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REVIEW

ATP-P2X7R-NLRP3 Axis as a Unifying Mechanism of ATP-Induced Cell Death in Degenerative Bone and Cardiovascular Diseases

Jingjing Zhang[1–3,*], Linzhu Li[4,*], Qianwen Guo[5], Xuesong Liu[6], Qian Qiao[1–3], Xuerui Ye[1–3], Hongyang Ding[1–3], Yi Liu[7], Kaikai Wang[8], Haoling Zhang[9], Lu Cheng[1–3]

[1]Fuwai Yunnan Hospital, Chinese Academy of Medical Sciences, Affiliated Cardiovascular Hospital of Kunming Medical University, Kunming, 650000, People's Republic of China; [2]Yunnan Provincial Cardiovascular Clinical Medical Center, Kunming, 650000, People's Republic of China; [3]Yunnan Provincial Cardiovascular Clinical Medical Research Center, Kunming, 650000, People's Republic of China; [4]Clinical College of Traditional Chinese Medicine, Gansu University of Chinese Medicine, Lanzhou, 730000, People's Republic of China; [5]School of Health Management, Gansu University of Chinese Medicine, Lanzhou, 730000, People's Republic of China; [6]Basic Medical College, Gansu University of Chinese Medicine, Lanzhou, 730000, People's Republic of China; [7]Department of Critical Care Medicine, The Second Afffliated Hospital of Kunming Medical University, Kunming, 650101, People's Republic of China; [8]College of Acupuncture-Moxibustion and Tuina, Gansu University of Chinese Medicine, Lanzhou, 730000, People's Republic of China; [9]Department of Biomedical Sciences, Advanced Medical and Dental Institute, Universiti Sains Malaysia, Kepala Batas, Penang, 13200, Malaysia

*These authors contributed equally to this work

Correspondence: Haoling Zhang; Lu Cheng, Email zhanghaolingedu@163.com; 17687176899@163.com

Abstract: Extracellular Adenosine triphosphate (ATP), acting as both an energy signal and damage-associated molecular pattern (DAMP), plays a critical role in the progression of degenerative bone diseases (DBD) and cardiovascular diseases (CVD). Through activation of purinergic receptors, particularly P2X7, ATP induces a cascade of events leading to ATP-induced cell death (AICD), characterized by calcium influx, mitochondrial dysfunction, oxidative stress, and inflammasome activation, culminating in pyroptosis, apoptosis, and ferroptosis. These processes are implicated in osteoarthritis (OA), intervertebral disc degeneration (IVDD), osteoporosis (OP), and cardiovascular conditions such as myocardial infarction and heart failure. The ATP-P2X7-NLRP3 axis emerges as a shared molecular mechanism linking these diseases, driven by energy imbalance and chronic inflammation. This review explores the molecular mechanisms of AICD in DBD and CVD, evaluates experimental and clinical evidence, and discusses potential therapeutic strategies targeting the ATP–purinergic–mitochondrial axis, offering insights into integrated treatment approaches for both disease types.

Keywords: ATP-induced cell death, purinergic signaling, P2X7 receptor, mitochondrial dysfunction, NLRP3 inflammasome, degenerative bone disorders, cardiovascular remodeling

Introduction

Degenerative bone diseases (DBD), including osteoarthritis (OA), intervertebral disc degeneration (IVDD), and osteoporosis (OP), have traditionally been regarded as localized musculoskeletal disorders. However, accumulating clinical and epidemiological evidence indicates that these conditions are frequently accompanied by cardiovascular complications, such as ischemic heart disease, myocardial remodeling, and heart failure. Patients with degenerative skeletal disorders exhibit increased cardiovascular morbidity and mortality, while CVD are often associated with accelerated bone loss, impaired bone remodeling, and elevated fracture risk. Despite this well-recognized clinical coexistence, the mechanistic basis underlying the interaction between DBD and cardiovascular disorders remains incompletely understood.

At the cellular and tissue levels, both skeletal and cardiovascular systems are continuously exposed to mechanical overload, metabolic stress, hypoxia, and inflammatory stimuli. These shared stress environments profoundly disrupt energy homeostasis and mitochondrial function, promoting chronic low-grade inflammation and progressive tissue degeneration. In this context, extracellular adenosine triphosphate (ATP) has emerged as a critical danger-associated signal released in response to tissue injury, ischemia, hypoxia, and sustained mechanical stress. ATP signaling, mediated

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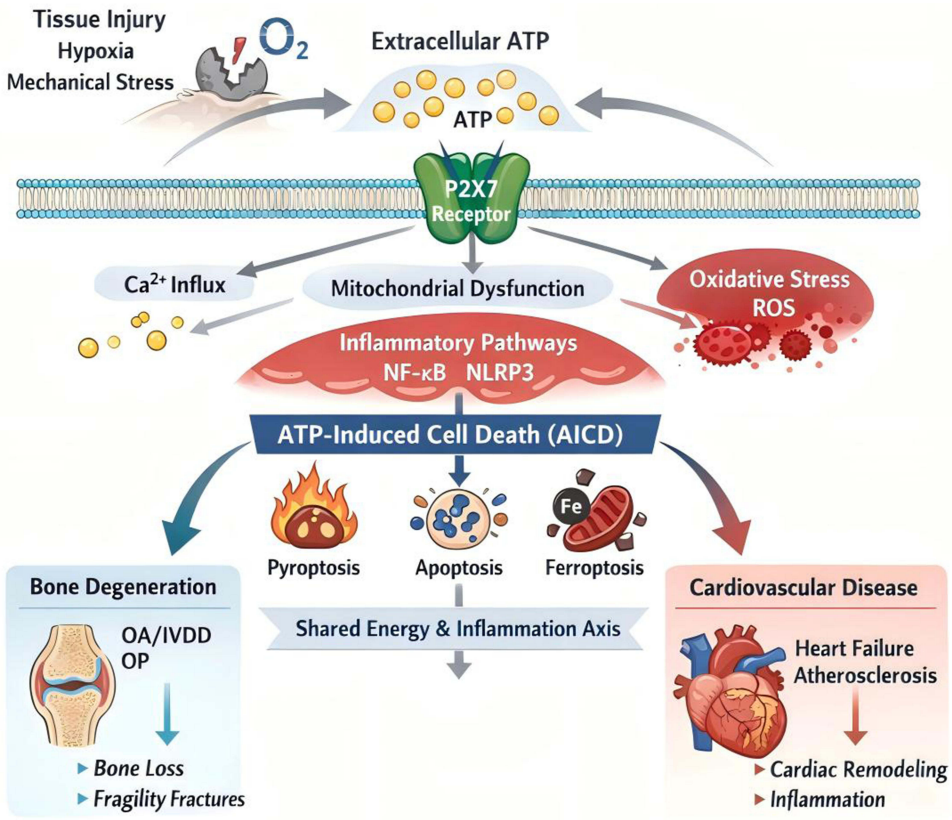
Graphical Abstract



by purinergic purinergic receptors (P2X and P2Y), plays a fundamental role in immune regulation, bone metabolism, neuroinflammation, and tissue regeneration.[1–3] Importantly, the cellular response to extracellular ATP is highly context dependent and varies across cell types and disease states.

Under physiological conditions, purinergic signaling is tightly regulated through a coordinated network of receptors and ectonucleotidases, allowing ATP to participate in adaptive calcium signaling, metabolic regulation, and tissue repair. Experimental studies have demonstrated that ATP signaling can be modulated by multiple regulatory mechanisms, including caveolin-1–mediated suppression of ATP-induced inflammasome activation and pyroptosis in macrophages,[1] as well as stem cell factor–dependent control of ATP-related mast cell activation thresholds in peripheral tissues.[2] In bone metabolism, the P2X7 receptor has been shown to regulate osteoclast differentiation and cytoskeletal stability via Ca^{2+}–mitogen-activated protein kinase (MAPK) signaling, implicating purinergic pathways in skeletal homeostasis and aging-related tissue degeneration.[3,4] These observations highlight the essential physiological roles of ATP signaling while underscoring the necessity of precise regulatory control.

When regulatory buffering mechanisms fail, sustained extracellular ATP accumulation can drive maladaptive cellular responses. In degenerative bone and cardiovascular tissues, excessive ATP exposure perturbs calcium homeostasis, impairs mitochondrial function, and amplifies oxidative stress and inflammatory signaling. Recent studies have suggested that these processes converge on a regulated form of cell death driven by persistent energy imbalance, rather than by acute nonspecific membrane injury. This process, referred to here as ATP-induced cell death (AICD), is characterized by coordinated activation of calcium overload, mitochondrial dysfunction, reactive oxygen species (ROS) accumulation, and inflammasome signaling, ultimately engaging multiple programmed cell death modalities, including pyroptosis, apoptosis, ferroptosis, and dysregulated autophagy. To clarify how extracellular ATP drives distinct cellular outcomes under

different exposure patterns, Table 1 summarizes ATP-associated response features ranging from transient ATP cytotoxicity to sustained AICD, and further to chronic programmed cell death phenotypes. These distinctions highlight that persistent ATP–P2X7 signaling and mitochondrial dysfunction are key determinants of degenerative tissue injury.

Evidence supporting the existence of AICD has independently emerged across diverse disease models. In musculoskeletal tissues, ATP-driven purinergic signaling contributes to chondrocyte apoptosis, extracellular matrix degradation, cellular senescence, and disruption of tissue homeostasis in OA, IVDD, and OP.[5–7] In the cardiovascular system, ATP accumulation and purinergic receptor activation promote myocardial inflammation, mitochondrial injury, and structural remodeling during ischemia–reperfusion injury, metabolic cardiomyopathy, myocardial fibrosis, and heart failure.[8–11] Although the downstream pathological manifestations differ between skeletal and cardiovascular tissues, these studies collectively point to a conserved upstream mechanism linking energy stress to inflammatory cell death.

Based on this body of evidence, we propose that AICD represents a shared energy–inflammation amplification axis bridging DBD and cardiovascular disorders. Rather than acting as a disease-specific trigger, AICD functions as a pathological integrator that translates unresolved metabolic and mechanical stress into progressive tissue degeneration across multiple organ systems. This framework provides a mechanistic explanation for the frequent clinical coexistence of skeletal degeneration and cardiovascular disease and suggests that targeting ATP-driven purinergic dysregulation may offer novel opportunities for integrated therapeutic intervention.

In this review, we systematically summarize the molecular mechanisms underlying AICD, focusing on purinergic signaling dynamics, mitochondrial dysfunction, oxidative stress, and inflammasome activation. We critically examine experimental and translational evidence supporting the role of AICD in DBD and cardiovascular disorders and discuss emerging biomarkers and therapeutic strategies targeting the ATP–purinergic–mitochondrial axis. By framing AICD as a unifying pathological mechanism, this review aims to provide new conceptual insights into multisystem degenerative diseases and to inform future precision therapeutic approaches.

