Highly sensitive magnetic particle imaging of abdominal aortic aneurysm NETosis with anti-Ly6G iron oxide nanoparticles. *Cell Death Discov*. 2024;10(1):395. doi:10.1038/s41420-024-02156-3
165. Kurihara T, Shimizu-Hirota R, Shimoda M, et al. Neutrophil-derived matrix metalloproteinase 9 triggers acute aortic dissection. *Circulation*. 2012;126(25):3070–3080. doi:10.1161/CIRCULATIONAHA.112.097097
166. Koch AE, Haines GK, Rizzo RJ, et al. Human abdominal aortic aneurysms. Immunophenotypic analysis suggesting an immune-mediated response. *Am J Pathol*. 1990;137(5):1199–1213.
167. Sagan A, Mikolajczyk TP, Mrowiecki W, et al. T cells are dominant population in human abdominal aortic aneurysms and their infiltration in the perivascular tissue correlates with disease severity. *Front Immunol*. 2019;10:1979. doi:10.3389/fimmu.2019.01979
168. Gong W, Tian Y, Li L. T cells in abdominal aortic aneurysm: immunomodulation and clinical application. *Front Immunol*. 2023;14:1240132. doi:10.3389/fimmu.2023.1240132
169. Xiong W, Zhao Y, Prall A, Greiner TC, Baxter BT. Key roles of CD4+ T cells and IFN-gamma in the development of abdominal aortic aneurysms in a murine model. *J Immunol*. 2004;172(4):2607–2612. doi:10.4049/jimmunol.172.4.2607
170. Teo FH, de Oliveira RTD, Villarejos L, et al. Characterization of CD4(+) T cell subsets in patients with abdominal aortic aneurysms. *Mediators Inflamm*. 2018;2018:6967310. doi:10.1155/2018/6967310
171. Lin Z, Zhao M, Zhang X, et al. CD8 + T-cell deficiency protects mice from abdominal aortic aneurysm formation in response to calcium chloride 2. *J Hypertens*. 2024;42(11):1966–1975. doi:10.1097/HJH.0000000000003823
172. Seo IH, Lee SJ, Noh TW, et al. Increase of Vdelta2(+) T cells that robustly produce IL-17A in advanced abdominal aortic aneurysm tissues. *Immune Netw*. 2021;21(2):e17. doi:10.4110/in.2021.21.e17

173. Zhang L, Wang Y. B lymphocytes in abdominal aortic aneurysms. *Atherosclerosis*. 2015;242(1):311–317. doi:10.1016/j.atherosclerosis.2015.07.036
174. Loste A, Clement M, Delbosc S, et al. Involvement of an IgE/Mast cell/B cell amplification loop in abdominal aortic aneurysm progression. *PLoS One*. 2023;18(12):e0295408. doi:10.1371/journal.pone.0295408
175. Shao F, Miao Y, Zhang Y, et al. B cell-derived anti-beta 2 glycoprotein I antibody contributes to hyperhomocysteinaemia-aggravated abdominal aortic aneurysm. *Cardiovasc Res*. 2020;116(11):1897–1909. doi:10.1093/cvr/cvz288
176. Spinosa MD, Montgomery WG, Lempicki M, et al. B cell-activating factor antagonism attenuates the growth of experimental abdominal aortic aneurysm. *Am J Pathol*. 2021;191(12):2231–2244. doi:10.1016/j.ajpath.2021.08.012
177. Qian G, Adeyanju O, Olajuyin A, Guo X. Abdominal aortic aneurysm formation with a focus on vascular smooth muscle cells. *Life*. 2022;12(2). doi:10.3390/life12020191
178. Rombouts KB, van Merrienboer TAR, Ket JCF, Bogunovic N, van der Velden J, Yeung KK. The role of vascular smooth muscle cells in the development of aortic aneurysms and dissections. *Eur J Clin Invest*. 2022;52(4):e13697. doi:10.1111/eci.13697
179. Hu Y, Cai Z, He B. Smooth Muscle heterogeneity and plasticity in health and aortic aneurysmal disease. *Int J Mol Sci*. 2023;24(14):11701.
