Archives of Oral Biology 192 (2026) 106783

Contents lists available at ScienceDirect

Archives of Oral Biology

journal homepage: www.elsevier.com/locate/archoralbio

# Regulated cell death in the temporomandibular joint: From disc internal derangement to osteoarthritis and tissue repair

Mugurel Constantin Rusu

*Division of Anatomy, Department 1, Faculty of Dentistry, "Carol Davila" University of Medicine and Pharmacy, Bucharest, 050474, Romania*

ARTICLE INFO

*Keywords:*
Temporomandibular joint
Regulated cell death
Apoptosis
PANoptosis
Temporomandibular joint osteoarthritis
Ferroptosis

ABSTRACT

*Objective:* This narrative review examines regulated cell death programmes underlying disc internal derangement and condylar osteoarthritis in the temporomandibular joint (TMJ), evaluating the balance between cell loss and endogenous repair capacity across both compartments.
*Design:* A narrative, mechanism-oriented review of PubMed-indexed literature, supplemented by citation tracking from core TMJ cell death studies, with evidence stratified by an explicit hierarchy prioritising human TMJ tissue and synovial fluid findings over animal, *in vitro*, and non-TMJ osteoarthritis data.
*Results:* In the disc, internal derangement is associated with apoptosis via extrinsic TRAIL/DR5/caspase-3 and intrinsic Bax/cytochrome c/caspase-9 pathways; chondrocyte-like apoptosis appears repair-limiting, whereas the CD34 + perivascular stromal niche may serve as a local repair reservoir. In condylar cartilage and synovium, necroptosis, pyroptosis and ferroptosis interact with autophagy dysregulation and senescence-related mitochondrial dysfunction in TMJ osteoarthritis (TMJOA), through overlapping mechanisms involving mechanical stress, inflammatory cytokines, oxidative injury, iron loading and altered vesicular communication. A PANoptosis-compatible model is proposed, in which caspase-3, GSDMD/caspase-1, and RIPK3/MLKL signalling may converge in inflamed TMJ tissues, though direct demonstration of a PANoptotic complex remains required.
*Conclusions:* Regulated cell death in the TMJ is compartment-specific and repair-coupled rather than uniformly degenerative. Distinguishing death programmes and repair reservoirs in the disc versus condylar cartilage offers a framework for pathway-specific and multi-pathway therapeutic targeting in future studies.

## 1. Introduction

The TMJ (Fig. 1) is among the most biomechanically complex articulations in the human body, executing translation, rotation, and lateral glide simultaneously under loads generated by mastication, speech, parafunctional habits, and craniofacial growth. Unlike appendicular synovial joints, its articular surfaces are covered by secondary fibrocartilage rather than hyaline cartilage, combining type I and type II collagen in a tissue that is uniquely responsive to both compressive and shear stresses (Lu et al., 2022). An avascular fibrocartilaginous disc interposes between the condyle and the glenoid fossa; in its central zone it lacks both blood vessels and innervation, relying entirely on diffusion for metabolite exchange and harbouring resident cell populations – fibroblast-like cells, fibrochondrocytes, and chondrocyte-like cells (CLCs) – whose proliferative index is exceptionally low (Galanti et al., 2013).

This site-specific biology has been recognised since the classic literature on degenerative joint disease. Haskin et al. (1995) emphasised that the TMJ has sparse fibrocartilaginous cellularity, a distinctive collagen-proteoglycan matrix and unusual loading conditions; consequently, mechanisms inferred from appendicular joints should be treated as supportive rather than automatically transferable to the TMJ (Haskin et al., 1995).

Cell death in the TMJ has historically been studied in two partially overlapping contexts: the internal derangement (ID, defined as an abnormal disc–condyle positional relationship, most commonly presenting as anterior disc displacement with or without reduction) literature, which focuses on the disc and where apoptosis correlates with the severity of displacement and histopathological damage; and the TMJOA literature, which focuses on condylar cartilage and the synovium, where research has expanded beyond apoptosis to encompass necroptosis, pyroptosis and ferroptosis, together with autophagy dysregulation, mitophagy failure and cellular senescence. The main pathological features of TMJOA – chondrocyte death, extracellular matrix (ECM) degradation, and subchondral bone remodelling – are mechanistically inseparable (Li et al., 2021). A unified framework linking disc cell death

*E-mail address:* mugurel.rusu@umfcd.ro.

https://doi.org/10.1016/j.archoralbio.2026.106783
Received 1 July 2026; Received in revised form 15 September 2026; Accepted 13 October 2026
Available online 17 October 2026
0003-9969/© 2026 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