AICD: Concept and Mechanisms

The Distinction Between ATP Cytotoxicity and AICD

High concentrations of ATP outside of cells may directly compromise plasma membrane integrity, ionic homeostasis, and induce acute stress responses. Damage caused by ATP—known as ATP cytotoxicity—does not satisfy the requirement for programmed cell death. Conversely, AICD's initiation depends on either purinergic receptors or intracellular signaling pathways and emerges via more clear-cut death modalities, pyroptosis, apoptosis, and ferroptosis. The regulatory mechanisms and biological characteristics therefore differ between the two processes.

Studies featuring AICD are now taking place in a variety of biological systems. In the nervous system, the organelle-specific γ-secretase-generated AICD from mitochondria interacts with Aβ, leading to mitochondrial dysfunction in

Table 1 ATP-Induced Cell Fate Outcomes in Degenerative Diseases

ATP Characteristics	Cellular Response	Cell Fate	References
Transient High ATP Concentration	Exogenous ATP induces acute ion imbalance and increased membrane permeability	Acute Cell Death (ATP Cytotoxicity)	[1–3]
Sustained High ATP Concentration	Persistent ATP presence, activation of P2X7, continuous Ca^{2+} influx, mitochondrial membrane potential decline	ATP-Induced Cell Death (AICD)	[4–6]
Chronic ATP-Induced Damage	Long-term ATP-induced chronic stress, Ca^{2+} and ROS accumulation, immune system activation	Programmed Cell Death (Including Apoptosis, Pyroptosis, Ferroptosis)	[7–10]
ATP-Induced Inflammatory Pathway Activation	ATP activates inflammatory pathways eg, NLRP3, NF-κB, release of inflammatory cytokines	Pyroptosis and Apoptosis	[11–13]
Clinical ATP and P2X7 Receptor Binding	Interaction between ATP and P2X7 receptor, membrane damage induces Ca^{2+} influx, leading to endogenous damage	ATP-Driven Tissue Pathological Cell Death	[14–16]
High ATP-Induced Bone and Cardiac Cell Damage	Activation of P2X7 receptor in bone/cardiac cells, interaction with CD39/CD73	ATP-Induced Bone Loss and Cardiac Remodeling	[17,18]

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neurons and causing injury in Alzheimer's disease.[12] The surface exposure of calreticulin on SBC-3 cells and ATP release in tumor cells indicates features of immunogenic cell death.[14] ATP may also control extracellular signal-regulated kinase (ERK) signaling via P2Y receptors to bring SAS cells to S-phase arrest; therefore, exhibiting some antitumor activity.[15] Regulation of immune homeostasis has a key role in purinergic. In liver ischemia-reperfusion injury (IRI), double negative T cells (DNT cells) use cluster of differentiation 39 (CD39) and adenosine A2A receptor (A2AR) signalling to keep a functional balance. Strategies that target and enhance this pathway may serve as a practical approach for rectifying innate immune dysregulation.[16] Iron metabolism disorders have been implicated in DBD and such diseases may involve with AICD. Bovine colostrum antibodies (BCA) reduces lipid peroxidation and iron-dependent damage by inhibiting transferrin receptor 1 (TfR1), activating ferroportin (FPN), and modulating the nuclear factor erythroid 2-related factor 2 (Nrf2)/system Xc^-/glutathione peroxidase 4 (GPX4) pathway. The action of an enzyme serves as a regulator of iron in an individual suffering from OA.[17] The growth of databases on antimicrobial peptides (AMPs) related to marine organisms is also important for the study of cell death and the development of new active molecules.[18]

In general, ATP cytotoxicity can be viewed as a chemical disruption but AICD is signal-dependent and can be regulated. Consequently, degenerative disease-related AICD holds more mechanistic significance than a cancer- or immune-related injury-associated AICD.

Molecular Mechanisms of AICD

The physiological functions of AICD are mediated by purinergic receptors, especially P2X7 receptor. High ATP levels rapidly open this receptor to cause Ca^{2+} influx and disturb cellular ionic homeostasis. These occurrences cause a dip in mitochondrial membrane potential that raises ROS generation and therefore causes an energy crisis. This causes the activation of effector pathways downstream—such as Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), MAPK, and the NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome—which together comprise the AICD main molecular platform. The same mechanisms recur in degenerative tissue injury and chronic inflammation.

Studies from different systems will show converging signaling features. Electroacupuncture alleviates cognitive impairment by downregulating P2X7R in an ischemic brain injury model, reducing ROS and inflammatory cytokines. The altered Nrf2 and NLRP3 expression affirms the neuroprotective therapeutic potential of targeting P2X7R.[19] In retinal tissues, activation of both exchange protein directly activated by cAMP 1 (Epac1) and protein kinase A (PKA) can suppress ROS-driven NLRP3 activation, thus alleviating inflammatory response;[20] P2X7R antagonists can also mitigate inflammation and neovascularization, while maintaining retinal function via modulation of the NLRP3 and NF-κB pathways.[21] Sen A, owing to its capability to inhibit caspase-1 and to block the NLRP3 and absent in melanoma 2 (AIM2) working through P2X7-dependent regulation of inflammasomes, could be a potential candidate compound which inhibits inflammasomes.[22] In the cardiovascular system, the ATP–P2X7–NLRP3 axis activated by sympathetic neural activity matches different injury features of heart failure with preserved ejection fraction (HFpEF). So, it has been recognized as a valid mechanism in HFpEF. Both renal denervation and the inhibition of vascular signaling have been proven to improve the ventricular remodeling and diastolic dysfunction.[23] Therefore, it makes sense to use these treatments to remedy these conditions. Research has demonstrated that dexamethasone (DEX) can diminish oxidative stress and relieve acute renal damage through silencing the P2X7R/NF-kB/NLRP3 pathway.[24] Myocarditis models show that palmitoylethanolamide (PE) binding to P2X7R inhibits NLRP3 and phosphatidylinositol 4,5-bisphosphate (PIP2) and MAPK signaling to exert strong anti-inflammatory effects.[25] Moreover, P2X7R activation can trigger specific secretory responses. This includes a rapid Ca^{2+}-dependent apical secretion of interleukin 6 (IL-6) from retinal pigment epithelium (RPE) cells. This response might contribute to local inflammation regulation.[26] Studies show that host protection has a novel way through the regulatory effects of diphenyleneiodonium (DPI). The leakage of ATP by tensioned connexin 43 (CX43) involves antibacterial defence.[27] The molecular mechanisms in detail are shown in Figure 1.

A central cascade of ATP–P2X/P2Y receptor activation, Ca^{2+} influx, mitochondrial dysfunction, and excessive ROS generation is at the core of the molecular network of AICD, which in turn converges on important inflammatory and cell-death pathways, such as the inflammasome, NF-κB and MAPK. The P2X7 receptor is seen at various regulatory sites across this continuum, thereby creating a high-value pathological axis in different forms of chronic tissue injury and degenerative disease.

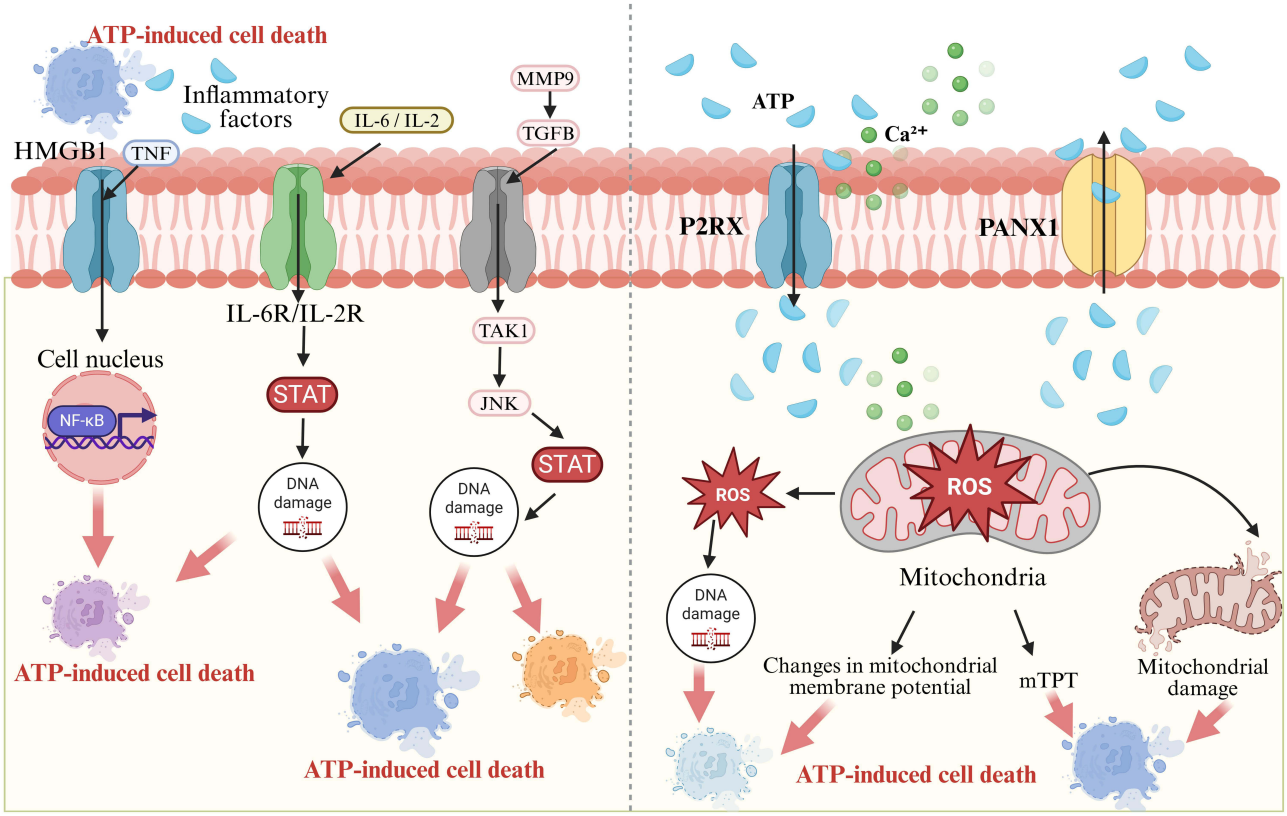

Figure 1 Schematic representation of the core molecular mechanisms underlying AICD. The abnormal elevation of extracellular ATP is first sensed by the purinergic receptors, notably the P2X7R that leads to calcium influx and ionic disturbance. Mitochondrial membrane potential starts to decline, indicating mitochondrial dysfunction and excess ROS generation at first. The upstream disturbance then activates downstream effector pathways, such as NF-κB, MAPK, and the NLRP3 inflammasome, leading to the release of inflammatory cytokines like IL-1β and TNF-α, causing DNA damage and driving multiple forms of programmed cell death (apoptosis, pyroptosis or necroptosis). This diagram correlates with the AICD core cascade noted in Molecular Mechanisms of AICD, which is the ATP–P2X or P2Y receptor activation, calcium influx, mitochondrial dysfunction, ROS amplification, inflammation, and cell death.