180. Callow B, He X, Juriga N, et al. Inhibition of vascular smooth muscle cell PERK/ATF4 ER stress signaling protects against abdominal aortic aneurysms. *JCI Insight*. 2025;10(2). doi:10.1172/jci.insight.183959
181. Xiao X, Li C, Huang X, et al. Single-cell RNA sequencing reveals that NRF2 regulates vascular smooth muscle cell phenotypic switching in abdominal aortic aneurysm. *FASEB J*. 2024;38(13):e23707. doi:10.1096/fj.202400001RR
182. Song T, Zhao S, Luo S, et al. SLC44A2 regulates vascular smooth muscle cell phenotypic switching and aortic aneurysm. *J Clin Invest*. 2024;134(16). doi:10.1172/JCI173690
183. Xing M, Chen W, Ji Y, Song W. SLC44A2-mediated phenotypic switch of vascular smooth muscle cells contributes to aortic aneurysm. *J Clin Invest*. 2024;134(16). doi:10.1172/JCI183527
184. Wang Y, Liu X, Xu Q, et al. CCN2 deficiency in smooth muscle cells triggers cell reprogramming and aggravates aneurysm development. *JCI Insight*. 2023;8(1):e162987.
185. Cao G, Xuan X, Li Y, et al. Single-cell RNA sequencing reveals the vascular smooth muscle cell phenotypic landscape in aortic aneurysm. *Cell Commun Signal*. 2023;21(1):113. doi:10.1186/s12964-023-01120-5
186. Gao R, Guo W, Fan T, et al. Phosphodiesterase 4D contributes to angiotensin II-induced abdominal aortic aneurysm through smooth muscle cell apoptosis. *Exp Mol Med*. 2022;54(8):1201–1213. doi:10.1038/s12276-022-00815-y
187. Tavris BS, Peters AS, Bockler D, Dihlmann S. Mitochondrial dysfunction and increased DNA damage in vascular smooth muscle cells of abdominal aortic aneurysm (AAA-SMC). *Oxid Med Cell Longev*. 2023;2023:6237960. doi:10.1155/2023/6237960
188. Chen CH, Ho HH, Jiang WC, et al. Cysteine-rich protein 2 deficiency attenuates angiotensin II-induced abdominal aortic aneurysm formation in mice. *J Biomed Sci*. 2022;29(1):25. doi:10.1186/s12929-022-00808-z
189. Cai Z, Huang J, Yang J, et al. LncRNA SENCR suppresses abdominal aortic aneurysm formation by inhibiting smooth muscle cells apoptosis and extracellular matrix degradation. *Bosn J Basic Med Sci*. 2021;21(3):323–330. doi:10.17305/bjbms.2020.4994
190. Siasos G, Mourouzis K, Oikonomou E, et al. The role of endothelial dysfunction in aortic aneurysms. *Curr Pharm Des*. 2015;21(28):4016–4034. doi:10.2174/1381612821666150826094156
191. Spartalis E, Spartalis M, Athanasiou A, et al. Endothelium in aortic aneurysm disease: new insights. *Curr Med Chem*. 2020;27(7):1081–1088. doi:10.2174/0929867326666190923151959
192. Aubdool AA, Moyes AJ, Perez-Ternero C, et al. Endothelium- and fibroblast-derived C-type natriuretic peptide prevents the development and progression of aortic aneurysm. *Arterioscler Thromb Vasc Biol*. 2025;45(7):1044–1063. doi:10.1161/ATVBAHA.124.322350
193. DeRoo E, Stranz A, Yang H, Hsieh M, Se C, Zhou T. Endothelial dysfunction in the pathogenesis of abdominal aortic aneurysm. *Biomolecules*. 2022;12(4):509. doi:10.3390/biom12040509
194. Macek jilkova Z, Deplano V, Verdier C, Toungara M, Geindreau C, Duperray A. Wall shear stress and endothelial cells dysfunction in the context of abdominal aortic aneurysms. *Comput Meth Biomech Biomed Eng*. 2013;16 Suppl 1:27–29. doi:10.1080/10255842.2013.815959
195. Cui R, Tieu B, Recinos A, Tilton RG, Brasier AR. RhoA mediates angiotensin II-induced phospho-Ser536 nuclear factor κB/RelA subunit exchange on the interleukin-6 promoter in VSMCs. *Circul Res*. 2006;99(7):723–730. doi:10.1161/01.RES.0000244015.10655.3f
196. Ramella M, Boccafoschi F, Bellofatto K, et al. Endothelial MMP-9 drives the inflammatory response in abdominal aortic aneurysm (AAA). *Am J Transl Res*. 2017;9(12):5485–5495.