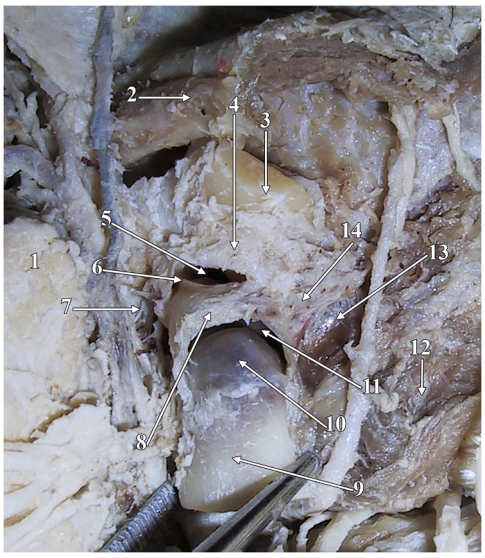



**Fig. 1. Dissection of the right temporomandibular joint (TMJ) of a human cadaveric specimen.** Right side. Lateral view. 1. parotid gland; 2. temporal muscle; 3. zygomatic root; 4. fibrous capsule; 5. superior joint compartment; 6. synovial membrane (dissected); 7. bilaminar zone; 8. TMJ disc; 9. neck of mandible; 10. articular cartilage, covers the mandibular condyle; 11. inferior joint compartment; 12. inferior head of the lateral pterygoid muscle; 13. superior head of the lateral pterygoid muscle; 14. anterior disc extension.

to condylar OA, with repair capacity as the central biological question, provides the conceptual architecture of this review (Table 2).

Despite this expanding literature, no prior review has simultaneously mapped regulated cell death pathways and associated autophagic and senescence responses across both TMJ compartments within a unified anatomical and evidence-stratified framework. Studies of disc apoptosis in internal derangement and condylar cell death in osteoarthritis have developed as largely parallel literatures; the repair-limiting consequences of compartment-specific cell death, the role of the CD34⁺ perivascular stromal niche as a death-programme-vulnerable repair reservoir, and the possibility of PANoptosis-compatible convergence in inflamed TMJ tissues have not previously been synthesised in an integrated model. The present review addresses these gaps.

## 2. Literature search and review strategy

This article was prepared as a narrative, mechanism-oriented review rather than as a systematic review. PubMed-indexed literature was prioritised, with additional references selected through backward and forward citation tracking from central TMJ cell death papers. Searches combined the terms temporomandibular joint, TMJ, temporomandibular joint osteoarthritis, internal derangement, disc, condylar cartilage and synovium with apoptosis, tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), caspase-3, autophagy, mitophagy, pyroptosis, inflammasome, NLR family pyrin domain-containing protein 3 (NLRP3), gasdermin D (GSDMD), necroptosis, receptor-interacting serine/threonine-protein kinase 1 (RIPK1), receptor-interacting serine/threonine-protein kinase 3 (RIPK3), mixed lineage kinase domain-like protein (MLKL), ferroptosis, glutathione peroxidase 4 (GPX4), transferrin receptor (TFRC), senescence, cluster of differentiation 34 (CD34), vascular endothelial growth factor (VEGF), exosomes, migrasomes and integrated inflammatory cell death combining Pyroptosis, Apoptosis, and Necroptosis (PANoptosis).

Human TMJ tissue and synovial fluid studies were treated as the most directly relevant evidence. Animal and *in vitro* TMJ models were included when they tested pathway activation, temporal sequence or therapeutic modulation. Non-TMJ osteoarthritis, skeletal development, and general studies on regulated cell death were used only to support mechanisms that have not yet been directly tested in TMJ tissues. This evidence hierarchy is made explicit to avoid presenting extrapolated mechanisms as established TMJ findings (Table 1).

## 3. The TMJ disc and condylar cartilage: different tissues, different vulnerabilities

### 3.1. Structural divergence

The TMJ disc's compactly arranged fibrocartilage is avascular except in the bilaminar zone and at the lateral and medial attachment margins (Loreto et al., 2010). This peripheral vascularisation contains perivascular stromal cells, which may contribute to a peripheral repair niche; the avascular central and intermediate zones must sustain themselves by diffusion alone. Under normal loading, disc CLCs maintain matrix homeostasis through balanced anabolic and catabolic activity; when loading exceeds adaptive capacity or disc position is displaced, the CLCs undergo phenotypic transformation – from fibroblast-like to fibrochondrocyte to chondrocyte-like – an adaptive response that is itself cut short by apoptosis (Galanti et al., 2013; Loreto et al., 2009).