Role of AICD in DBD

Consistent with the mechanistic framework described above, Table 2 summarizes major ATP–P2X7-centered signaling cascades implicated in DBD, including the IRE1–mTOR–PERK axis and the NF-κB/NLRP3 pathway. Together, these pathways converge on Ca^{2+} overload, mitochondrial stress, inflammasome activation, and downstream cartilage/bone degeneration.

OA

The chondrocytes' disturbed energy metabolism combined with the local inflammatory response becomes a major pathogenic basis for OA. An abnormal buildup of ATP in the microenvironment of joints can activate P2X7R, resulting in calcium dysregulation, mitochondrial dysfunction and excessive production of mitochondrial ROS. AICD phenotype, which enhances extracellular matrix (ECM) breakdown and chondrocyte senescence, is induced by these upstream disturbances due to release of inflammatory cytokines by IL-1β and tumor necrosis factor-alpha (TNF-α).

The P2X7R–inflammasome pathway is central to arthritis tissue degeneration. Recent studies show this. Quercetin inhibits transient receptor potential vanilloid 1 (TRPV1) and alters the P2X7/NLRP3 pathway to cause macrophage phenotypic switching from classical activation macrophages 1 (M1) to alternative activation macrophages 2 (M2), thereby slowing cartilage degeneration.[57] The benefits of exercise on OA also require P2X7 and their downstream pathways, we also know that the duration and intensity of exercise canmaterially modulate inflammatory responses.[28] In temporomandibular joint OA, pannexin 3 (Panx3) assists with ATP release from the cell and subsequent activation of P2X7R which enhances inflammatory signals and causes matrix degeneration.[40] OA-associated AICD also apparently involves the regulation of pyroptosis. Baicalin reduces chondrocyte damage via tripartite motif containing 24 (TRIM24) regulation of the NLRP3/caspase-1 pathway.[58]

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Table 2 Associations Between AICD Signaling Pathways and DBD

Signaling Pathway	Key Molecules	Cellular Effects	Relevance to DBD	References
P2X7–IRE1–mTOR–PERK Axis	ATP, P2X7, IRE1, PERK	ATP-Induced Ca^{2+} Influx Promotes Early Autophagy and Late-Stage Apoptosis	Closely Associated With the Onset and Progression of OA	[28]
HMGB1–RAGE–TGF-β1/SMAD3	ATP, IL-1β, IL-18, HMGB1, RAGE, SMAD3	ATP-Induced Macrophage Pyroptosis Releases InflammatoryCytokines, Driving Fibroblast Activation and Fibrotic Remodeling	Promotes Synovial Fibrosis inKOA	[29]
P2X7 Receptor–Mediated AICD Pathway	P2X7 Receptor, Caspase-3/7, PGE2	Apoptosis, LDH Release, and Inflammatory Responses	Chondrocyte Death and the Development of OA	[30]
P2X7R–NF-κB/NLRP3 Pathway	P2X7R, NF-κB p65, NLRP3, Caspase-1, IL-1β	Pyroptotic Inflammation, Increased ROS, and Matrix Degradation	ATP–P2X7–Driven Cartilage Degeneration in OA	[31]
Mechanical Overload Activates the ATP/P2X7 Axis	ATP and the P2X7 Receptor	ATP Promotes Osteoclast Differentiation	Peri-implant Bone Loss and Prosthesis Loosening	[32]
ATP–P2X7–IL-1β–NETs Axis	ATP, P2X7R, IL-1β, NETs	ATP-Induced Inflammation and Cell Death	N-BPs–Associated Osteonecrosis of the Jaw	[33]
ATP–P2X7–Ca^{2+}–IRE1/mTOR/PERK Axis	P2X7, Ca^{2+}, IRE1, PERK, mTOR	ATP-Induced Autophagy Provides Early Cytoprotective Effects Followed by Stress-Induced Apoptosis at Later Stages	Regulation of OA Progression and Therapeutic Potential	[34]
ATP–P2X7R–Caspase-1 Pathway	P2X7R, Caspase-1, rs3751143	ATP Regulates Osteoclast Apoptosis	Increased Susceptibility to OP	[35]
ATP–P2X7R Signaling Pathway	P2X7R −762C>T and 489C>T	Mediates Cell Death and Bone Lesions	Increases Susceptibility to Spinal Tuberculosis	[36]
ATP–P2X7R Signaling Pathway	P2X7R Knockout Model	Regulates Osteoclast Survival and Activity	Promotes Estrogen Deficiency–Induced Bone Loss	[37]
ATP–P2X7R Receptor Signaling Pathway	P2X7 Receptor (Activated by BzATP)	Induces Macrophage Inflammatory Cytokine Release	Inflammation-Related Bone Destruction in Ankylosing Spondylitis	[38]
ATP–P2X7–AMPK–mTOR Axis	P2X7, AMPK, NLRP3	ATP-Dependent Enhancement of Autophagy, Inflammasome Degradation, and Suppression of Pyroptosis	Mitigation of OA-Related Pathological Damage	[39]
Panx3–ATP–P2X7R/NLRP3 Axis	Panx3, P2X7R, NLRP3	ATP-Mediated Inflammation and Matrix Degradation	ATP–P2X7R–Driven Progression of TMJOA	[40]
ATP–P2X7/PI3K–Akt–GSK3β Axis	P2X7, PI3K, Akt, GSK3β	ATP-Induced Osteoclast Differentiation and Bone Resorption	Bone Mass Reduction and Bone Loss in OP	[41]
ROS/Mitochondrial Function–ATP Metabolic Pathway	KLF2, SIRT1, GPX4, MT-ATP6	Inhibition of Ferroptosis and Enhancement of ATP Production	Delays Cartilage Degeneration and Slows OA Progression	[42,43]
LPS/ATP–Inflammasome–Pyroptosis Axis	HIF-1α and GSDMD	Pyroptosis of Fibroblast-like Synoviocytes	Synovial Fibrosis in KOA	[44]
LPS/ATP–Inflammasome–Pyroptosis Axis	Caspase-1 and GSDMD	Pyroptosis of Synovial Macrophages	Synovitis and Fibrosis in KOA	[45]
ATP–P2X7 Receptor–Inflammasome Pathway	P2X7, IL-1β, IL-17, Foxp3	Calcium Signaling Disruption and AICD	Th17/Treg Imbalance Promotes OA Progression	[46,47]

P2X7–NF-κB Signaling	ATP, P2X4R, P2X7R	ATP Promotes Degranulation and Upregulation of Inflammatory Mediators	Alleviation of Inflammation and Pain in OA	[48,49]
ATP–P2X7/IL-17–JAK–STAT3Axis	ATP, P2X7R, IL-17, MCP-1	ATP Drives Th17-Mediated Inflammation and Induces Cell Death	Exacerbation of Inflammatory Responses in OA	[50,51]
LPS/ATP–Nrf2/NLRP3 and PGC-1α/Δψm signaling axis	PPAR-γ, NLRP3, and PGC-1α regulatory pathways	ATP-induced pyroptosis in chondrocytes	OA cartilage degeneration and arthritis progression	[52]
p53/p21–NLRP3–Caspase-1 pathway	p53, p21, NLRP3, and Caspase-1	ATP-induced pyroptosis and apoptosis	Accelerates OA cartilage damage and disease progression	[53]
ATP–SQSTM1/PKM2–autophagy pathway	SQSTM1, PKM2, and IL1B	Inhibits the maturation and release of inflammatory cytokines	Improves OA synovitis and gait function	[54]
LPS/ATP–NLRP3 inflammasome pathway	NLRP3, IL-1β, and IL-18	ATP-induced inflammasome activation	Promotes inflammatory progression of KOA	[55]
ATP–P2X4/P2X7–PAR2 pathway	P2X4, P2X7, PAR2, and tryptase	ATP-induced mast cell degranulation	Promotes OA-associated pain and inflammation	[56]
NLRP3 inflammasome signaling pathway	NLRP3, ATP, and IL-1β	ATP-induced inflammatory activation	Promotes OA progression	[55]

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Conversely, increasing research has shown the driving role that mitochondrial stress plays in AICD. Sirtuin 4 (Sirt4) overexpression promotes mitophagy, mitochondrial function, and chondrocyte senescence delay;[59] methyltransferase Like 1 (METTL1)/7-methylguanosine (m^7G)/mitochondrial tRNA-derived fragment 3b-leucine tRNA TAA (mt-tRF3b-LeuTAA) axis suppresses autophagy and worsens mitochondrial dysfunction, which accelerates cartilage degradation and offers a target for OA intervention.[60] The compound judatin has been believed to reduce pathological changes to cartilage by increasing mitochondrial membrane potential and exhibiting antioxidant effects via SIRT3/superoxide dismutase 2 (SOD2)/mitochondrial reactive oxygen species (mtROS) pathway modulation and was identified through high-content screening (HCS).[61] circPAFAH1B2 reduces caseinolytic peptidase B (ClpB) activity in a manner that depends on the translocation of mitochondria. This promotes mitochondrial damage and cartilage degradation and facilitates a mechanism of organelle regulation in OA.[62] Acetylshikonin A VI (ASA VI), which is derived from Clematis, helps reduce endoplasmic reticulum (ER) stress and damage to mitochondria through the AMP-activated protein kinase (AMPK)–SIRT3 pathway. Through this pathway ASA VI reduces chondrocyte apoptosis, which refers to programmed cell death. In addition, it helps maintain the organization of cartilage.[63] The intermittent knee pain experienced in OA may be due to signal amplification of mast cells involving PAR2 and ATP with respect to pain mechanisms. Intra-articular transplantation of BMMCs has been used to study molecular pathways involved in OA pain.[56]

AICD has high consistency of molecular features between inflammation maintenance, cartilage degradation and pain generation via the ATP–P2X7R–inflammasome–mitochondrial injury axis in OA. The various methods assist with the advancement of therapies with this idea in mind.