197. Shiraya S, Miwa K, Aoki M, et al. Hypertension accelerated experimental abdominal aortic aneurysm through upregulation of nuclear factor κB and ets. *Hypertension*. 2006;48(4):628–636. doi:10.1161/01.HYP.0000240266.26185.57
198. Zhong L, He X, Si X, et al. SM22 (Smooth Muscle 22) prevents aortic aneurysm formation by inhibiting smooth muscle cell phenotypic switching through suppressing reactive oxygen species/NF-κB (Nuclear Factor-κB). *Arteriosclerosis Thrombosis Vasc Biol*. 2019;39(1):e10–e25. doi:10.1161/ATVBAHA.118.311917
199. Nischan J, Gatalica Z, Mindee C, Lenk GM, Gerard T, Kuivaniemi H. Binding sites for ETS family of transcription factors dominate the promoter regions of differentially expressed genes in abdominal aortic aneurysms. *Circulation*. 2009;2(6):565–572. doi:10.1161/CIRCGENETICS.108.843854
200. Miyake T, Kurashiki T, Miyake T, Morishita R. Molecular pharmacological approaches for treating abdominal aortic aneurysm. *Ann Vascular Dis*. 2019;12(2):137–146. doi:10.3400/avd.ra.18-00076
201. Miyake T, Aoki M, Osako MK, Shimamura M, Nakagami H, Morishita R. Systemic administration of ribbon-type decoy oligodeoxynucleotide against nuclear factor B and ets prevents abdominal aortic aneurysm in rat model. *Mol Ther*. 2011;19(1):181–187. doi:10.1038/mt.2010.208
202. Ijaz T, Sun H, Pinchuk IV, Milewicz DM, Tilton RG, Brasier AR. Deletion of NF-κB/RelA in angiotensin II-sensitive mesenchymal cells blocks aortic vascular inflammation and abdominal aortic aneurysm formation. *Arteriosclerosis Thrombosis Vasc Biol*. 2017;37(10):1881–1890. doi:10.1161/ATVBAHA.117.309863
203. Qi J, Yang P, Yi B, et al. Heat shock protein 90 inhibition by 17-DMAG attenuates abdominal aortic aneurysm formation in mice. *Am J Physiol Heart Circ Physiol*. 2015;308(8):H841–H52. doi:10.1152/ajpheart.00470.2014
204. Wang Q, Ding Y, Song P, et al. Tryptophan-derived 3-hydroxyanthranilic acid contributes to angiotensin II-induced abdominal aortic aneurysm formation in mice in vivo. *Circulation*. 2017;136(23):2271–2283. doi:10.1161/CIRCULATIONAHA.117.030972

205. Dimusto PD, Lu G, Ghosh A, et al. Increased JNK in males compared with females in a rodent model of abdominal aortic aneurysm. *J Surg Res*. 2012;176(2):687–695. doi:10.1016/j.jss.2011.11.1024
206. Guo ZZ, Cao QA, Li ZZ, et al. SP600125 attenuates nicotine-related aortic aneurysm formation by inhibiting matrix metalloproteinase production and CC chemokine-mediated macrophage migration. *Mediators Inflamm*. 2016;2016. doi:10.1155/2016/9142425
207. Zhang XJ, He C, Tian K, Li P, Su H, Wan JB. Ginsenoside Rb1 attenuates angiotensin II-induced abdominal aortic aneurysm through inactivation of the JNK and p38 signaling pathways. *Vasc Pharmacol*. 2015;73:86–95. doi:10.1016/j.vph.2015.04.003
208. Pirianov G, Torsney E, Howe F, Cockerill GW. Rosiglitazone negatively regulates c-Jun N-terminal kinase and toll-like receptor 4 proinflammatory signalling during initiation of experimental aortic aneurysms. *Atherosclerosis*. 2012;225(1):69–75. doi:10.1016/j.atherosclerosis.2012.07.034
209. Tsai SH, Huang PH, Peng YJ, et al. Zoledronate attenuates angiotensin II-induced abdominal aortic aneurysm through inactivation of Rho/ROCK-dependent JNK and NF-κB pathway. *Cardiovasc Res*. 2013;100(3):501–510. doi:10.1093/cvr/cvt230
210. Wang L, Cheng X, Li H, et al. Quercetin reduces oxidative stress and inhibits activation of c-Jun N-terminal kinase/activator protein-1 signaling in an experimental mouse model of abdominal aortic aneurysm. *Mol Med Rep*. 2014;9(2):435–442. doi:10.3892/mmr.2013.1846
211. Lemaître V, Dabo AJ, D'Armiento J. Cigarette smoke components induce matrix metalloproteinase-1 in aortic endothelial cells through inhibition of mTOR signaling. *Toxicol Sci*. 2011;123(2):542–549. doi:10.1093/toxsci/kfr181
