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REVIEW

The Mechanosensation-Metabolism-Inflammation Axis: The Central Role of Piezo1 and TRPV4 in Hypertension-Related Atherosclerosis

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Abstract: Atherosclerosis is a core independent risk factor for cardiovascular events. The abnormal hemodynamic microenvironment mediated by hypertension is a key initiating factor for its development and progression, and mechanosensitive ion channels are the core molecules connecting vascular mechanical forces to intracellular biochemical signals. Piezo1 and Transient Receptor Potential Vanilloid 4 (TRPV4), as important mechanosensitive ion channels in blood vessels, are widely expressed in vascular endothelial cells, smooth muscle cells, and immune cells. They can sense and be activated by abnormal circumferential stress and shear stress under hypertensive conditions. This review systematically synthesizes current evidence to test the central hypothesis that Piezo1 and TRPV4 form a functionally synergistic signaling axis, converting pathological mechanical forces into sustained Ca^{2+} influx, which subsequently drives an integrated network of metabolic imbalance and chronic inflammation in hypertension-related atherosclerosis. It focuses on the activation modes of these channels by abnormal mechanical forces in hypertension and the subsequent early Ca^{2+} signaling dysregulation. The regulatory pathways of channel-mediated lipid and glucose metabolism disorders are deeply analyzed. The specific mechanisms by which both channels participate in the regulation of endothelial dysfunction, inflammatory infiltration, foam cell formation, and plaque stability in atherosclerosis through key signaling pathways such as NF-κB, NLRP3, and YAP/TAZ are comprehensively summarized. Furthermore, intervention strategies using natural compounds targeting this channel axis are discussed. Research indicates that Piezo1 and TRPV4 form a functionally synergistic signaling axis. By converting abnormal mechanical forces into sustained Ca^{2+} influx, they drive metabolic imbalance and chronic inflammation in vascular cells, realizing a functional transition from physiological protection to pathological damage. The cell-specific, environment-dependent regulatory characteristics and the bidirectional interaction network of these two channels constitute an important pathological regulatory mechanism for hypertension-related atherosclerosis. This review aims to establish a complete regulatory network of "mechanosensation-ion channel-calcium signal-metabolic inflammation-atherosclerosis" and provide an integrated framework for clarifying the molecular mechanisms of hypertension-associated atherosclerosis, and exploring potential targets and intervention strategies for the precise prevention and treatment of the disease.

Keywords: Piezo1, TRPV4, mechanosensitive ion channel, hypertension, atherosclerosis, calcium signal, metabolic disorder, vascular remodeling

Introduction

Atherosclerosis is a core independent risk factor for cardiovascular events, characterized pathologically by lipid deposition in the arterial wall, inflammatory cell infiltration, and abnormal proliferation and migration of smooth muscle cells. Hypertension, as a globally prevalent cardiovascular syndrome, mediates an abnormal hemodynamic microenvironment that is a key initiating factor in the development and progression of atherosclerosis.[1–3] Sustained elevation of vascular circumferential stress and disturbed blood flow shear stress directly damage vascular endothelial function,[4]

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induce pathological remodeling of vascular smooth muscle cells,[5] and activate oxidative stress and chronic inflammatory responses,[6,7] forming a vicious cycle where hypertension and atherosclerosis promote each other. Mechanosensitive ion channels are core molecules through which cells sense changes in the physical microenvironment and transduce them into biochemical signals.[8–11] Among these, Piezo1 and Transient Receptor Potential Vanilloid 4 (TRPV4) are widely expressed in vascular endothelial cells, smooth muscle cells, and immune cells, making them key targets regulating vascular physiological function and pathological remodeling.

Existing research has confirmed that Piezo1 and TRPV4 can independently participate in vascular mechanotransduction,[12] calcium homeostasis regulation,[13] and inflammatory metabolic processes.[14,15] However, in the hypertensive pathological context, the precise molecular mechanisms by which they are synergistically activated by abnormal mechanical forces, amplifying lipid and glucose metabolic disorders and inflammatory responses via disrupted calcium signals, and driving atherosclerotic plaque formation, progression and destabilization remain incompletely understood. The upstream and downstream regulatory networks, cell-specific functional differences, and translational value as therapeutic targets also lack systematic integration.[16] Current studies often focus on isolated mechanisms of single channels, while an integrated view of the mechanosensation-metabolism-inflammation axis mediated by Piezo1 and TRPV4 in hypertensive atherosclerosis is still missing. This review is structured around a central hypothesis: that Piezo1 and TRPV4 form a functionally synergistic signaling axis. By converting abnormal mechanical forces from hypertension into a pathological, sustained Ca^{2+} signal, they collectively drive a state of metabolic imbalance and chronic inflammation, which is essential for the initiation and progression of atherosclerotic plaques. To test this hypothesis, we systematically synthesize evidence from recent literature, prioritizing studies that address channel synergy, calcium signal dynamics, and metabolic-inflammatory crosstalk in the context of hypertensive atherosclerosis. The goal is to establish a complete regulatory network of "mechanosensation-ion channel-calcium signal-metabolic inflammation-atherosclerosis", providing new insights and targets for mechanistic research and precision clinical treatment of hypertension complicated with atherosclerosis.