Intervertebral Disc Degeneration (IVDD)

Due to ischemia, hypoxia, and nutrient deprivation within the intervertebral disc, nucleus pulposus (NP) cells are subjected to a state of persistent metabolic stress, which induces them to efflux ATP and disrupts energy homeostasis. All these conditions ultimately favor the emergence of AICD. Under high concentrations of extracellular ATP, excessively activated P2X7R in the NP cells causes prolonged Ca^{2+} influx and decreased mitochondrial membrane potential which in turn causes ROS production, secretion of inflammatory mediators and the development of a programmed cell death phenotype. Eventually these events lead to a decline in ECM and loss NP cells. This purinergic signalling is now known to be at the centre of the IVDD.[64,65] Mitochondrial homeostatic impairment in patients could lead to disease. BNIP3 is essential for mitophagy regulation and energy metabolism maintenance. Its impairment aggravates mitochondrial damage and accelerates the progression of IVDD.[66] In the intervertebral disc where hypoxic conditions predominate, hypoxia-inducible factor 1-alpha (HIF-1α) exerts protective effects by decreasing mitochondrial ROS production, alleviating metabolic disorder and lowering NP cell apoptosis, thus aiding in the maintenance of NP homeostasis.[67,68] NP cells heavily rely on glycolytic activity; when it gets inhibited, it sabotages energy supply and cellular physiology. As a result, it is thought that lactate dehydrogenase A (LDHA) could be a target in IVDD for energy metabolism regulation.[69] Methods to fix mitochondrial injury have also been expanded. The drug BSHXF can improve the function of mitochondria by increasing autophagic flux and reducing excess ROS via the AMPK/SIRT1 axis. In this case, the drug has the potential to prevent the degradation of extracellular matrix and apoptosis induced by TNF-α. After treatment with 3-methyladenine (3-MA) or AMPK inhibitors, its protective effects were lost, indicating a proper level of autophagic activity is essential for alleviating IVDD.[70]

Overall, the ATP–P2X7R–mitochondrial injury axis forms a highly coherent pathological cascade in IVDD, encompassing ATP metabolic imbalance, Ca^{2+} overload, ROS amplification, inflammatory activation, and ECM degradation. As we keep investigating how purinergic signaling regulates disc metabolism, we will develop a more comprehensive theoretical framework that accounts for its simultaneously inflammatory and metabolic effects in IVDD.

OP

Bone cells are incredibly sensitive to ATP, which contributes to the development of OP. Bone tissue has an elevated ATP level that can control the survival of osteoblasts and osteocytes via purinergic receptors, and it can also affect osteoclast activation, thus disturbing the balance in bone-remodeling process. P2X7R is a regulatory node of this process and its inhibition preserves bone and periodontal tissue structure, which could be exploited for the treatment of pathologies

associated with excessive bone resorption.[71] ATP regulation focuses significantly on osteoblasts. Increased transforming growth factor beta 1 (TGF-β1) levels upregulate pannexin1 and enhance its channel activity, causing osteoblast apoptosis in an ERK-dependent manner, suggesting that regulation of ATP efflux contributes to the impaired bone formation.[72] Moreover, ATP-P2X4 signalling has also been demonstrated to be important for the maintenance of mature plasma cells by PANX3 in the bone marrow niche which underlies the functional role of ATP in immune-bone metabolic coupling.[73] ATP regulation of mechanosensitivity of osteocytes is quite significant as well. Mechanosensitivity is an expression of the degree to which a tissue or organism responds to mechanical stimuli, which can be either a toxicity or a benefit depending on the circumstances. Key regulators of mechanosensitivity are water and cytoskeleton structural calcium and the autonomic and sensory nervous systems and hormones.[74,75] Osteogenic differentiation is governed by ATP as a metabolic regulator. Calcium oscillations caused by ATP operating in the cell environment activate AMPK-associated oxidative metabolism to induce osteogenic differentiation and increases metabolic efficiency.[76] There has been growing attention to immune-derived purinergic regulation. ApoEVs from T cells enriched with CD39 and CD73 can hydrolyze ATP to adenosine and promote bone regeneration via the adenosine A2B receptor (A2BR)–PKA signaling pathway. Related analyses suggest that this mechanism may be useful for tissue repair strategies in OP.[77] P2X7R enhances osteoclastic differentiation and bone resorption by activating PI3K-Akt-glycogen synthase kinase 3 beta (GSK3β) signaling pathway in osteoclasts, suggesting that ATP-P2X7R signaling plays an important positive role in the bone resorption under a low bone mass condition.[41]

ATP regulates osteogenesis and osteocyte survival in bone formation while inhibiting osteoclast activity and modulating immune signaling in bone resorption. Through P2X and P2Y receptors, it can maintain skeletal metabolic homeostasis, and contributes to various disease and injury biology. The AICD associated pathways in the progression of OP provide a mechanistic basis for intervention to modulate bone remodelling and prevent bone loss.

When viewed as a whole system, AICD is a conserved injury axis seen across OA, IVDD, and OP. The death of chondrocytes, NP cells, and osteogenic/bone-resident cells takes place through the abnormal accumulation of ATP, activation of P2X/P2Y receptors, Ca^{2+} overload, mitochondrial malfunction, and excess production of ROS. Although the three diseases arise from variances in their cellular origins and pathological endpoints, AICD is the common link that connects energy metabolic dysregulation, inflammatory amplification, and tissue degeneration. As illustrated in Figure 2, this cross-tissue shared mechanism integrates the major AICD-related cell types and injury phenotypes observed in OA, IVDD, and OP, providing a conceptual framework for understanding the mechanistic continuity underlying skeletal degenerative disorders.

Translational Perspectives

From a translational standpoint, Table 3 provides an overview of representative biomarkers and therapeutic candidates targeting ATP-driven inflammatory cell death in DBD. These strategies collectively aim to suppress excessive purinergic signaling, restore metabolic homeostasis, and block inflammasome-associated degeneration.

Biomarkers

The continuous activity of AICD in skeletal degenerative conditions makes the state of ATP, its degradation products and the expression of purinergic receptors a pathological feature. Abnormal elevations in peripheral blood ATP concentrations and upregulation of P2X7R involvement are often associated with mitochondrial dysfunction, inflammasome activation and tissue damage. These molecular changes are important for understanding how the disease is progressing.

A new dimension to biomarker development has come from research centred on metabolic stress. Curcumenol enhances metabolic balance in knee osteoarthritis (KOA) cartilage by upregulating lysine demethylase 6 (BKDM6B) as well as reducing histone H3 lysine 27 (H3K27) methylation. This regulatory axis provides the ability to indicate both the energetic and epigenetic status of cartilage.[107] The release of IL-1β, IL-18, and high mobility group box 1 (HMGB1) due to macrophage pyroptosis in the milieu of synovitis could activate the HMGB1–receptor for advanced glycation end-products (RAGE) axis and stimulate TGF-β1/SMAD family member 3 (SMAD3) pathway in relation to degree of fibrosis. These pyroptosis-related factors may serve as important biomarkers for the pathological progression of synovial disease.[29] After the research, the team found that β-hydroxybutyrate activates mitophagy through the hydroxycarboxylic

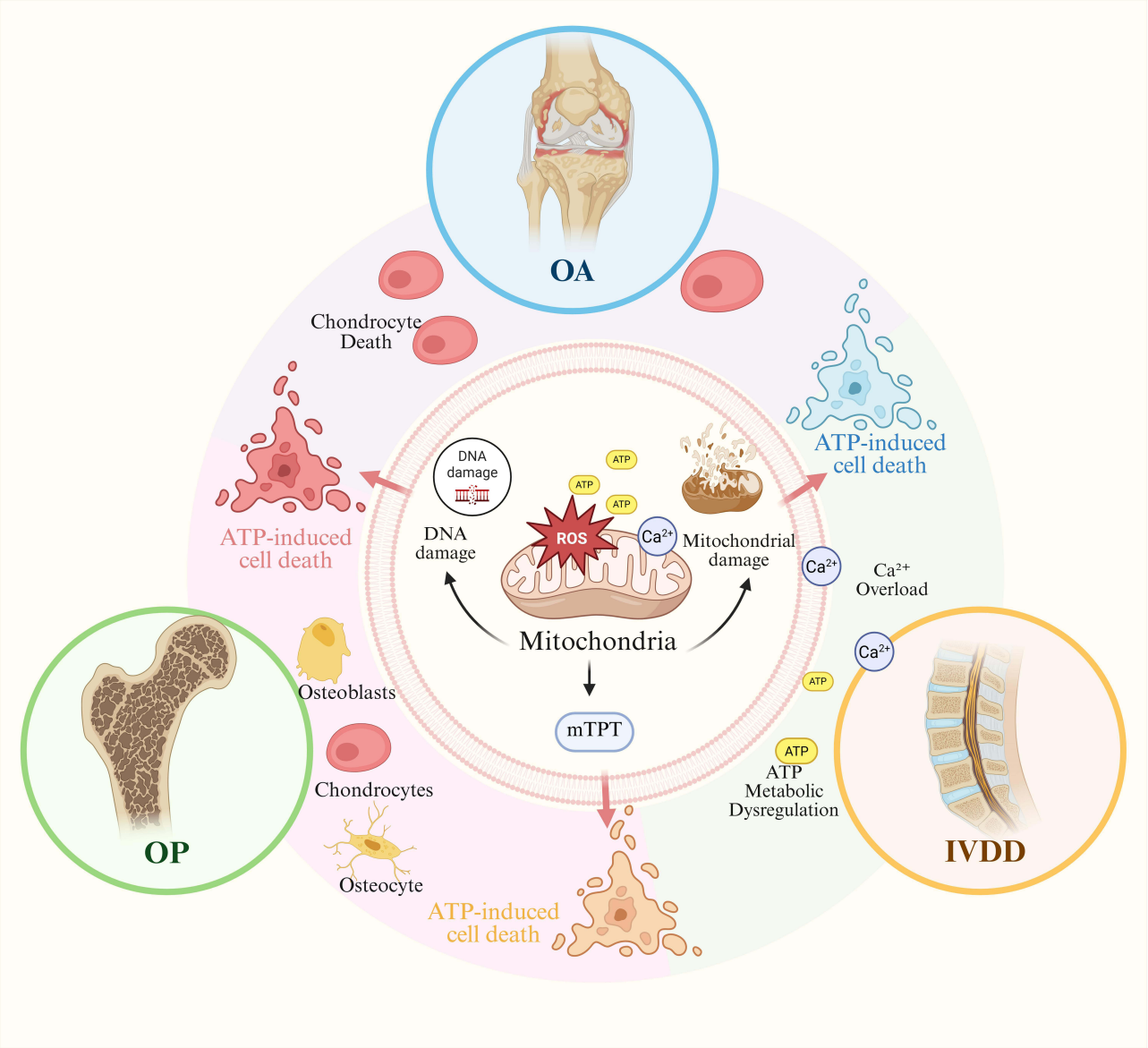

Figure 2 Shared mechanisms and disease-specific features of AICD in degenerative bone disorders. The abnormal accumulation of extracellular ATP activates the purinergic receptors, causing the influx of Ca^{2+}, the decline in mitochondrial membrane potential, and the excess generation of ROS. This leads to DNA damage and several types of programmed cell death. This central feature is shared between OA, IVDD and OP — namely, that chondrocytes, NP cells, and osteocytes are altered under intensified ATP signalling and mitochondrial damage, although they have differing tissue origins and pathology. The diagram highlights how AICD is implicated in the immune–metabolic imbalance of skeletal tissues in these three degenerative bone conditions as it integrates the common AICD cascade and the specific death phenotypes of varying cell types.