212. Habashi JP, Doyle JJ, Holm TM, et al. Angiotensin II Type 2 receptor signaling attenuates Aortic aneurysm in mice through ERK antagonism. *Science*. 2011;332(6027):361–365. doi:10.1126/science.1192152
213. Holm TM, Habashi JP, Doyle JJ, et al. Noncanonical TGFβ signaling contributes to aortic aneurysm progression in marfan syndrome mice. *Science*. 2011;332(6027):358–361. doi:10.1126/science.1192149
214. Ghosh A, Dimusto PD, Ehrlichman LK, et al. The role of extracellular signal-related kinase during abdominal aortic aneurysm formation. *J Am College Surg*. 2012;215(5):668–80.e1. doi:10.1016/j.jamcollsurg.2012.06.414
215. Groeneveld ME, van Burink MV, Begieneman MPV, et al. Activation of extracellular signal-related kinase in abdominal aortic aneurysm. *Eur J Clin Invest*. 2016;46(5):440–447. doi:10.1111/eci.12618
216. Zhang Y, Naggar JC, Welzig CM, et al. Simvastatin inhibits angiotensin II-induced abdominal aortic aneurysm formation in apolipoprotein e-knockout mice: possible role of ERK. *Arteriosclerosis Thrombosis Vasc Biol*. 2009;29(11):1764–1771. doi:10.1161/ATVBAHA.109.192609
217. Liao M, Xu J, Clair AJ, Ehrman B, Graham LM, Eagleton MJ. Local and systemic alterations in signal transducers and activators of transcription (STAT) associated with human abdominal aortic aneurysms. *J Surg Res*. 2012;176(1):321–328. doi:10.1016/j.jss.2011.05.041
218. Qin Z, Bagley J, Sukhova G, et al. Angiotensin II-induced TLR4 mediated abdominal aortic aneurysm in apolipoprotein E knockout mice is dependent on STAT3. *J Mol Cell Cardiol*. 2015;87:160–170. doi:10.1016/j.yjmcc.2015.08.014
219. Lindeman JHN, Abdul-Hussien H, Schaapherder AFM, et al. Enhanced expression and activation of pro-inflammatory transcription factors distinguish aneurysmal from atherosclerotic aorta: IL-6- and IL-8-dominated inflammatory responses prevail in the human aneurysm. *Clin Sci*. 2008;114(11–12):687–697. doi:10.1042/CS20070352
220. Xiong Y, Liu S, Liu Y, et al. PI3Kgamma promotes neutrophil extracellular trap formation by noncanonical pyroptosis in abdominal aortic aneurysm. *JCI Insight*. 2024;9(16):e183237.
221. Yu J, Liu R, Huang J, Wang L, Wang W. Inhibition of Phosphatidylinositol 3-kinase suppresses formation and progression of experimental abdominal aortic aneurysms. *Sci Rep*. 2017;7(1):15208. doi:10.1038/s41598-017-15207-w
222. Chen X, Lu H, Rateri DL, Cassis LA, Daugherty A. Conundrum of angiotensin II and TGF-beta interactions in aortic aneurysms. *Curr Opin Pharmacol*. 2013;13(2):180–185. doi:10.1016/j.coph.2013.01.002
223. Lin F, Yang X. TGF-beta signaling in aortic aneurysm: another round of controversy. *J Genet Genomics*. 2010;37(9):583–591. doi:10.1016/S1673-8527(09)60078-3
224. Doyle AJ, Redmond EM, Gillespie DL, et al. Differential expression of Hedgehog/Notch and transforming growth factor-beta in human abdominal aortic aneurysms. *J Vasc Surg*. 2015;62(2):464–470. doi:10.1016/j.jvs.2014.02.053
225. Spin JM, Hsu M, Azuma J, et al. Transcriptional profiling and network analysis of the murine angiotensin II-induced abdominal aortic aneurysm. *Physiol Genomics*. 2011;43(17):993–1003. doi:10.1152/physiolgenomics.00044.2011
226. Dai J, Losy F, Guinault AM, et al. Overexpression of transforming growth factor-beta1 stabilizes already-formed aortic aneurysms: a first approach to induction of functional healing by endovascular gene therapy. *Circulation*. 2005;112(7):1008–1015. doi:10.1161/CIRCULATIONAHA.104.523357
227. Wang Y, Ait-Oufella H, Herbin O, et al. TGF-beta activity protects against inflammatory aortic aneurysm progression and complications in angiotensin II-infused mice. *J Clin Invest*. 2010;120(2):422–432. doi:10.1172/JCI38136