Overview of Mechanosensitive Ion Channels Piezo1 and TRPV4

Piezo1 Channel

Piezo1 is a core mechanically activated, non-selective cation channel of the mammalian Piezo family.[17] It possesses a three-bladed propeller-like three-dimensional structure crucial for sensing membrane tension.[18–20] Piezo1 operates via a force-gated mechanism, directly transducing mechanical forces into electrochemical signals.[21] Upon activation, it mediates rapid Ca^{2+} influx, forming characteristic Ca^{2+} transients.[22] In the cardiovascular system, Piezo1 is crucial for maintaining vascular physiological function. Under physiological conditions, Piezo1 in vascular endothelial cells senses laminar shear stress, activating endothelial nitric oxide synthase (eNOS) via Ca^{2+} influx to generate nitric oxide (NO)[23] and mediating vasodilation.[24,25] Its expression in neurons is also involved in baroreflexes.[26] However, under hypertension, Piezo1 can become overactivated, leading to pathological vascular remodeling[27,28] and directly linking abnormal hemodynamics to immune-inflammatory responses.[29–32]

TRPV4 Channel

TRPV4 is a non-selective cation channel with a tetrameric structure, activated by multiple modes including mechanical forces, temperature, and chemical ligands.[33–36] TRPV4 exhibits functional duality in the cardiovascular system. Under physiological conditions, it maintains vascular health by activating eNOS and inhibiting inflammation.[37,38] However, under pathological conditions like hypertension, abnormal TRPV4 activation can promote disease progression, including vascular calcification.[39–41] This represents a transition from a protective, anti-inflammatory role to a pathological, pro-injury role.

Expression and Interaction of Piezo1 and TRPV4 in Vascular Cells

Piezo1 and TRPV4 are widely expressed in endothelial cells,[42] smooth muscle cells,[43] and immune cells of the vessel wall.[44,45] They are not parallel mechanosensors but form a functionally coupled signaling axis that jointly regulates vascular physiology and pathology.

In endothelial cells, Piezo1 and TRPV4 act as core mechanosensors. Under physiological laminar shear stress, they synergistically activate to promote Ca^{2+} influx, subsequently activating eNOS to produce NO, mediating vasodilation and anti-inflammatory effects.[46,47] However, under hypertensive disturbed blood flow or abnormal shear stress, the activation patterns and downstream effects of both channels change, directly leading to endothelial dysfunction. In vascular smooth muscle cells, they sense hypertension-mediated circumferential stress, regulating cell proliferation,[48] migration,[49] and phenotypic switching,[50] participating in hypertension-induced vascular remodeling. Functional interaction between them has been confirmed to involve a clear upstream-downstream hierarchy: upon activation by shear stress, Piezo1 stimulates phospholipase A2 (PLA2) to generate the arachidonic acid metabolite 5′,6′-EET, which in turn activates TRPV4 channels, mediating sustained Ca^{2+} influx.[51] This cascade ultimately leads to pathological changes such as disruption of endothelial adherens junctions and monocyte adhesion. Concurrently, there is evidence of mutual inhibitory crosstalk, offering diverse perspectives on channel regulatory mechanisms (Figure 1).

Direct experimental evidence for their physical co-localization on the cell membrane is still relatively scarce. However, based on their distribution in membrane microdomains, it is hypothesized that Piezo1 and TRPV4 do not require direct protein-protein interaction.[52] Instead, they are co-recruited to membrane signaling platforms, such as mechanotransduction complexes, spatially integrating with key molecules like cPLA2 and CYP enzymes.[53] This allows for efficient signal transmission from mechanical force perception, to chemical messenger generation, to downstream channel activation. Piezo1 is responsible for directly sensing the mechanical force and initiating the signal, while TRPV4 amplifies and sustains it. This sophisticated synergistic mechanism enables vascular cells to respond precisely to complex mechanical environments. Under hypertensive pathological conditions, this regulatory system can malfunction, becoming a core driver of atherosclerosis.

Mechanical Alterations in the Hypertensive Microenvironment

Abnormal Mechanical Forces in the Vascular System Under Hypertension

Under physiological conditions, vascular wall cells are regulated by physiological levels of laminar shear stress and pulse-induced circumferential stress.[54] Laminar shear stress, in particular, maintains the anti-inflammatory, anti-coagulant, and vasodilatory functions of endothelial cells, serving as a crucial guarantee for vascular homeostasis. In