acid receptor 2 (HCAR2)/AMPK/PTEN-induced kinase 1 (PINK1)/Parkin pathway. Also, changes in activity showed mitochondrial homeostasis is reflective of chondrocytes. β-Hydroxybutyrate is a potential metabolic biomarker for OA.[108] Multi-omics analyses revealed increased expression of CD14 and colony stimulating factor 1 receptor (CSF1R) in OA and other inflammatory disorders; their upregulation in OA cartilage shows higher specificity. The results provided new insights to stratifying inflammatory phenotypes.[109] The decrease in alpha-ketoglutarate (α-KG) in OA cartilage is associated with impaired mitophagy and increased oxidative stress, whereas restoring α-KG levels can improve degenerative cartilage phenotypes. These results suggest the potential of α-KG as OA biomarker.[110] NLRP3-driven pyroptotic signaling enhances ROS amplification and cartilage degradation in TMJ Osteoarthritis (TMJOA), with its activation intensity closely related to the degree of local tissue damage.[111] Furthermore, the increased expression of

Table 3 Potential Translational Applications of AICD in DBD

Category	Representative Biomarkers/ Drugs	Mechanistic Actions/Mechanism of Action	Clinical or Translational Prospects	References
P2X7-mediated cell death	P2X7 antagonists and PLA2/COX-2 inhibitors	ATP activates P2X7 → Ca^{2+} influx → caspase activation → PGE_2 release	A potential therapeutic target for intervening in OA-related cartilage damage	[30]
Macrophage pyroptosis	Caspase-1 inhibitor Ac-YVAD-CMK and caspase-1/GSDMD siRNA	LPS+ATP activates NLRP3 → caspase-1/GSDMD → IL-1β and IL-18 release → synovitis and fibrosis	Inhibition of pyroptosis alleviates inflammation and fibrosis in KOA	[78]
Pyroptosis	HIF-1α, NLRP1/NLRP3, and GSDMD	LPS/ATP-induced FLS pyroptosis leading to fibrosis	Targeting HIF-1α or GSDMD ameliorates KOA	[44]
ATP–P2X7–mediated chondrocyte apoptosis	ATP/BzATP, A740003, and rapamycin	ATP–P2X7 activates the IRE1–mTOR–PERK pathway	Regulates autophagy and apoptosis to delay OA progression	[28]
ATP–P2X7–mediated pyroptosis	BzATP, A740003, and CY-09	ATP activates P2X7R to trigger the NF-κB/NLRP3 pathway	A potential therapeutic target for blocking inflammation in OA	[31]
OP	P2X7R rs3751143 SNP	ATP-induced differences in caspase-1 activity affecting osteoclast apoptosis	A genetic susceptibility marker for OP	[35]
ATP-induced inflammatory cell death	Panx3 and P2X7R antagonists	Panx3 promotes ATP efflux to activate P2X7R-mediated inflammation	Targeting Panx3/P2X7R to delay disease progression	[40]
ATP-driven inflammatory cell death	ATP–P2X7R/NLRP3/IL-1β	ATP activates P2X7R to trigger inflammasome activation	Targeting the ATP–P2X7R axis as a therapeutic strategy for IVD degeneration	[64]
ATP-induced pyroptotic cell death	Acetyl zingerone	ATP activates NLRP3, while AZ enhances PINK1/Parkin-mediated	A potential candidate for OA prevention and therapy	[79]
ATP-induced macrophage pyroptosis	HMGB1 and RAGE inhibitors	ATP-triggered pyroptosis releases HMGB1 to activate SMAD3	Targets for intervening in synovial fibrosis progression in KOA	[29]
ATP–P2X7/NLRP3–mediated cell death	Quercetin	Inhibits the TRPV1–ATP release–P2X7/NLRP3 pathway	Delays OA progression and modulates macrophage polarization	[57]
miRNA-based modulation of the ATP–P2X7 pathway	miR-150 mimics/inhibitors	Suppresses ATP–P2X7–NF-κB–mediated inflammatory apoptosis	miR-150 as a therapeutic candidate for IVDD	[80]
ATP-induced inflammatory cell death	Curcumin	Inhibits LPS/ATP-induced NLRP3 inflammasome activation	Delays OA inflammation and disease progression	[81]
ATP-induced macrophage death	Chrysin and HMGB1	LPS/ATP activates the HMGB1/RAGE/PI3K/AKT pathway	Mitigates KOA-related tissue damage and sensitization	[47,82]
ATP-induced death of macrophages and microglia	Astragalus polysaccharides(APS) and TXN	ATP activates the P2X7–ASK1/p38 apoptotic pathway	Improves OA-related cartilage damage	[83,84]
Articular cartilage senescence/ apoptotic loss of immune T cells	HDAC3, Parkin, and the P2X7 receptor	HDAC3 modulates Parkin acetylation and P2X7 expression, thereby promoting AICD	Restoring HDAC3 activity or inhibiting P2X7 may delay OA progression	[85,86]
ATP-induced inflammation/ pyroptosis	Punicalin and loganin	Inhibits ATP-mediated ROS–NLRP3-dependent pyroptosis	Delays the progression of DBD	[87,88]
ATP–NLRP3–mediated pyroptosis	Degrasyn and KM	Inhibits ATP-induced activation of NLRP3/GSDMD	Alleviates synovitis and cartilage degradation	[89,90]

(*Continued*)

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Table 3 (Continued).

Category	Representative Biomarkers/ Drugs	Mechanistic Actions/Mechanism of Action	Clinical or Translational Prospects	References
ATP-induced inflammasome activation	ATP and Cucurbitacin B	Mitochondria-dependent NLRP3–pyroptosis pathway	Delays OA inflammation and cartilage degeneration	[91,92]
ATP-induced immune regulation/ cell death	CFI and ATP/ADP/AMP	P2X7 receptor–mediated cell death; CFI promotes inflammatory responses	Potential implications for OA diagnosis and immunotherapy	[93,94]
ATP/P2X4–P2X7 receptor–mediated inflammation and cell death	ATP, IL-1, MMP-3/9, and ginsenosides CK and Rd	ATP activates P2X4 to drive inflammation, while P2X7 induces cell death	A novel therapeutic target for OA and a basis for ginsenoside-based drug development	[95,96]
AICD	ATP, MRS2578, and UDP	ATP release activates the P2Y6–NF-κB pathway to regulate cell survival	Targeting the ATP–P2Y6 axis to ameliorate degenerative bone disorders	[97,98]
ATP-induced Ca^{2+} signaling and cell death	P2X7, P2Y(1), P2Y(11), and METP nanoparticles(METP NPs)	ATP triggers Ca^{2+} influx, promoting inflammation and cell migration	Blocking Ca^{2+} overload ameliorates degenerative bone disorders	[99,100]
ATP-related Ca^{2+}/channel-mediated cell death	ATP, TRPV4, and HC067047	ATP accumulation or depletion activates TRPV4, inducing pyroptosis and functional impairment	Targeting the TRPV4/ATP axis to improve OA and provide analgesic effects	[101,102]
ATP-induced inflammatory cell death	CoQ(0) and acetyl zingerone	Inhibits LPS/ATP-induced NLRP3activation and enhances mitochondria-associated autophagy	Alleviates OA inflammation and cartilage degeneration	[79,103]
ATP–BMMC–PAR2–mediated pain signaling	Apyrase and FSLLRY-NH_2	ATP induces mast cell degranulation and tryptase release	Mechanistic model and therapeutic intervention for OA-associated joint pain	[56]
ATP–NLRP3–mediated inflammation and apoptosis	Dicoumarol and MG132	Promotes NLRP3 degradation to suppress AICD	A therapeutic strategy for targeting inflammation and fibrosis in KOA	[104]
ATP-induced inflammatory celldeath	PIM-1 and SMI-4a	Suppresses NLRP3 inflammasomeactivation and GSDME-mediated pyroptosis under ATP stimulation	Improves OA synovitis and protects cartilage	[105]
ATP-induced inflammatory celldeath	miR-107	ATP amplifies LPS-induced pyroptosis, which is suppressed by miR-107	Improves cartilage inflammation and ECM degradation in KOA	[106]

NLRP3 in postmenopausal osteoporosis (PMOP) has been identified as a possible diagnostic indicator and an appropriate targeted strategy using CH6-LNPs-siNLRP3.[112]

At the molecular level, these changes can be mapped to the ATP–purinergic signalling axis, including the main operators of metabolic control, inflammatory amplification, mitochondrial homeostasis, and pyroptotic cascades. Integrated analysis of these processes has considerable translational potential for early diagnosis, disease prognosis and biological subtyping of degenerative skeletal diseases.