228. Chen X, Rateri DL, Howatt DA, et al. TGF-beta neutralization enhances AngII-induced aortic rupture and aneurysm in both thoracic and abdominal regions. *PLoS One*. 2016;11(4):e0153811. doi:10.1371/journal.pone.0153811
229. Angelov SN, Hu JH, Wei H, Airhart N, Shi M, Dichek DA. TGF-beta (Transforming Growth Factor-beta) signaling protects the thoracic and abdominal aorta from angiotensin II-induced pathology by distinct mechanisms. *Arterioscler Thromb Vasc Biol*. 2017;37(11):2102–2113. doi:10.1161/ATVBAHA.117.309401
230. Zheng YH, Li FD, Tian C, Ren HL, Du J, Li HH. Notch gamma-secretase inhibitor dibenzazepine attenuates angiotensin II-induced abdominal aortic aneurysm in ApoE knockout mice by multiple mechanisms. *PLoS One*. 2013;8(12):e83310. doi:10.1371/journal.pone.0083310
231. Ni XQ, Zhang YR, Jia LX, et al. Inhibition of Notch1-mediated inflammation by intermedin protects against abdominal aortic aneurysm via PI3K/Akt signaling pathway. *Aging*. 2021;13(4):5164–5184. doi:10.18632/aging.202436
232. Sharma N, Dev R, Ruiz-Rosado JD, et al. Pharmacological inhibition of Notch signaling regresses pre-established abdominal aortic aneurysm. *Sci Rep*. 2019;9(1):13458. doi:10.1038/s41598-019-49682-0
233. Jespersen K, Li C, Batra R, et al. Impact of Notch3 activation on aortic aneurysm development in Marfan syndrome. *J Immunol Res*. 2022;2022:7538649. doi:10.1155/2022/7538649
234. Sachdeva J, Mahajan A, Cheng J, et al. Smooth muscle cell-specific Notch1 haploinsufficiency restricts the progression of abdominal aortic aneurysm by modulating CTGF expression. *PLoS One*. 2017;12(5):e0178538. doi:10.1371/journal.pone.0178538
235. Yang L, Shen L, Gao P, et al. Effect of AMPK signal pathway on pathogenesis of abdominal aortic aneurysms. *Oncotarget*. 2017;8(54):92827–92840. doi:10.18632/oncotarget.21608

236. Fisslthaler B, Fleming I. Activation and signaling by the AMP-activated protein kinase in endothelial cells. *Circ Res*. 2009;105(2):114–127. doi:10.1161/CIRCRESAHA.109.201590
237. Tai HC, Tsai PJ, Chen JY, et al. Peroxisome proliferator-activated receptor gamma level contributes to structural integrity and component production of elastic fibers in the aorta. *Hypertension*. 2016;67(6):1298–1308. doi:10.1161/HYPERTENSIONAHA.116.07367
238. Wang WD, Sun R, Chen YX. PPARgamma agonist rosiglitazone alters the temporal and spatial distribution of inflammation during abdominal aortic aneurysm formation. *Mol Med Rep*. 2018;18(3):3421–3428. doi:10.3892/mmr.2018.9311
239. Motoki T, Kurobe H, Hirata Y, et al. PPAR-gamma agonist attenuates inflammation in aortic aneurysm patients. *Gen Thorac Cardiovasc Surg*. 2015;63(10):565–571. doi:10.1007/s11748-015-0576-1
240. Hamblin M, Chang L, Zhang H, Yang K, Zhang J, Chen YE. Vascular smooth muscle cell peroxisome proliferator-activated receptor-gamma deletion promotes abdominal aortic aneurysms. *J Vasc Surg*. 2010;52(4):984–993. doi:10.1016/j.jvs.2010.05.089
241. Ivanova EA, Myasoedova VA, Melnichenko AA, Orekhov AN. Peroxisome proliferator-activated receptor (PPAR) gamma agonists as therapeutic agents for cardiovascular disorders: focus on atherosclerosis. *Curr Pharm Des*. 2017;23(7):1119–1124. doi:10.2174/1381612823666161118145850
242. Li S, Xiao X, Chang Y, et al. Berberine inhibits abdominal aortic aneurysm formation and vascular smooth muscle cell phenotypic switching by regulating the Nrf2 pathway. *J Cell Mol Med*. 2025;29(7):e70509. doi:10.1111/jcmm.70509
243. Hasan M, Al-Thani H, El-Menyar A, Zeidan A, Al-Thani A, Yalcin HC. Disturbed hemodynamics and oxidative stress interaction in endothelial dysfunction and AAA progression: focus on Nrf2 pathway. *Int J Cardiol*. 2023;389:131238. doi:10.1016/j.ijcard.2023.131238
244. Kasprzak MP, Gryszczynska B, Olasinska-Wisniewska A, et al. Blb-NRF2-PON1 cross-talk in abdominal aortic aneurysm progression. *Antioxidants*. 2023;12(8). doi:10.3390/antiox12081568