The condylar cartilage, by contrast, is underlaid by richly vascularised subchondral bone and organised into four zones (fibrous, proliferative, pre-hypertrophic, hypertrophic) whose architecture allows incremental mechanical adaptation. The superficial zone retains progenitor-like qualities: its cells can proliferate and differentiate into deep-zone chondrocytes, thereby constituting a critical repair reservoir for progressive OA (Liu et al., 2021b). Nevertheless, this capacity is finite; under sustained abnormal loading or inflammatory insult, it is overwhelmed.

This distinction is consistent with contemporary TMJOA reviews, which describe the joint as a fibrocartilaginous, mechanically adaptive articulation in which chondrocyte survival, extracellular matrix degradation and subchondral bone remodelling evolve as an osteochondral unit (Cardoneanu et al., 2022; Lu et al., 2022). It also explains why regenerative approaches must address both cellular survival and tissue repair capacity rather than only symptomatic inflammation (Zhao & Xie, 2021).

### 3.2. Implications for cell death pathways

Differences in vascularity, inflammatory exposure and cellular composition may influence the distribution of regulated cell death pathways across TMJ compartments. Pyroptosis, necroptosis and ferroptosis do not inherently require blood-borne signals; however, TMJ-

**Table 1**
Evidence hierarchy used in this narrative review.

| Evidence level | Role in this review | Examples |
|---|---|---|
| Human TMJ tissue or synovial fluid | Highest relevance for compartment-specific claims. | Disc apoptosis; synovial-fluid pyroptosis markers; iron/ferroptosis-related biofluid data. |
| TMJ animal models | Used for temporal sequence, pathway activation and preclinical intervention. | Disc displacement, UAC, MIA, CFA and mechanical-loading models. |
| TMJ in vitro or ex vivo models | Used to infer directionality and molecular nodes. | Chondrocytes, synoviocytes, macrophage-FLS co-culture and organoid systems. |
| Non-TMJ OA or skeletal biology | Used only for mechanistic support where TMJ-specific data are absent. | VEGF-mediated cartilage-bone coupling; general PANoptosis and cell-death crosstalk. |
| Reviews or computational models | Used for background, terminology and integrative hypotheses, not as primary TMJ evidence. | Regulated cell-death and PANoptosis reviews; multi-pathway modelling papers. |

specific evidence for these pathways currently derives predominantly from condylar cartilage and synovium. In the disc, the strongest direct evidence concerns extrinsic and intrinsic apoptosis associated with mechanical stress and local death signalling. Disc cell death may be especially repair-limiting compared with condylar chondrocyte death: every CLC lost from the avascular disc interior cannot be replaced by vascular progenitor recruitment, and loss of perivascular stromal cells in the disc periphery could further compromise local repair capacity. Death of condylar chondrocytes, while also harmful, occurs in a tissue that retains subchondral bone vascularity and a progenitor-containing superficial zone – both of which provide partial regenerative backup. These compartment-specific differences in vascularity, inflammatory cell access, and regenerative reserve provide the anatomical framework for interpreting regulated cell death in the TMJ (Galanti et al., 2013; Liu et al., 2021b; Loreto et al., 2010) (Table 2, Fig. 2).

## 4. Apoptosis in the TMJ disc

### 4.1. Chondrocyte-like apoptosis as a repair-limiting mechanism

The defining conceptual contribution of the disc apoptosis literature is that cell death in the degenerated disc is not incidental but mechanistically repair-limiting. In TMJ ID, disc fibrocartilage responds to abnormal loading through progressive phenotypic transformation: fibroblast-like cells transition to fibrochondrocytes and eventually to CLCs, a shift that is considered an adaptive attempt to generate fibrocartilage capable of withstanding compression. However, only small patches of chondral tissue are ever achieved in displaced discs. The reason proposed by Loreto et al. (2009) in an immunohistochemical study of 21 discs from 19 patients with ID is that the very CLCs generated by this adaptive transformation overexpress TRAIL and its death receptor, DR5, and are TUNEL-positive. The apoptotic death of CLCs, regulated at least in part through TRAIL/DR5 signalling, thus undercuts adaptive chondroid metaplasia before it can produce functional repair tissue, eventually leading to disc perforation. This framing – apoptosis as the mechanism that aborts repair – establishes the biological logic connecting cell death to structural failure (Loreto et al., 2009).

These findings are contextualised by a contemporary review (Galanti et al., 2013) that confirms: histopathological investigations of degenerated TMJ disc have documented an association between TMJ arthropathy and loss of tissue cellularity via apoptosis-related processes that lead to diminished ECM generation, organisation, and repair. The disc contains three cell populations – elongated fibroblast-like cells (most numerous), rounded fibrochondrocytes (without a pericellular halo), and CLCs (with a pericellular halo) – and fibrocartilage requires intermittent compression or shear to maintain its phenotype; abnormal loading disrupts this balance and triggers apoptotic cascades (Galanti et al., 2013).