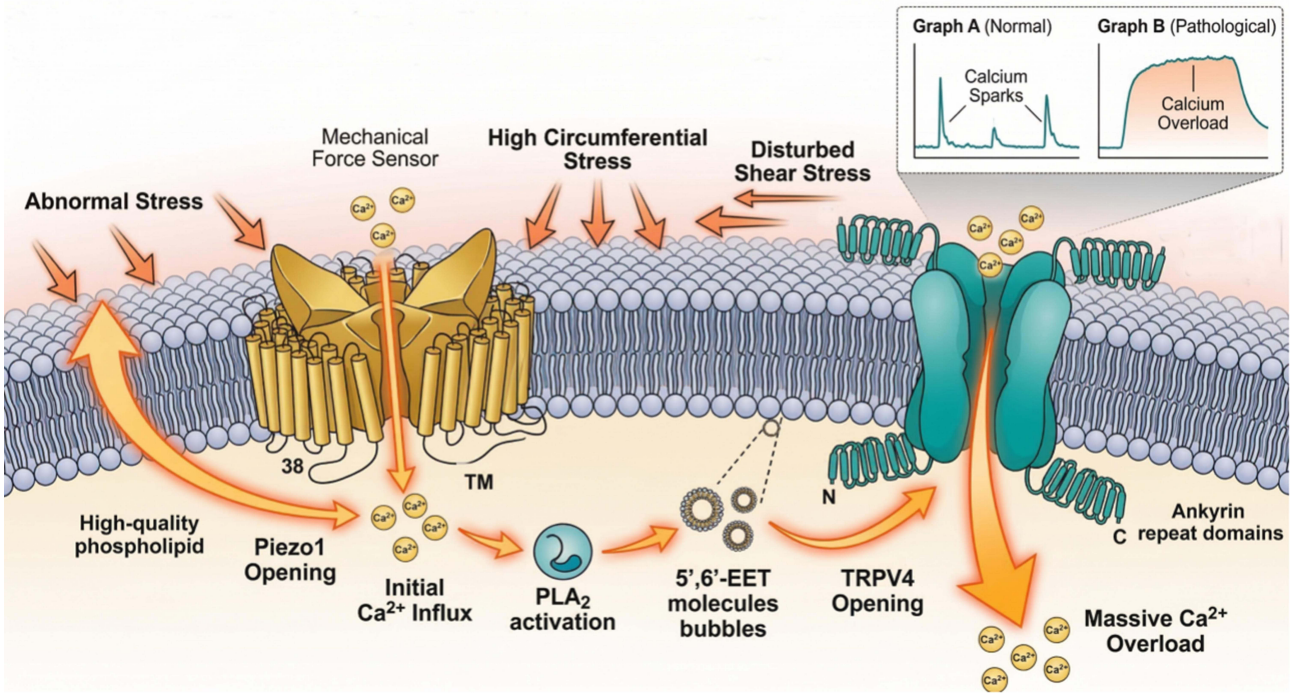

Figure 1 Schematic diagram of the structure, activation mechanism, and signaling axis of Piezo1 and TRPV4.

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contrast, under hypertensive conditions, the mechanical environment of the vasculature undergoes significant and persistent abnormal changes, primarily characterized by abnormal blood flow shear stress and elevated circumferential stress.[55] Both types of stress initiate and accelerate the pathological process of atherosclerosis and are closely linked to the abnormal activation of Piezo1 and TRPV4.

Abnormal blood flow shear stress mainly manifests as low shear stress or oscillatory shear stress in areas of vascular branching,[56] curvature, and stenosis.[57] These non-physiological flow patterns induce endothelial cell dysfunction and inflammation, promoting their transition to an inflammatory phenotype, enhancing adhesion molecule expression, and mediating inflammatory cell aggregation. They are significant triggers for endothelial dysfunction and vascular inflammation, directly associated with an atherosclerosis-prone phenotype. Elevated circumferential stress is directly caused by a sustained increase in arterial blood pressure.[58] According to the Law of Laplace, the vessel wall can initially compensate for increased wall tension through thickening in early hypertension. However, long-term high pressure load leads to the conversion of vascular smooth muscle cells from a contractile to a synthetic phenotype, causing abnormal cell proliferation, migration, and excessive extracellular matrix deposition.[59–61] Concurrently, it is accompanied by elastic fiber degradation and the release of inflammatory mediators like elastin-derived peptides (EDPs), activating the inflammatory phenotype of vascular wall cells, ultimately resulting in pathological vascular remodeling characterized by wall thickening and increased stiffness.

The vascular remodeling resulting from chronic hypertension further exacerbates the deterioration of the vascular mechanical environment. Increased vessel wall stiffness alters the vascular response to pulsatile pressure,[62] leading to a widened pulse pressure and further elevating the mechanical stress experienced by vascular wall cells.[63,64] Simultaneously, pathological changes in the extracellular matrix exacerbate vascular remodeling through molecules like matrix metalloproteinases (MMPs)[65] and extracellular matrix metalloproteinase inducer (EMMPRIN),[66] forming a vicious cycle of "abnormal mechanical force - vascular remodeling - more severe abnormal mechanical force". This lays the pathological foundation for the development and progression of atherosclerosis.

Activation of Piezo1/TRPV4 Channels by Abnormal Mechanical Forces

As the primary mechanosensitive ion channels in vascular wall cells, Piezo1 and TRPV4 are highly sensitive to the abnormal mechanical signals in the hypertensive microenvironment.[67] They are the core molecules transducing macroscopic hemodynamic changes into intracellular biochemical signals. Abnormal shear stress and circumferential stress can activate both channels through direct or indirect mechanisms, thereby initiating intracellular signal transduction and regulating the development and progression of atherosclerosis.

Piezo1, with its high sensitivity to membrane tension, serves as an ideal mechanosensor for perceiving hypertensive circumferential high tension. The stretched state of the vascular endothelial cell membrane under sustained high pressure can directly gate Piezo1 channels, significantly increasing their open frequency and probability.[68] Simultaneously, Piezo1 can also sense changes in shear stress. Under physiological laminar shear stress, its activation exerts a vasoprotective effect, whereas in atherosclerosis-prone regions with abnormal shear stress, its expression and activity are significantly upregulated, fundamentally altering its activation pattern.[69] In vascular smooth muscle cells, changes in hydrostatic pressure can upregulate Piezo1 expression via the GPR146/Gαs-cAMP-CREB pathway,[70] forming a positive feedback loop linking mechanical signals and gene transcription, thereby exacerbating the hypertensive process. Compensatory regulatory mechanisms also exist in the body; for instance, Piezo1 activation in renal juxtaglomerular cells can promote PGE_2 synthesis via Ca^{2+} signaling, inhibiting renin release and exerting a blood pressure-lowering effect.[71] This highlights that Piezo1's functional effects are dependent on the cellular context and downstream signaling pathways.