245. Li ZY, Liu Y, Wang YY, et al. NOX4 stimulates ANF secretion via activation of the Sirt1/Nrf2/ATF3/4 axis in hypoxic beating rat atria. *Mol Med Rep*. 2022;25(3). doi:10.3892/mmr.2022.12600
246. Wu W, Zhang J, Su X, et al. Nrf2 regulates the expression of NOX1 in TNF-alpha-induced A549 cells. *Allergol Immunopathol*. 2023;51(1):54–62. doi:10.15586/aei.v51i1.732
247. Mir S, Ormsbee Golden BD, Griess BJ, et al. Upregulation of Nox4 induces a pro-survival Nrf2 response in cancer-associated fibroblasts that promotes tumorigenesis and metastasis, in part via Birc5 induction. *Breast Cancer Res*. 2022;24(1):48. doi:10.1186/s13058-022-01548-6
248. Wu QY, Cheng Z, Zhou YZ, et al. A novel STAT3 inhibitor attenuates angiotensin II-induced abdominal aortic aneurysm progression in mice through modulating vascular inflammation and autophagy. *Cell Death Dis*. 2020;11(2):131. doi:10.1038/s41419-020-2326-2
249. Liu H, Zhang J, Li L, et al. miR-9-5p alleviates the development of abdominal aortic aneurysm by regulating the differentiation of CD4(+)IL-10(+)T cells via targeting the crosstalk between Nrf2 and NF-kappaB signaling pathways. *Turk J Biol*. 2025;49(4):380–391. doi:10.55730/1300-0152.2754
250. Miyake T, Aoki M, Masaki H, et al. Regression of abdominal aortic aneurysms by simultaneous inhibition of nuclear factor kappaB and ets in a rabbit model. *Circ Res*. 2007;101(11):1175–1184. doi:10.1161/CIRCRESAHA.107.148668
251. Miyake T, Aoki M, Nakashima H, et al. Prevention of abdominal aortic aneurysms by simultaneous inhibition of NFkappaB and ets using chimeric decoy oligonucleotides in a rabbit model. *Gene Ther*. 2006;13(8):695–704. doi:10.1038/sj.gt.3302704
252. Li D, Ma J, Wang L, Xin S. Apigenin prevent abdominal aortic aneurysms formation by inhibiting the NF-kappaB signaling pathway. *J Cardiovasc Pharmacol*. 2020;75(3):229–239. doi:10.1097/FJC.0000000000000785
253. Ren J, Liu Z, Wang Q, et al. Andrographolide ameliorates abdominal aortic aneurysm progression by inhibiting inflammatory cell infiltration through downregulation of cytokine and integrin expression. *J Pharmacol Exp Ther*. 2016;356(1):137–147. doi:10.1124/jpet.115.227934
254. Zhou X, Zhang C, Xie F, et al. Allosteric activation of PP2A inhibits experimental abdominal aortic aneurysm. *Clin Sci*. 2021;135(17):2085–2097. doi:10.1042/CS20210315
255. Griepke S, Grupe E, Lindholt JS, et al. Selective inhibition of soluble tumor necrosis factor signaling reduces abdominal aortic aneurysm progression. *Front Cardiovasc Med*. 2022;9:942342. doi:10.3389/fcvm.2022.942342
256. Yoshimura K, Aoki H, Ikeda Y, Furutani A, Hamano K, Matsuzaki M. Regression of abdominal aortic aneurysm by inhibition of c-Jun N-terminal kinase in mice. *Ann N Y Acad Sci*. 2006;1085:74–81. doi:10.1196/annals.1383.031
257. Verma S, Lindsay TF. Regression of aortic aneurysms through pharmacologic therapy? *N Engl J Med*. 2006;354(19):2067–2068. doi:10.1056/NEJMcibr060899
258. Jones A, Deb R, Torsney E, et al. Rosiglitazone reduces the development and rupture of experimental aortic aneurysms. *Circulation*. 2009;119(24):3125–3132. doi:10.1161/CIRCULATIONAHA.109.852467
259. Liu J, Liu M, Feng J, et al. Alpha-ketoglutarate ameliorates abdominal aortic aneurysm via inhibiting PXDN/HOCL/ERK signaling pathways. *J Transl Med*. 2022;20(1):461. doi:10.1186/s12967-022-03659-2
260. Hao Q, Chen X, Wang X, Dong B, Yang C. Curcumin attenuates angiotensin II-induced abdominal aortic aneurysm by inhibition of inflammatory response and ERK signaling pathways. *Evid Based Complement Alternat Med*. 2014;2014:270930. doi:10.1155/2014/270930
261. Liu YF, Bai YQ, Qi M. Daidzein attenuates abdominal aortic aneurysm through NF-kappaB, p38MAPK and TGF-beta1 pathways. *Mol Med Rep*. 2016;14(1):955–962.