Therapeutic Strategies

Leveraging the ATP–purinergic signalling axis holds promise as a therapeutic target owing to the multifaceted involvement of AICD in skeletal degenerative diseases. P2X7R antagonists are the main strategy components because of the role of P2X7R in the amplification of inflammation, pyroptosis (an inflammatory form of programmed cell death), and matrix degradation and tissue protective effects in many models. Cancer-specific studies reveal that P2X7R gets highly expressed in tumor cells as well as in the fibroblasts. The antagonist AZ10606120 inhibits pancreatic stellate cells (PSC) function and collagen buildup, indicating that it may have the ability to block ATP-driven inflammation and fibrosis.[113] A nucleic acid-based solution involving the microRNA (miR)-373–P2X7R pathway can mitigate cartilage injury in osteoarticular diseases;[114] the P2X7R impact on matrix metalloproteinase (MMP)-13 and NF-κB offers a target to impact pain and inflammation in OA therapeutically.[49] In OP-related models, P2X7R inhibition lessens the impairment in bone formation due to estrogen deficiency, thus providing evidence in support of P2X7R as a potential therapeutic target to alleviate bone loss.[115] The emerging schemes that control ATP hydrolysis and its metabolic by-products may also regulate the AICD. MSC-derived microvesicles (MSC-MVs) can indirectly ameliorate early cartilage injury in rheumatoid arthritis (RA) by modulating the immune microenvironment for the inhibition of inflammatory cytokines and matrix degradation by altering extracellular nucleotide metabolism.[116] Apolipoprotein-enriched extracellular vesicles (ApoEVs) and systemic lupus erythematosus (SLE) strategies, that is, ATP-hydrolyzing capacity or P2X7R inhibition, may protect chondrocytes; decrease MMP production; and inactivate the NF-κB cascade. According to the results of this study, regulating ATP metabolism along with anti-inflammatory interventions may induce a synergistic therapeutic effect.[117] We could also look at the approaches of cellular and tissue engineering for therapeutic expansion. Chondrogenic fate of menstrual stem cells (MenSCs) is distinct from that of bone marrow mesenchymal stem cells (BMMSCs) in the presence of activin A indicating the presence of different cartilage-regeneration programmes in different lineages. With proper optimization, these cells can be good candidates for regenerative therapies in OA.[118] The sustained release of sperm-derived extracellular vesicles (SP-EVs) from microalgae-derived herbal hydrogels can enhance cartilage repair through regulation of energy metabolism and inflammation pathways. Merging delivery systems with metabolism regulation has potential in regenerative applications, according to this approach.[119]

Efforts to develop ATP–P2X7R axis–targeted intervention strategies are converging into a framework centered on suppressing excessive ATP signaling, restoring energy metabolism homeostasis, and blocking inflammation and cell death. P2X7R antagonists, ATP hydrolysis enhancers, stem cell–derived vesicles, exosome-based delivery systems, and combined anti-inflammatory/metabolic regulatory approaches are expected to form a complementary therapeutic repertoire for the precision treatment of skeletal degenerative diseases in the future.

Future Directions

The role of AICD in skeletal degenerative diseases is still being progressively refined. With advances in single-cell sequencing, multi-omics integration, and spatial transcriptomics, AICD-associated cellular populations and their subtypes are gradually being delineated. 5′-Nucleotidase E (NT5E) and transmembrane protein 158 (TMEM158) have been identified as key markers of necroptosis-related IDD and exhibit causal associations with IVDD, providing a foundation for the precise annotation of specific cell-death modalities.[120] Within the immunometabolic network of KOA, the driving role of ferroptosis has been substantiated. Homeobox C (HomC) exerts central regulatory functions in fibroblast growth factor (FGF) signaling–mediated synovitis and ECM remodeling. The associated SREBF1/YY1 regulatory subnetwork provides a methodological foundation for early disease detection and subtype stratification, while also highlighting the potential significance of mast cell homeostasis disruption in the development of

immunotherapeutic strategies.[121] The significance of multi-dimensional omics in IVDD research is becoming more appreciated. Gamma-aminobutyric acid receptor associated protein like 1 (GABARAPL1), prostaglandin-endoperoxide synthase 2 (PTGS2) and solute carrier family 40 member 1 (SLC40A1) have been suggested as possible therapeutic targets for interfering with IDD;[122] the miR-874-3p/activating transcription factor 3 (ATF3) axis displays biomarkers which can also interfere with a therapeutic route with intervention potential;[123] the regulation of $CD4^+CD39^+$ Tregs by miR-27b-3p underscores its immunomodulatory functions, suggesting substantial translational potential for clinical application.[124] The integration of multiple omics techniques further highlights important molecules involved in the immune regulation of intervertebral disc tissues, providing a basis for the development of new diagnostic strategies and therapeutic targets.[125] AICD-related injury mechanisms continue to expand. A number of programmed cell death-differentially expressed genes (PCD-DEGs) (tumor necrosis factor alpha-induced protein 3 (TNFAIP3), jun proto-oncogene (JUN), protein phosphatase 1 regulatory subunit 15A (PPP1R15A), inhibin subunit beta (BINHBB), DNA damage inducible transcript 4 (DDIT4)) in OA tissues are implicated in the regulation of synovitis, providing a candidate gene set with utility for subtype diagnosis.[126] Benzophenone-3 (BP-3) and other exposure factors affecting the environment may accelerate cartilage degeneration through apoptosis and ECM degradation followed by mitophagy inhibition. These mechanisms can be used as a reference for studying the pathogenic effects of external factors.[127] In IVDD, myeloid differentiation primary response gene 88 (MyD88) signalling is involved in necrotic cell death of NP cells, which is useful for refining the role of AICD in disc degeneration.[128]

There are still challenges to overcome on the therapeutic side which include tissue-specific delivery of AICD inhibitors, evaluating the safety of purinergic receptor-targeted interventions, and developing precision strategies that will deal with a microenvironment where multiple cell death pathways interact. The fusion of multi-omics and spatial omics platforms will clarify the cellular origins, subpopulation dynamics and microenvironment of AICD to promote the translational development of therapeutic targeting along the ATP–P2X7R axis.

AICD in the Pathogenesis of CVD

In the cardiovascular system, Table 4 summarizes key pathological contexts in which ATP-dependent signaling contributes to myocardial injury, fibrosis, hypertrophy, and vascular inflammation. These observations support that ATP–P2X7–inflammasome activation is a recurring mechanistic axis linking energy stress to inflammatory remodeling in CVD. Intelligent cardiovascular imagings, including cardiac magnetic resonance with mapping techniques and low-field magnetic resonance, computed tomography, and nuclear medicine imaging, have improved the detection of myocardial energy metabolic imbalance, enhanced oxidative stress, and structural–functional remodeling. These changes are related to the pathways of cell death caused by ATP depletion and mitochondrial destabilization. They provide measurable histological and metabolic indicators for ATP-mediated myocardial damage.[129] In the case of damage caused by ischemia-reperfusion, pyroptosis causes damage by itself, and it synergizes with other forms of damage, such as oxidative stress; calcium dysregulation; autophagy dysfunction; ferroptosis and apoptosis. Collaboration network has become a major focal point for discovery of treatable molecular targets and mechanism-based therapeutics.[130] After a heart attack, the huge amount of ATP released activates the P2X7 receptor. This triggers the NADPH Oxidase 4 (Nox4)/PKR-like endoplasmic reticulum kinase (PERK)/ATF4 signaling pathway. The end result is excessive autophagy of cardiomyocytes which aggravates injury to the tissues. Evidence from this study points to ATP-induced cell death linked to dysfunctional cell remodeling.[131]

P2X7 receptor exerts detrimental effects on heart disease. Activation of the P2X7 receptor by high concentrations of ATP triggers inflammatory signalling, hypertrophy, fibrosis, and apoptosis in cardiomyocytes. Inhibition of P2X7 receptor can cause significant protective structural and functional effects. The findings indicate that the ATP–P2X7 may be a major regulatory mechanism in cardiac disease pathology.[148] Ischemic and hypoxic conditions cause a significant increase of ATP in the extracellular space, which leads to direct cardiomyocyte death through P2Y2 and P2X7 receptors, while P2Y4 activation has an opposing protective effect. This variation illustrates a complex and opposing signalling balance in the ATP–P2 receptor system, which may play a role in defining phenotypic expressions during a cardiac injury.[149] Distinct G-protein coupled receptors (GsPCRs) govern how cardiomyocytes respond to ATP stress, either by enabling survival or triggering death, due to the formation of different cyclic adenosine monophosphate

Table 4 Association Between CVD and AICD

Cardiovascular Pathological Processes	Key Molecules/Signaling Axes	Mechanistic Features	Relevance to AICD	References
Myocardial I/R Injury	P2X7–NLRP3–Caspase-1–GSDMD Axis	Activation of Pyroptosis and Enhanced Pro-inflammatory Cytokine Release	ATP Upregulates P2X7 and Triggers the Pyroptotic Cascade	[132]
Diabetes-Exacerbated Myocardial I/R Injury	P2X7 Receptor and Its Inflammatory Signaling Pathways	Augmented Inflammation and Enhanced Apoptotic Activity	P2X7 Hyperactivation Aggravates the Cell-Death Phenotype	[133]
Diabetic Cardiomyopathy (DCM)	P2X7 Receptor–NLRP3–Caspase-1–GSDMD Pathway	Inhibition of the Pyroptotic Pathway Attenuates Inflammatory Injury	P2X7R Is an ATP-Dependent Receptor That Orchestrates Pyroptosis Activation	[134]
Ventricular Remodeling After Acute Myocardial Infarction	ATP–P2X7–Inflammasome–Caspase-1 Axis	Inflammasome Activation Amplifies Inflammation and Induces Cellular Injury	ATP-Dependent P2X7 Activation Promotes Inflammation-Related Cell Death	[135]
Pressure Overload–Induced Cardiac Hypertrophy and Inflammation	ATP–P2X7–NLRP3–IL-1β Axis	Sympathetic Nerve–Derived ATP Activates NLRP3	ATP Triggers P2X7–NLRP3–IL-1β–Mediated Inflammatory Responses	[136]
Multifactorial Myocardial Remodeling in HFpEF	ATP–P2X7–NLRP3 Inflammasome Pathway	Elevated Mitochondrial ROS and Pyroptosis Activation	ATP Triggers P2X7-Mediated Inflammatory Cell Injury	[137]
Pressure Overload–Induced Myocardial Fibrosis	P2X7R–NLRP3/IL-1β Pathway	Fibroblast Overactivation Leading to Fibrotic Remodeling	P2X7–NLRP3–Driven Fibrotic Pathway	[138]
Post-AMI Myocardial Fibrotic Remodeling	eATP–P2X7R–TGF-β1/Smad Pathway	P2X7R Promotes Inflammation and Drives the Fibrotic Process	eATP Activates P2X7R and Enhances Inflammatory Injury	[139]
Isoproterenol-Induced Myocardial Fibrosis	P2X7R–NLRP3–Cytokine Inflammatory Pathway	P2X7R Upregulation Enhances Inflammation and Fibrotic Progression	P2X7R-Dependent Inflammatory Injury Intensifies the Propensity for Cell Death	[140]
Progression of Non-Ischemic Heart Failure and Cardiac Hypertrophy	PANX1 Channel–Mediated ATP Release	PANX1 Deficiency Enhances Glycolysis and Reduces Immune Infiltration	No Direct Evidence of Cell Death; Indicates ATP Release as the Primary Contributor	[141]
T2D-Induced Myocardial Inflammation and Fibrosis	Panx1–P2X7R–NLRP1 Pathway	Increased Inflammation, Enhanced Apoptosis, and Impaired Cardiac Function	ATP Channel Activation Promotes Inflammation and Triggers Cell Death	[142]
T2D-Induced Myocardial Inflammation, Fibrosis, and Functional Impairment	Panx1–ATP–P2X7R–NLRP1 Inflammatory Cell-Death Pathway	Promotes Inflammatory Amplification, Myocardial Apoptosis, and Fibrotic Remodeling	ATP Release and Upregulated P2X7 Drive Inflammatory and Apoptotic Programs	[142]
DCM-Associated Myocardial Inflammation	P2X4–PANX1–NLRP3–GSDMD Pathway	P2X4 Mediates Lipid-Induced Enhancement of Pyroptosis	PANX1-Mediated ATP Release Drives Inflammatory Cell Death	[143]
Exacerbated Ischemia and Tissue Injury After Myocardial Infarction	ATP–P2X7R–Nox4/PERK/ATF4 Pathway	Promotes Excessive Autophagic Responses in Cardiomyocytes	ATP-Activated P2X7 Induces Maladaptive Autophagy	[131]
Aberrant Sympathetic Reinnervation After Myocardial Infarction	P2X7R–NLRP3–IL-1β Axis	Inflammatory Cascade Drives Neural Remodeling and Arrhythmogenesis	ATP-Like Agonists Trigger P2X7-Mediated Inflammatory Cell-Death Signaling	[144]
Abnormal Sympathetic Reinnervation After Myocardial Infarction	P2X7R–Akt/ERK–NF-κB Axis	Enhanced Inflammation and NGF-Induced Sympathetic Reinnervation	P2X7R Functions as an ATP-Sensitive Inflammatory Pathway (No Evidence of Cell Death Reported)	[145]
Depression-Associated Atrial Fibrillation and Structural Remodeling	P2X7R–NLRP3 Inflammatory Pathway	Inflammatory Amplification Promotes Fibrosis and Electrical Remodeling	ATP Triggers P2X7R-Mediated Inflammatory Cellular Responses	[146]
Initiation and Progression of Arterial Intimal Calcification	$P2Y_2$ Receptor–Runx2 Antagonistic Axis	Inhibits Osteogenic Transdifferentiation of Vascular Smooth Muscle Cells	ATP/Nucleotide–Activated $P2Y_2$ Signaling Suppresses Calcification (No Direct Involvement of AICD)	[147]