The activation mechanism of TRPV4 is more complex. Besides directly sensing mechanical forces, it is also regulated by upstream signaling pathways. Notably, 5′,6′-EET, generated downstream of Piezo1 activation, is an important endogenous activator.[72] Concurrently, local micro-inflammation and oxidative stress in the hypertensive microenvironment can further activate TRPV4. Hypertension can lead to upregulated TRPV4 expression and downregulated IP_3 receptor expression in endothelial cells, making the vascular response to TRPV4 bidirectional: low-intensity activation promotes vasodilation through calcium oscillations, exerting a compensatory protective effect; high-intensity activation mediates sustained Ca^{2+} influx, inducing vasoconstriction and exhibiting pathological effects.[73] Under physiological

laminar shear stress, TRPV4 activation exerts vasoprotective effects, whereas hypertensive abnormal shear stress alters its activation pattern and downstream effects. While it synergizes with Piezo1 to regulate vascular function, the specific molecular regulatory mechanisms require further elucidation.

Early Ca^{2+} Signaling Events Triggered by Channel Activation

The abnormal activation of Piezo1 and TRPV4 ultimately leads to pathological disruption of intracellular Ca^{2+} signals. The spatiotemporal pattern shift of Ca^{2+} signals is the key switch from physiological regulation to pathological driving. Under physiological conditions, Piezo1 and TRPV4 activation is typically transient and localized.[74] They mediate calcium sparks or flickers that form microdomain Ca^{2+} signals confined to the vicinity of the open channel. This allows for the precise activation of adjacent effector molecules, achieving physiological functions like vascular tone regulation, while avoiding the cytotoxicity of Ca^{2+} overload.[75,76] However, under sustained stimulation by abnormal hypertensive mechanical forces, their overactivation leads to a dual pathological alteration in Ca^{2+} signaling patterns: First, a change in signal intensity and duration. Sustained Piezo1 activation combined with TRPV4-mediated signal amplification transforms the Ca^{2+} signal from a brief "spike" into a chronically elevated "plateau", leading to a sustained increase in intracellular basal Ca^{2+} concentration ($[Ca^{2+}]i$).[77–79] Second, a change in spatial distribution. Pathological Ca^{2+} overload spreads from subcellular locales throughout the entire cytoplasm, losing the precise spatiotemporal regulation characteristic of the physiological state (Table 1).

This pathological Ca^{2+} signal disruption is a key trigger for downstream metabolic disorders and inflammatory responses: Sustained Ca^{2+} influx directly causes mitochondrial Ca^{2+} overload, inhibiting key metabolic enzymes like pyruvate dehydrogenase and uncoupling the electron transport chain.[80] This not only reduces ATP production efficiency but also induces substantial reactive oxygen species (ROS) generation, triggering intense oxidative stress. ROS can directly damage cellular structures and activate various inflammatory pathways.[81] Simultaneously, Ca^{2+} overload and ROS jointly induce the opening of the mitochondrial permeability transition pore (mPTP), initiating endothelial cell apoptosis and disrupting the vascular barrier function.[82] Furthermore, sustained Ca^{2+} influx can deplete endoplasmic reticulum Ca^{2+} stores, activating store-operated calcium entry (SOCE) via STIM proteins and Orai channels on the cell membrane. Chronic abnormal activation of SOCE is a potent pro-proliferative and pro-inflammatory signal. Elevated $[Ca^{2+}]i$ also activates calcium-dependent enzymes such as CaMK, PKC, and PLA2,[83–86] altering cellular signal transduction pathways, leading to eNOS uncoupling, cytoskeletal remodeling, and regulating inflammatory gene transcription through pathways like calcineurin/NFAT and YAP, further amplifying vascular inflammation.

Current research on mechano-evoked Ca^{2+} signal transduction has limitations: Existing conclusions are largely derived from isolated cell models and pharmacological agonists, making it difficult to replicate the complex in vivo

Table 1 Spatiotemporal Patterns of Physiological versus Pathological Ca^{2+} Signals Mediated by Piezo1/TRPV4

Feature	Physiological Ca^{2+} Signal	Pathological Ca^{2+} Signal
Trigger	Physiological laminar shear stress, transient mechanical stimulation	Hypertensive abnormal mechanical forces (high circumferential stress/ oscillatory shear stress)
Temporal pattern	Transient (calcium sparks/ flickers)	Sustained plateau
Spatial range	Microdomain confined to channel vicinity	Diffuse throughout the cytoplasm
Mitochondrial Ca^{2+} load	Low, maintains oxidative phosphorylation efficiency	Overload, inhibits metabolic enzymes, induces ROS burst
ER Ca^{2+} homeostasis	Maintained fullness, no SOCE activation	Depletion, activates SOCE (pro-proliferative/pro-inflammatory)
Ca^{2+}-dependent enzyme activity	Localized, transient activation (eg, eNOS)	Sustained activation (CaMK, PKC, PLA2, etc.)
Cellular fate	Homeostasis maintained (vasodilation, anti-inflammation)	Dysfunction, apoptosis/pyroptosis, inflammatory activation

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mechanical environment and channel desensitization/adaptation phenomena. Regarding the genesis of pathological Ca^{2+} signals, the relative contributions of Piezo1/TRPV4-mediated active influx versus passive leakage due to disrupted intracellular calcium homeostasis remain unclear. Most studies have only established a correlation between channel activation and Ca^{2+} elevation, lacking direct evidence proving that a specific Ca^{2+} spatiotemporal pattern is a necessary and sufficient condition for driving downstream pathological effects. The threshold for the protective-to-destructive functional transition of Piezo1 and TRPV4, as well as the endogenous negative feedback regulatory mechanisms, are also core issues requiring urgent clarification. Based on this, future potential therapeutic strategies may not involve completely blocking Piezo1/TRPV4, but rather pharmacologically correcting the pathological Ca^{2+} signaling pattern back towards a physiological state, inhibiting pathological effects while preserving normal physiological functions.