262. Bernal S, Lopez-Sanz L, Jimenez-Castilla L, et al. Protective effect of suppressor of cytokine signalling 1-based therapy in experimental abdominal aortic aneurysm. *Br J Pharmacol*. 2021;178(3):564–581.
263. Zhai M, Guo J, Ma H, et al. Ursolic acid prevents angiotensin II-induced abdominal aortic aneurysm in apolipoprotein E-knockout mice. *Atherosclerosis*. 2018;271:128–135.
264. Wang Z, Guo J, Han X, et al. Metformin represses the pathophysiology of AAA by suppressing the activation of PI3K/AKT/mTOR/autophagy pathway in ApoE(-/-) mice. *Cell Biosci*. 2019;9:68. doi:10.1186/s13578-019-0332-9
265. Liu R, Huang J, Ge Y, et al. Inhibition of phosphatidylinositol 3-kinase gamma by IPI-549 attenuates abdominal aortic aneurysm formation in mice. *Eur J Vasc Endovasc Surg*. 2020;60(2):254–263.
266. Cao J, Wu Q, Geng L, et al. Rapamycin inhibits CaCl2-induced thoracic aortic aneurysm formation in rats through mTOR-mediated suppression of proinflammatory mediators. *Mol Med Rep*. 2017;16(2):1911–1919.
267. Chen J, G-z X, D-y L, Q-q Z, Y-y-j W, G-s B. Daxx ameliorates abdominal aortic aneurysm through inhibiting the TGF-β1-mediated PI3K/AKT/ID2 signaling pathway. *Eur J Inflamm*. 2022;20:1721727X221091532.

268. Cheng J, Koenig SN, Kuivaniemi HS, Garg V, Hans CP. Pharmacological inhibitor of notch signaling stabilizes the progression of small abdominal aortic aneurysm in a mouse model. *J Am Heart Assoc*. 2014;3(6):e001064.
269. Hans CP, Sharma N, Dev R, Blain JM, Tonniges J, Agarwal G. DAPT, a potent Notch inhibitor regresses actively growing abdominal aortic aneurysm via divergent pathways. *Clin Sci*. 2020;134(12):1555–1572. doi:10.1042/CS20200456
270. Wang J, Ye W, Zou J, et al. Targeting the smooth muscle cell Keap1-Nrf2-GSDMD-pyroptosis axis by cryptotanshinone prevents abdominal aortic aneurysm formation. *Theranostics*. 2024;14(17):6516–6542. doi:10.7150/thno.98400
271. Song H, Xu T, Feng X, et al. Itaconate prevents abdominal aortic aneurysm formation through inhibiting inflammation via activation of Nrf2. *EBioMedicine*. 2020;57:102832. doi:10.1016/j.ebiom.2020.102832
272. Wang JC, Tsai MC, Tsai SH, Huang PH. MicroRNA-325 ameliorates angiotensin II-induced abdominal aortic aneurysm by inhibiting the endothelial-to-mesenchymal transition through regulation of the MAPK/SNAI1/MMP-2 pathway. *Biomed Pharmacother*. 2025;188:118140. doi:10.1016/j.biopha.2025.118140
273. Tasopoulou KM, Karakasiliotis I, Argyriou C, et al. Next-generation sequencing of microRNAs in small abdominal aortic aneurysms: miR-24 as a biomarker. *Ann Vasc Surg*. 2024;99:366–379. doi:10.1016/j.avsg.2023.09.065
274. Lopez JL, Ramirez JL, Phu TA, et al. Patients with abdominal aortic aneurysms have reduced levels of microRNA 122-5p in circulating exosomes. *PLoS One*. 2023;18(2):e0281371. doi:10.1371/journal.pone.0281371
275. Liu Y, Tian X, Liu D, Zhang X, Yan C, Han Y. RelB represses miR-193a-5p expression to promote the phenotypic transformation of vascular smooth muscle cells in aortic aneurysm. *Biochim Biophys Acta Gene Regul Mech*. 2023;1866(2):194926. doi:10.1016/j.bbagrm.2023.194926
276. Hasemaki N, Andreou NP, Legaki E, Katsargyris A, Gazouli M, Klonaris C. Association of miRNA-145 single nucleotide polymorphisms in abdominal aortic aneurysms. *Vivo*. 2022;36(3):1120–1125. doi:10.21873/invivo.12810