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(cAMP) signaling complexes. The adenylyl cyclase 5 (AC5)–protein kinase A (PKA)–PANX1 cascade is crucial for the β1-adrenoceptor (β1AR) and H2 receptor (H2R)-dependent ATP efflux and triggering of cell death via the P2X7 receptor (P2X7R)–calcium/calmodulin-dependent protein kinase II (CaMKII) axis. In contrast to the former, A2R, calcitonin gene-related peptide receptor (CGRPR), and relaxin family peptide receptor 1 (RXFP1) are protective via AC6–multidrug resistance-associated protein 4 (MRP4)–dependent cAMP efflux and adenosine signaling. This shows that the transmembrane energy–second messenger coupling is important for cardiomyocyte death.[150] In vivo studies confirm that vascular inflammation, leukocyte adhesion and migration, and atherosclerosis development are accelerated through P2Y2 receptor stimulation by extracellular ATP. The results suggest that ATP–P2Y2 signaling also plays a role in permanent damage and the structural progression of blood vessels.[151]

AICD as a Molecular Bridge Between CVD and DBD

Taken together, the evidence summarized in Tables 1–4 supports a unified model in which extracellular ATP functions as a shared upstream danger signal across skeletal and cardiovascular tissues. This ATP–P2X7-driven energy–inflammation amplification axis provides a mechanistic explanation for the frequent clinical coexistence of DBD and CVD. The cardiovascular and musculoskeletal systems vary widely in their tissue makeup and physiological functions. Nevertheless, their degenerative disorders exhibit prominent similarities at the molecular pathology level, particularly the excessive accumulation of extracellular ATP and the activation of P2X7 receptor-mediated programmed cell death. Studies of various experimental cardiovascular models have shown that the signalling axis is crucial in deciding the fate of energy-deficient cells. In cardiac I/R injury, the protein ATP-driven activation of the P2X7-NLRP3 pathway triggers a pyroptotic cascade that is a major amplifier of tissue injury; the ability of sevoflurane to effectively inhibit this pathway demonstrates the important role of ATP-P2X7 signalling in programmed cell death of cardiomyocytes.[152] In the pathological condition of diabetes with reperfusion injury, P2X7 is upregulated to a greater extent, and its inflammatory and proapoptotic downstream responses are much larger. These findings suggest that, in the presence of a metabolic disarrangement, ATP-dependent signalling becomes increasingly sensitized and cardiac vulnerability is amplified.[133] Angiotensin II (Ang II) can directly occupy the ATP-binding pocket of P2X7 to induce cardiomyocyte ferroptosis and pathological remodeling, which is markedly alleviated in the absence of P2X7. P2X7 represents a key energy-sensing death hub for the control of myocardial remodeling.[153] In HFpEF, sympathetic overactivation causes both increased amounts of ATP in the external cell environment as well as excess P2X7–NLRP3 pathway activation, which triggers myocardial oxidative stress. Upon excessive stimulation of the P2X7 receptor, myocardial pyroptosis and structural remodeling appear. Both drugs and renal denervation can reverse the effects of this signaling axis in diastolic dysfunction showing that it is a modifiable target.[137] Furthermore, in diabetic heart muscle, the overdrive of the Panx1–ATP–P2X7 system causes inflammation and death of heart muscle cells while high-intensity interval training lessens damage to the heart by switching down the system. These two important contributors to metabolic cardiomyopathy are energy imbalance and dysregulated ATP signaling, as the studies show.[142] A similar mechanism observed in pressure overload–induced cardiomyopathy is sympathetic nerve–derived ATP activating the P2X7–NLRP3–IL-1β axis, thus causing myocardial inflammation and hypertrophic remodeling.[136]

Just as it happens in the heart and cardiovascular system, the ATP–P2X7 axis is an important driver of cellular stress and cell injury in DBD. P2X7-mediated Ca^{2+} influx in chondrocytes regulates autophagy and apoptosis in response to ER stress through the inositol-requiring enzyme 1 (IRE1)–mechanistic target of rapamycin (mTOR)–PKR-like endoplasmic reticulum kinase (PERK) pathway, with biphasic effects that largely determine the progression of OA.[28] In OA of the temporomandibular joint, Panx3-dependent ATP release contributes to excessive activation of P2X7, leading to activation of inflammatory pathways and degradation of the cartilage matrix. This is a major source of focal degenerative changes.[40] Quercetin mitigates inflammatory phenotypes and delays cartilage degeneration by inhibiting transient receptor potential vanilloid 1 (TRPV1)-mediated Ca^{2+} influx and ATP release, thereby downregulating P2X7/NLRP3 activation in chondrocytes and macrophages. The research illustrates that ATP-dependent pathways can be therapeutically targeted.[57] The colocalization of P2X7 and NLRP3 is notably increased in IVDD while further stimulation by ATP analogs leads to pro-inflammatory microenvironment;[64] finite-element modeling shows that in degenerative intervertebral discs, the distribution of extracellular ATP declines specifically in certain regions and that this decline couples with matrix metabolic activity. This implies an

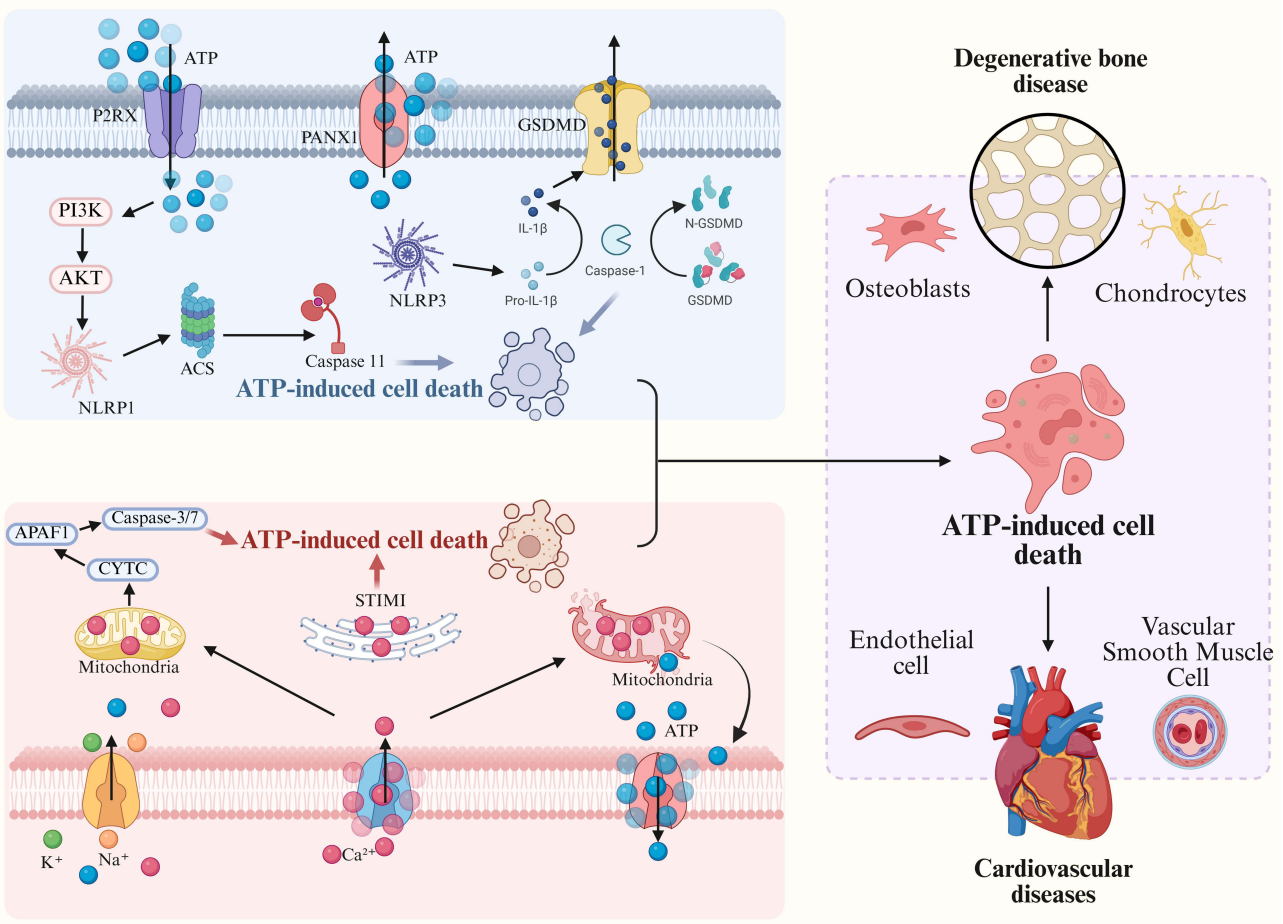

Figure 3 Schematic representation of the molecular mechanisms and cellular effects of AICD in the cardiovascular system. The main events that take place causing cell death in the cardiovascular system is caused by ATP in the extracellular space and this figure highlights this effect on major cell populations. ATP instigates Ca^{2+} influx, ionic disbalance and mitochondrial malfunction via activation of P2X receptors and PANX1 channels and consequently cytochrome c egress along with activation of caspase-3/7–mediated apoptosis. Simultaneously, ATP-driven activation of P2X7 triggers the assembly of inflammasomes such as NLRP3, activating caspase-1, cleaving GSDMD, and releasing IL-1β, which are hallmarks of inflammatory cell death. All these events induce programmed death of endothelial cells and vascular smooth muscle cells. Consequently, they lead to vascular dysfunction. Furthermore, they amplify inflammatory responses. And they also initiate and propagate CVD.