Piezo1/TRPV4-Mediated Disorders of Lipid and Glucose Metabolism

The abnormal Ca^{2+} signals triggered by Piezo1 and TRPV4 activation initiate vascular cell metabolic disorders and form a critical bridge linking early mechanical stress to late atherosclerotic plaque formation.[87] This metabolic regulation is cell-specific and signaling pathway-dependent, representing an important pathological mechanism in hypertension-related atherosclerosis.

Lipid Metabolism Disorders

Lipid metabolism disorder is the core pathological basis of atherosclerosis.[88] The synergistic effect of hypertension and dyslipidemia significantly exacerbates atherosclerotic risk. Piezo1/TRPV4, by mediating Ca^{2+} signals, regulate cellular lipid homeostasis at two levels: transcription factor regulation and lipid transport modulation.[89] They also form a bidirectional regulatory network with membrane lipid components, collectively participating in the process of hypertension-related lipid metabolism disorders.

Piezo1/TRPV4 can regulate the activity of core lipid metabolism transcription factors via Ca^{2+} signals, subsequently affecting lipid synthesis, breakdown, and transport: Ca^{2+} influx mediated by Piezo1 activation can activate calcium-dependent transcription factors such as NFAT and YAP1.[90,91] Through the CaM-CaMK-AMPK signaling axis, it can upregulate anti-inflammatory metabolic genes like peroxisome proliferator-activated receptor (PPAR), enhancing lipid oxidation capacity.[92] It can also inhibit the nuclear translocation of sterol regulatory element-binding protein (SREBP), reducing cholesterol and fatty acid synthesis. Conversely, transient Ca^{2+} elevation triggered by TRPV4 activation can inhibit PGC1α expression via activation of the ERK1/2 signaling pathway,[93] weakening mitochondrial biogenesis and fatty acid oxidation capacity, manifesting as a negative regulatory role in lipid metabolism. Ca^{2+} signals mediated by both channels can also directly or indirectly regulate transcription factors like liver X receptor (LXR) and SREBP through pathways such as CaMKKβ-AMPK and CaMK, forming a calcium signaling network for transcriptional regulation of lipid metabolism.

Regarding the regulation of lipid transport, transient Ca^{2+} influx from Piezo1 activation can inhibit adipogenesis in adipocytes via the AMPK pathway. In vascular smooth muscle cells, it can regulate lipid metabolism enzymes through calcineurin, upregulating the expression of the fatty acid translocase CD36, promoting lipid droplet formation and exogenous fatty acid uptake, thus driving abnormal lipid accumulation.[94] Ca^{2+} signals from TRPV4 activation can promote ABCA1 expression via CaMKII, accelerating macrophage cholesterol reverse transport.[95,96] Its function is also subject to feedback regulation by membrane cholesterol content; cholesterol depletion enhances its calcium influx effect, while a high-cholesterol environment inhibits its activity, forming a feedback loop for lipid transport regulation.

A bidirectional regulatory relationship exists between Piezo1/TRPV4 and cell membrane lipid composition: Membrane lipid composition is a key factor regulating the activity of both channels. Piezo1 forms stable interactions with cholesterol and phosphatidylinositol 4,5-bisphosphate (PIP_2).[97–99] Cholesterol concentration non-linearly modulates its membrane embedding and channel activity, while PIP_2 stabilizes its open conformation.[97] Lipid peroxidation can also promote Piezo1 opening by increasing membrane tension. Cholesterol inhibits the mechanosensitivity of TRPV4, and polyunsaturated fatty acids can modulate its activation threshold by altering membrane fluidity. Concurrently, Piezo1/TRPV4 channel activity can feedback-regulate lipid metabolism.[100] Piezo1 deficiency downregulates cholesterol synthesis-related genes, and its activation in macrophages can promote the uptake of oxidized phospholipids, participating in

foam cell formation. TRPV4 activation inhibits the expression of genes related to oxidative metabolism in white adipose tissue mitochondria, reducing fat oxidation and thermogenesis, while its inhibition enhances energy expenditure and alleviates lipid accumulation.

Furthermore, hypertension-induced oxidative stress is closely linked to lipid metabolism disorders. Elevated blood pressure activates vascular NAD(P)H oxidase, generating substantial ROS and promoting lipid peroxidation.[101] The formation of oxidized low-density lipoprotein (oxLDL) further activates endothelial cells and macrophages, promoting foam cell formation and plaque accumulation. Ca^{2+} signal disruption mediated by Piezo1/TRPV4 exacerbates oxidative stress, creating a synergistic pathological effect of "abnormal calcium signal - oxidative stress - lipid metabolism disorder".

Glucose Metabolism Disorders

Glucose metabolism disorders such as hyperglycemia and insulin resistance are significant risk factors for atherosclerosis. Insulin resistance is often accompanied by endothelial dysfunction, while hyperglycemia exacerbates vascular damage by promoting oxidative stress and inflammation. Piezo1/TRPV4 regulate core processes like glycolysis and glucose uptake by mediating Ca^{2+} signals.[72] Their function is, in turn, regulated by the hyperglycemic environment. Both are involved in the pathological process of hypertension complicated by glucose metabolism disorders, with their regulatory effects exhibiting significant tissue specificity.