277. Lim GB. Nanotherapy for abdominal aortic aneurysm. *Nat Rev Cardiol*. 2019;16(2):71.
278. Hans CP, Sharma N, Downey E, Khoobchandani M, Katti K, Katti KV. Mangiferin conjugated gold nanoparticles protect against the development of abdominal aortic aneurysm in an Apoe−/− mouse model. *JVS-Vascular Sci*. 2022;3:418–419. doi:10.1016/j.jvssci.2022.05.038
279. Lin W, Hu K, Li C, et al. A multi-bioactive nanomicelle-based "One stone for multiple birds" strategy for precision therapy of abdominal aortic aneurysms. *Adv Mater*. 2022;34(44):e2204455. doi:10.1002/adma.202204455
280. Fukuhara N, Honda Y, Ukita N, Matsui M, Miura Y, Hoshina K. Efficient suppression of abdominal aortic aneurysm expansion in rats through systemic administration of statin-loaded nanomedicine. *Int J Mol Sci*. 2020;21(22):8702. doi:10.3390/ijms21228702
281. Chao CL, Applewhite B, Reddy NK, Matiuto N, Dang C, Jiang B. Advances and challenges in regenerative therapies for abdominal aortic aneurysm. *Front Cardiovasc Med*. 2024;11:1369785. doi:10.3389/fcvm.2024.1369785
282. Hashizume R, Yamawaki-Ogata A, Ueda Y, Wagner WR, Narita Y. Mesenchymal stem cells attenuate angiotensin II-induced aortic aneurysm growth in apolipoprotein E-deficient mice. *J Vasc Surg*. 2011;54(6):1743–1752. doi:10.1016/j.jvs.2011.06.109
283. Li X, Wen H, Lv J, et al. Therapeutic efficacy of mesenchymal stem cells for abdominal aortic aneurysm: a meta-analysis of preclinical studies. *Stem Cell Res Ther*. 2022;13(1):81. doi:10.1186/s13287-022-02755-w
284. Schneider F, Saucy F, de Blic R, et al. Bone marrow mesenchymal stem cells stabilize already-formed aortic aneurysms more efficiently than vascular smooth muscle cells in a rat model. *Eur J Vasc Endovasc Surg*. 2013;45(6):666–672. doi:10.1016/j.ejvs.2013.03.007
285. Tian X, Fan J, Yu M, et al. Adipose stem cells promote smooth muscle cells to secrete elastin in rat abdominal aortic aneurysm. *PLoS One*. 2014;9(9):e108105. doi:10.1371/journal.pone.0108105
286. Zilberman B, Kooragayala K, Lou J, et al. Treatment of abdominal aortic aneurysm utilizing adipose-derived mesenchymal stem cells in a porcine model. *J Surg Res*. 2022;278:247–256. doi:10.1016/j.jss.2022.04.064
287. Blose KJ, Ennis TL, Arif B, Weinbaum JS, Curci JA, Vorp DA. Periadventitial adipose-derived stem cell treatment halts elastase-induced abdominal aortic aneurysm progression. *Regener Med*. 2014;9(6):733–741. doi:10.2217/rme.14.61
288. Xie J, Jones TJ, Feng D, et al. Human adipose-derived stem cells suppress elastase-induced murine abdominal aortic inflammation and aneurysm expansion through paracrine factors. *Cell Transplant*. 2017;26(2):173–189. doi:10.3727/096368916X692212
289. Parvizi M, Petersen AH, van Spreuwel-Goossens C, Kluijtmans S, Harmsen MC. Perivascular scaffolds loaded with adipose tissue-derived stromal cells attenuate development and progression of abdominal aortic aneurysm in rats. *J Biomed Mater Res A*. 2018;106(9):2494–2506. doi:10.1002/jbm.a.36445
290. Wen H, Wang M, Gong S, et al. Human umbilical cord mesenchymal stem cells attenuate abdominal aortic aneurysm progression in sprague-dawley rats: implication of vascular smooth muscle cell phenotypic modulation. *Stem Cells Dev*. 2020;29(15):981–993. doi:10.1089/scd.2020.0058
291. Sharma AK, Salmon MD, Lu G, et al. Mesenchymal stem cells attenuate NADPH oxidase-dependent high mobility group box 1 production and inhibit abdominal aortic aneurysms. *Arterioscler Thromb Vasc Biol*. 2016;36(5):908–918. doi:10.1161/ATVBAHA.116.307373