alteration of purinergic signaling in degenerative tissues.[65] In human intervertebral disc cells, P2X7 forms a functional interaction with nuclear factor of activated T-cells, cytoplasmic 1 (NFATc1) and lamin A/C which is linked to cellular stress and structural degeneration when activated abnormally.[154] In models of periodontal disease, inflammation-induced ATP release leads to excessive P2X7 activation, which blocks osteoblast activity and increases bone loss. However, pharmacological antagonism of P2X7 markedly reverses these effects.[155] Further analyses along with in vivo and in vitro assays show that P2X7 significantly promotes osteoclast differentiation and bone resorption via activation of PI3K–Akt–GSK3β signalling, establishing a pivotal molecular basis for OP development.[41] As shown in Figure 3, ATP activates P2X receptors and PANX1 channels, causing calcium homeostasis disturbances, mitochondrial dysfunction and inflammasome activation. Endothelial cells and vascular smooth muscle cells suffer various types of programmed cell death due to these events, which speeds up cardiovascular pathology.

Conclusion

The role of AICD in the pathophysiology of DBD and cardiovascular disorders has emerged as a crucial area of research. ATP, a vital cellular energy source, when released into the extracellular space during tissue injury, hypoxia, or mechanical stress, acts as both a damage-associated molecular pattern (DAMP) and an energy signal. Its accumulation initiates a cascade of cellular responses, particularly through the activation of the P2X7 receptor, which ultimately leads to the

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activation of multiple programmed cell death pathways such as pyroptosis, apoptosis, and ferroptosis. These mechanisms share a common underlying energy-inflammation axis that plays a central role in the progression of both DBD and CVD.

This review has provided a detailed exploration of how AICD contributes to the pathogenesis of diseases such as OA, IVDD, OP, and various forms of CVD, including myocardial infarction, heart failure, and atherosclerosis. The shared molecular mechanisms driving these diseases are rooted in excessive ATP release, impaired purinergic signaling, mitochondrial dysfunction, and chronic inflammation. Despite the distinct tissue contexts, the downstream cellular responses converge on a common axis of metabolic failure, oxidative stress, and maladaptive immune activation, culminating in tissue degeneration and dysfunction. By examining these converging pathways, we provide a novel conceptual framework that links two seemingly disparate disease domains through a shared pathological mechanism: AICD.

While this framework offers a unified model of disease pathogenesis, several critical gaps remain that warrant further investigation. First, the exact role of ectonucleotidases, such as CD39 and CD73, in regulating ATP concentrations and modulating the AICD process is not fully understood. These enzymes, which degrade extracellular ATP and its metabolites, could represent potential therapeutic targets for modulating AICD in both bone and cardiovascular tissues. The complex interplay between P2X/P2Y receptors, adenosine signaling, and purinergic modulation needs to be more rigorously explored to determine how these pathways may be altered in chronic disease conditions and how they can be therapeutically targeted.

Furthermore, clinical evidence supporting the contribution of AICD to disease progression remains limited. While preclinical studies have provided compelling evidence for ATP-mediated cell death in bone and cardiovascular models, translational research that directly links extracellular ATP levels to clinical outcomes, such as bone loss, cardiac fibrosis, and vascular inflammation, is crucial. The development of non-invasive biomarkers for ATP-related damage, as well as the use of targeted therapies aimed at purinergic signaling, could provide valuable clinical tools for early diagnosis and personalized treatment strategies.

In conclusion, ATP-induced cell death represents a critical yet underexplored mechanism bridging DBD and cardiovascular disorders. The shared energy-inflammation axis offers new insights into the molecular links between these diseases, opening avenues for future research into targeted therapeutic interventions. By better understanding the intricate relationship between ATP, purinergic signaling, and cellular stress responses, we can develop innovative strategies to modulate AICD and mitigate its detrimental effects in both bone and cardiovascular systems. As our understanding of these shared mechanisms deepens, it will pave the way for novel, integrated treatment approaches that address the root causes of both degenerative bone and CVD, ultimately improving patient outcomes and quality of life.

Abbreviations

3-MA, 3-methyladenine; α-KG, Alpha-ketoglutarate; A2AR, Adenosine A2A receptor; AC5, Adenylyl cyclase 5; AICD, ATP-induced cell death; AIM2, Absent in melanoma 2; AMPK, AMP-activated protein kinase; AMPs, Antimicrobial peptides; Ang II, Angiotensin II; ApoEVs, Apolipoprotein-enriched extracellular vesicles; ASA VI, Acetylshikonin A VI; ATF3, Activating transcription factor 3; ATP, Adenosine triphosphate; BCA, Bovine colostrum antibodies; BINHBB, Inhibin subunit beta; BKDM6B, lysine demethylase 6; BMMSCs, Bone marrow mesenchymal stem cells; BP-3, Benzophenone-3; BzATP, 2′,3′-O-(4-benzoyl)ATP; CaMKII, Calcium/calmodulin-dependent protein kinase II; CD39, Cluster of differentiation 39; CD73, Cluster of differentiation 73; CGRPR, Calcitonin gene-related peptide receptor; ClpB, caseinolytic peptidase B; CSF1R, colony stimulating factor 1 receptor; CVD, Cardiovascular diseases; CX43, Connexin 43; DAMP, Damage-associated molecular pattern; DBD, Degenerative bone diseases; DDIT4, DNA damage inducible transcript 4; DEX, Dexamethasone; DNT, Double negative T; DPI, Diphenyleneiodonium; ECM, Extracellular matrix; ER, Endoplasmic reticulum; Epac1, Exchange protein directly activated by cAMP 1; ERK, Extracellular signal-regulated kinase; FasL, Fas ligand; FGF, Fibroblast growth factor; FPN, Ferroportin; GABARAPL1, Gamma-aminobutyric acid receptor associated protein like 1; GSK3β, Glycogen synthase kinase 3 beta; H3K27, Histone H3 lysine 27; HCAR2, Hydroxycarboxylic acid receptor 2; HCS, High-content screening; HFpEF, Heart failure with preserved ejection fraction; HIF-1α, Hypoxia-inducible factor 1-alpha; HMGB1, High mobility group box 1; HomC, Homeobox C; IRI, Ischemia-reperfusion injury; IL-6, Interleukin 6; JUN, Jun proto-oncogene; KOA, Knee osteoarthritis; IRE1, Inositol-requiring enzyme 1; IVDD, Intervertebral disc degeneration; LDHA, Lactate dehydrogenase A; M1,

Classical activation macrophages 1; M2, Alternative activation macrophages 2; m^7G, 7-methylguanosine; MAPK, Mitogen-activated protein kinase; MenSCs, Menstrual stem cells; METTL1, Methyltransferase Like 1; MiR, MicroRNA; MMP, Matrix metalloproteinase; MRP4, Multidrug resistance-associated protein 4; mTOR, mechanistic target of rapamycin; mt-tRF3b-LeuTAA, Mitochondrial tRNA-derived fragment 3b-leucine tRNA TAA; mtROS, Mitochondrial reactive oxygen species; MyD88, Myeloid differentiation primary response gene 88; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; NFATc1, Nuclear factor of activated T-cells, cytoplasmic 1; NLRP3, NOD-like receptor pyrin domain-containing protein 3; Nox4, NADPH Oxidase 4; NP, Nucleus pulposus; Nrf2, Nuclear factor erythroid 2-related factor 2; NT5E, 5′-Nucleotidase E; OA, Osteoarthritis; OP, Osteoporosis; P2X7, Purinergic receptor P2X7; P2Y, Purinergic receptor P2Y; Panx3, Pannexin 3; PCD-DEGs, Programmed cell death-differentially expressed genes; PE, Palmitoylethanolamide; PERK, PKR-like endoplasmic reticulum kinase; PGE2, Prostaglandin E2; PINK1, PTEN-induced kinase 1; PIP2, Phosphatidylinositol 4,5-bisphosphate; PKA, Protein kinase A; PMOP, Postmenopausal osteoporosis; PPP1R15A, Protein phosphatase 1 regulatory subunit 15A; PSC, Pancreatic stellate cells; PTGS2, Prostaglandin-endoperoxide synthase 2; RA, Rheumatoid arthritis; RAGE, receptor for advanced glycation end-products; ROS, Reactive oxygen species; RPE, Retinal pigment epithelium; RXFP1, relaxin family peptide receptor 1; SIRT3, Sirtuin 3; Sirt4, Sirtuin 4; SLC40A1, Solute carrier family 40 member 1; SLE, Systemic lupus erythematosus; SMAD3, SMAD family member 3; SOD2, Superoxide dismutase 2; SP-EVs, Sperm-derived extracellular vesicles; TfR1, Transferrin receptor 1; TGF-β1, transforming growth factor beta 1; TMEM158, Transmembrane protein 158; TNF-α, Tumor necrosis factor-alpha; TNFAIP3, Tumor necrosis factor alpha-induced protein 3; TRPV1, Transient receptor potential vanilloid 1.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Author Contributions

Jingjing Zhang and Linzhu Li contributed equally to this work. Co-first authors: Jingjing Zhang and Linzhu Li. Jingjing Zhang and Linzhu Li were responsible for Conceptualization, Methodology, Formal analysis, and Writing – original draft. Lu Cheng contributed to Conceptualization, development of the theoretical framework, critical intellectual content design, and Writing – original draft. Lu Cheng also provided overall supervision of the study and secured funding support. Qianwen Guo, Xuesong Liu, Qian Qiao, Xuerui Ye, and Hongyang Ding contributed to Investigation, Data curation, and Visualization. Yi Liu, Kaikai Wang, and Haoling Zhang contributed to Writing – review & editing and Validation. Lu Cheng and Haoling Zhang were responsible for Supervision, Project administration. All authors made a significant intellectual contribution to the work, approved the final manuscript, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflict of interest.

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