Activation of the Piezo1 channel primarily manifests as pro-glycolytic and pro-inflammatory effects in glucose metabolism regulation. In macrophages, its activation upregulates key glycolytic genes such as GLUT1 and HK2 via the Ca^{2+}-CaMKII-HIF-1α signaling axis, driving the cell's transition towards a pro-inflammatory phenotype highly dependent on aerobic glycolysis.[102] This links the mechanical environment, metabolic state, and immune inflammation. Simultaneously, sustained Ca^{2+} influx mediated by Piezo1 can impair mitochondrial function, forcing vascular endothelial cells to increase glycolysis to compensate for energy supply, thereby enhancing cell proliferation, migration, and inflammatory responses, exacerbating atherosclerosis.[103] The role of TRPV4 in glucose metabolism regulation shows opposing effects depending on the tissue: In white adipose tissue, its activation promotes glucose uptake and inhibits lipolysis, potentially improving peripheral tissue insulin sensitivity.[104] However, in pancreatic β-cells, short-term activation can promote insulin secretion, but long-term or excessive activation leads to calcium overload, causing cell failure and apoptosis. This explains why TRPV4 antagonists can ameliorate insulin resistance induced by a high-fat diet.

Ca^{2+} signals mediated by Piezo1/TRPV4 can also regulate glucose metabolism through core kinase pathways. CaMKII, activated by Ca^{2+} signals, can upregulate GLUT4 expression, enhancing cellular glucose uptake capacity.[105–107] AMPK can enhance glycolytic flux by phosphorylating and activating PFKFB3.[108] Concurrently, oxidative stress triggered by Ca^{2+} overload induces HIF-1α expression, further upregulating glycolytic genes like HK2, forming a positive feedback loop for glycolysis. Metabolic products of glycolysis, such as lactate and succinate, can in turn stabilize HIF-1α, persistently driving the cell towards a pro-inflammatory metabolic phenotype.[109–112]

The hyperglycemic environment exerts differential regulation on Piezo1 and TRPV4 function: High glucose leads to abnormal activation of Piezo1. In vascular endothelial cells, Piezo1-mediated calcium influx activates CaMKII, interfering with the Nrf2-mediated antioxidant defense system, exacerbating oxidative stress and inflammation, and impairing endothelial repair and angiogenesis.[113,114] Endothelial-specific knockout of Piezo1 significantly alleviates the metabolic abnormalities and vascular dysfunction induced by high glucose. Conversely, hyperglycemia significantly reduces TRPV4 gene and protein expression in tissues like retinal microvascular endothelial cells,[115] weakening its mediated calcium influx and ionic currents, impairing its physiological function in maintaining vascular tone and blood flow, thereby further aggravating vascular dysfunction.

Current research on Piezo1/TRPV4-mediated metabolic disorders still has many knowledge gaps: Regarding lipid metabolism regulation, the causal link between channel activity and core transcriptional programs requires more in vivo experimental evidence.[116] The molecular mechanisms underlying the differential roles of Piezo1 in regulating lipid metabolism[117] in macrophages versus vascular smooth muscle cells remain unclear. In terms of glucose metabolism, whether HIF-1α expression and stability are directly regulated by mechanical forces or channel activity requires further validation. Moreover, systematic studies are lacking on how signals from both channels interact and influence the final

metabolic phenotype in the complex context of hypertension combined with metabolic syndrome. Future research should integrate cell-specific experiments, real-time metabolite detection, and other technologies to reveal the specific molecular mechanisms of their metabolic regulation and complete the signal transmission pathway from mechanosensation to metabolic disorder.

Signaling Pathways and Mechanisms of Piezo1/TRPV4 in Atherosclerosis

Piezo1 and TRPV4 participate in the entire pathological process of atherosclerosis, including endothelial dysfunction,[118] vascular inflammation,[119] foam cell formation,[120] and plaque stability regulation,[121] by integrating calcium, metabolic, and inflammatory signals. They form a synergistic pathological regulatory network by modulating key signaling nodes such as NF-κB, NLRP3, and YAP/TAZ. Natural compounds and small molecule modulators exert anti-atherosclerotic effects by targeting this channel axis and its downstream pathways, confirming their potential value as clinical intervention targets.

Endothelial Dysfunction and Vascular Inflammation

In endothelial dysfunction, the initiating step of atherosclerosis, Piezo1 and TRPV4 are core targets through which abnormal mechanical forces regulate endothelial homeostasis: Disturbed blood flow or low shear stress upregulates Piezo1 expression, activates the YAP signaling axis, and inhibits endothelial cell autophagy, disrupting endothelial homeostasis.[122] It can also activate integrin α5β1 via the Piezo1-PTP1B-Annexin A2 axis, driving endothelial activation and monocyte recruitment. Increased vascular matrix stiffness inhibits TRPV4 channel function, leading to upregulated endothelin-1 (ET-1) expression and impaired eNOS activity via downregulation of miR-6740-5p, inducing vasodilatory dysfunction.[123] In the context of aging, aberrant interaction between TRPV4 and GPR35 further exacerbates endothelial Ca^{2+} signal disruption and worsens vascular functional decline. Notably, TRPV4 exhibits context-dependent dual effects; the specific agonist GSK1016790A can inhibit monocyte adhesion and reduce plaque formation by activating the AMPK/eNOS pathway, demonstrating its potential for pharmacological intervention.[124]

In the regulation of vascular inflammation and immune responses, Piezo1 and TRPV4 continuously amplify vascular inflammation through epigenetic regulation, signaling pathway activation, etc.: TRPV4 can negatively regulate the expression of the anti-inflammatory microRNA miR-146a via epigenetic mechanisms, relieving the inhibition of inflammatory responses and promoting sustained inflammation in macrophages.[125] Piezo1, activated by disturbed flow, can upregulate the histone demethylase KDM5B via ETS1/c-JUN, altering the epigenetic landscape of endothelial cells and activating inflammatory genes.[126] It can also directly promote the expression of inflammatory factors in the vessel wall via the YAP/JNK signaling axis. Furthermore, low shear stress, by downregulating Piezo1 expression, triggers HDAC2-dependent neutrophil extracellular trap (NETosis) formation, directly linking the mechanical environment to innate immune responses and further exacerbating plaque inflammation.[127]

Foam Cell Formation and Plaque Stability

Foam cell formation is a core pathological event in atherosclerosis, and Piezo1 and TRPV4 are deeply involved in its regulation through different pathways, exhibiting cell specificity: In macrophages, TRPV4 activation enhances JNK phosphorylation, promoting oxLDL uptake. Conversely, oxLDL can feedback-downregulate TRPV4 expression by activating PPARγ, forming a self-regulatory loop.[128] Piezo1 activation is critical in disrupting the balance between oxidative stress and inflammation in macrophages. Inhibiting Piezo1 significantly reduces CD36 expression, mitochondrial ROS generation, and MAPK/NF-κB signaling activation,[129] while activating the Nrf2/HO-1 antioxidant pathway, thereby inhibiting foam cell formation. In vascular smooth muscle cells, Piezo1 activation has dual detrimental effects. Its agonist Yoda1 can induce Ca^{2+} overload, mitochondrial damage, and ROS burst, leading to vascular smooth muscle cell apoptosis and weakening plaque stability.[130] More importantly, hypertensive mechanical pressure can drive the direct transdifferentiation of vascular smooth muscle cells into foam cells via Piezo1 activation,[131] revealing a novel mechanism where mechanical force can directly promote atherosclerosis without requiring excessive lipid deposition. Additionally, extracellular matrix stiffening can upregulate scavenger receptors like CD36, promoting lipid uptake, while TRPV4 channel activity can specifically inhibit macrophage uptake of acetylated low-density lipoprotein (acLDL),

suggesting differential regulation of lipid uptake pathways.[132] In the regulation of plaque stability and cell fate, Piezo1-mediated macrophage pyroptosis is a key pathological link. Ca^{2+} influx resulting from channel opening is a potent signal for activating the NLRP3 inflammasome, subsequently triggering Caspase-1-dependent pyroptosis, exacerbating intraplaque inflammation and necrotic core formation.[133]

Clinical pathological studies confirm that Piezo1 expression is significantly upregulated in myofibroblasts of symptomatic carotid plaques and is closely associated with instability features like plaque rupture and thin fibrous cap, marking its potential as a biomarker for plaque stability. TRPV4 expression is linked to vascular remodeling and blood flow recovery; its downregulation in skeletal muscle in a severe ischemia model of peripheral artery disease (PAD) reflects its role as a shear stress sensor in pathological vascular remodeling.[134] Furthermore, both channels are involved in cross-organ pathological regulation. Periodontal pathogens can promote atherosclerosis through channels like TRPV4, while 5,6-EET can cause hypotension through excessive TRPV4 activation,[135] illustrating the complex interplay between lipid metabolism, vasoactive substances, and ion channels (Figure 2).

Therapeutic Potential: Targeting the Piezo1-TRPV4 Axis

Given the central pathological roles of Piezo1 and TRPV4 in atherosclerosis, they have become potential intervention targets. A series of natural compounds exert effects by directly targeting the channels, multi-target synergistic regulation, or intervening in downstream signaling pathways: Salvianolic acid B directly inhibits Piezo1 channel current and Ca^{2+} influx, reverses Yoda1-induced foam cell formation, and suppresses plaque formation.[136] Ginkgetin, as an effective TRPV4 inhibitor, blocks macrophage Ca^{2+} influx, inhibiting oxLDL uptake and foam cell formation.[137] Cannabis extracts downregulate scavenger receptors and inhibit the NF-κB pathway by regulating non-canonical receptors like TRPV4, reducing lipid uptake.[138] Compounds like Kaempferol, Hydroxysafflor yellow A, Ginsenoside complexes, and Guizhi Tongluo tablets exert anti-inflammatory effects, inhibit foam cell formation, and stabilize plaques by suppressing Piezo1-mediated Ca^{2+} influx and regulating downstream pathways such as Nrf2/HO-1, YAP/JNK, and NLRP3.[139] These examples validate the concept that pharmacologically resetting the pathological Ca^{2+} signal towards a physiological pattern is a viable and novel approach. Future development should focus on isoform-specific modulators that correct channel function without completely abolishing its essential physiological roles.

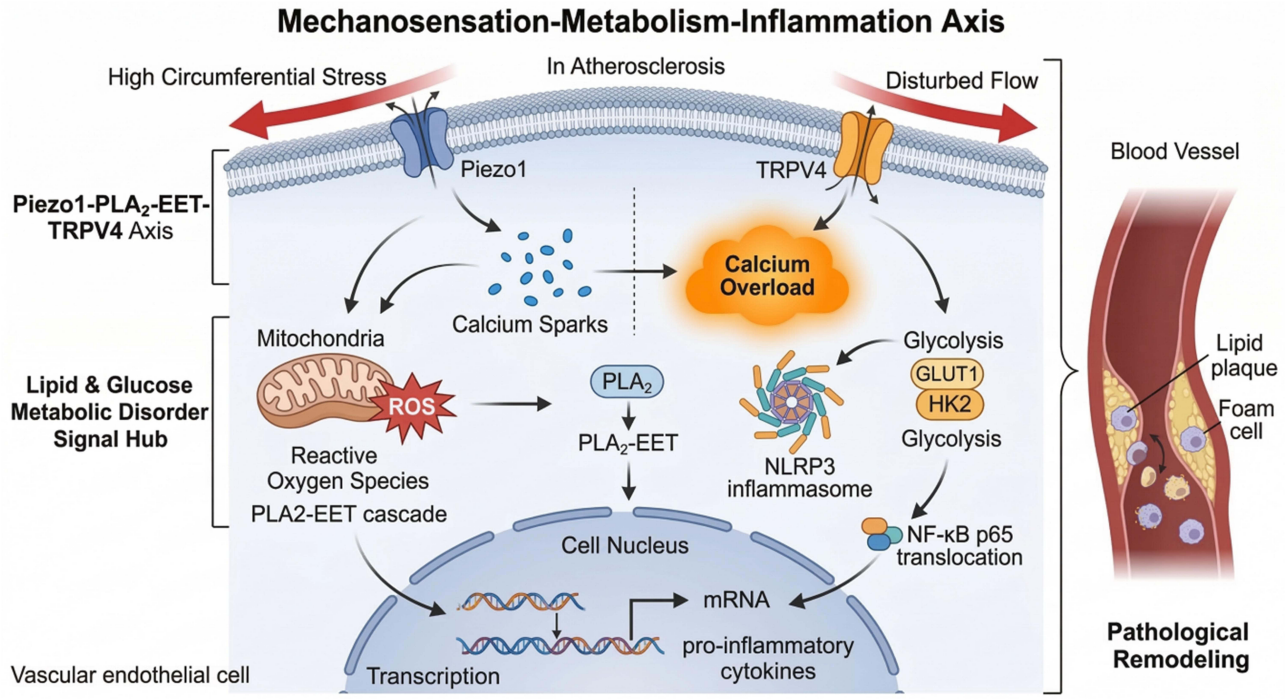

Figure 2 Integrated mechanism model of hypertensive abnormal mechanical force → Ca^{2+} signal spatiotemporal conversion → metabolism-inflammation axis.

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Conclusion

The abnormal hemodynamic microenvironment induced by hypertension is a core initiating factor in the development and progression of atherosclerosis. Piezo1 and TRPV4, as functionally synergistic core mechanosensitive ion channels in vascular wall cells, serve as critical bridges connecting macroscopic mechanical force stimuli to microscopic cellular biochemical responses. By forming the Piezo1-PLA2-EET-TRPV4 signaling axis,[140] they transduce the abnormal circumferential stress and shear stress of hypertension into intracellular Ca^{2+} signal disruption, subsequently driving lipid and glucose metabolic imbalances, chronic inflammatory activation, and pathological vascular cell remodeling, participating in the entire pathological process of atherosclerosis. We demonstrate that the pathological conversion of Ca^{2+} signals from a physiological "spark" to a pathological "plateau" is the key mechanistic link.

The functions of Piezo1 and TRPV4 exhibit significant cell-specificity, environmental dependence, and bidirectionality: Under physiological conditions, they mediate brief, localized microdomain Ca^{2+} signals, maintaining vascular tone homeostasis and endothelial integrity by activating eNOS to generate NO and inhibiting inflammatory gene expression. However, under sustained stimulation by abnormal hypertensive mechanical forces, they become overactivated or dysfunctional. This transforms the Ca^{2+} signal from a physiological transient to a sustained plateau,[141] spreading from subcellular locales throughout the cytoplasm. By regulating kinase pathways such as CaMK, AMPK, and ERK, and influencing the activity of core transcription factors like SREBP, PPAR, and HIF-1α,[142] they induce lipid and glucose metabolic disorders in vascular cells. Simultaneously, they activate key signaling pathways including NF-κB and the NLRP3 inflammasome, driving endothelial dysfunction, inflammatory cell infiltration, foam cell formation, and plaque destabilization.[143] They are not parallel mechanosensors but form a complex interaction network involving upstream-downstream activation and mutual inhibition. Their bidirectional regulation with cell membrane lipid components further enriches the mechanistic landscape of mechanical force-mediated vascular pathology.

Natural products and small-molecule modulators targeting Piezo1/TRPV4 can suppress inflammation, inhibit foam cell formation, and stabilize atherosclerotic plaques by blocking pathological Ca^{2+} signals or regulating downstream inflammatory and metabolic pathways,[144–146] validating the axis as a promising therapeutic target for hypertensive atherosclerosis. Current research confirms that natural compounds can target Piezo1 and TRPV4 signaling axis, but several core questions remain. Future research should focus on: 1) Defining the molecular basis of Piezo1-TRPV4 physical co-localization in membrane microdomains. 2) Mapping the complete, cell-specific downstream signaling network using systems biology approaches[147,148] (eg, single-cell sequencing, phosphoproteomics) to understand how signals from both channels integrate. 3) Developing highly specific, non-toxic channel modulators that aim to "correct" the pathological Ca^{2+} signal pattern (dampening the sustained plateau) rather than completely blocking channel function, thereby preserving essential physiological roles. 4) Validating these therapeutic strategies in advanced in vivo models that recapitulate the complex hypertensive mechanical environment. The regulatory network of "mechanosensation-ion channel-calcium signal-metabolic inflammation-atherosclerosis" constructed in this review provides a new framework for mechanistic research on hypertension combined with atherosclerosis. In-depth analysis and targeted intervention of the Piezo1 and TRPV4 signaling axis hold promise for providing new theoretical foundations and clinical tools for the precise prevention and treatment of this disease.

Generative AI Statement

The authors declared that generative AI was not used in the creation of this manuscript.

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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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Disclosure

The authors declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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