### 4.2. The TRAIL/DR5 extrinsic pathway

The TRAIL ligand and its death receptor DR5 constitute the primary extrinsic apoptotic axis in the TMJ disc. In 21 displaced discs (12 with anterior disc displacement with reduction, ADDwR; 9 with anterior disc displacement without reduction (ADDwoR)), TRAIL immunostaining was detected in the cytoplasm of disc cells in every specimen, with the degree of staining positively correlated with the histopathological degeneration score (Spearman $\rho = 0.617$), supporting a quantitative association between extrinsic apoptosis and structural disc failure (Leonardi et al., 2011). Regional analysis showed that in ADDwoR, TRAIL/DR5-positive cells were significantly more numerous in the posterior disc attachment than in the anterior and intermediate bands; in ADDwR, greater positivity characterised the anterior and intermediate bands, reflecting the anatomical locus of greatest mechanical derangement in each displacement type (Leonardi et al., 2011; Loreto et al., 2009).

### 4.3. Caspase-3 as the executioner: biomechanical topography of irreversible cell death

Downstream of the TRAIL/DR5 axis, caspase-3 – the terminal executioner caspase whose activation marks the execution phase of apoptosis – has been spatially mapped across disc regions. In 18 patients with ID (13 ADDwR; 5 ADDwoR) plus four cadaveric control discs, caspase-3 immunoreactivity was significantly greater in both ADDwR and ADDwoR than in controls, with distinct regional patterns that precisely corresponded to the biomechanical stress topography of each displacement type. In ADDwoR, where the disc remains fixed in the anteriorly displaced position and does not revert on mouth opening, maximum compressive stresses concentrate in the posterior disc attachment (PDA); caspase-3-positive cells were accordingly significantly more numerous in the PDA than in the anterior or intermediate bands ($P < 0.01$). In ADDwR, before disc recapture, stress peaks in the anterior band; after reduction during jaw opening, the intermediate zone is loaded; the proportion of caspase-3-positive cells was highest in the anterior and intermediate bands of ADDwR compared with the corresponding regions of ADDwoR discs ($P < 0.05$). No regional differences in caspase-3 were observed in control discs. The spatial distribution of irreversible apoptosis thus mirrors the mechanical stress distribution determined by disc position and movement pattern,

**Table 2**
Regulated cell death pathways, associated cellular responses and evidence anchors in TMJ tissues.

| Pathway | Main TMJ compartment(s) | Markers or axes | Evidence and targetable nodes |
|---|---|---|---|
| Apoptosis | Disc cells; condylar chondrocytes; synovium | TRAIL/DR5, Bax/cytochrome c/caspase-9, caspase-3, TUNEL | Strongest direct TMJ evidence. Potential nodes include TNF/iNOS inhibition, PI3K/AKT survival signalling and BMSC-derived exosomes. |
| Autophagy/mitophagy | Condylar cartilage; synovium; possibly disc | Beclin-1, LC3B-II, LAMP2, p62/SQSTM1, MTORC1, PINK1-related pathways | Early adaptive response that may fail during progression. Nodes include MTORC1 inhibition, migrasome-mediated autophagy support and mitochondrial quality control. |
| Pyroptosis | Synovium and condylar chondrocytes; disc not yet defined | NLRP3, ASC, caspase-1, GSDMD, IL-1β, IL-18, TLR4 | Direct TMJ evidence is present in the synovium and condylar cartilage. Nodes include MCC950, Ac-YVAD-cmk, resatorvid and ALPK1/NLRP3/ROS modulation. |
| Necroptosis | Condylar cartilage and synovium | RIPK1, RIPK3, p-MLKL, SDC4, TNFα | Preclinical evidence from the TMJ supports an inflammatory feedforward loop. Nodes include RIPK1/RIPK3/MLKL inhibition, SDC4 blockade and BRD4 inhibition. |
| Ferroptosis | Condylar chondrocytes; inflamed synovial fluid environment | HIF-1α/TFRC, Fe2 + , 4-HNE, ACSL4, GPX4, system Xc- | Human biofluid and experimental evidence support inflammation-to-iron-loading injury. Nodes include Fer-1, Lip-1, Nrf2/ARE activation, HIF-1α and TFRC inhibition. |
| Senescence and repair exhaustion | Condylar cartilage; disc perivascular niche | p16, p21, p53, SA-β-gal, SASP mediators | Links cell-cycle arrest, inflammatory secretion and progenitor-niche attrition. Interventions remain largely experimental. |
| PANoptosis-compatible convergence | Inflamed synovium and condylar cartilage | Caspase-3 plus GSDMD/caspase-1 plus RIPK3/MLKL | Hypothesis-generating model. Direct TMJ proof would require combined pathway inhibition or knockdown. |

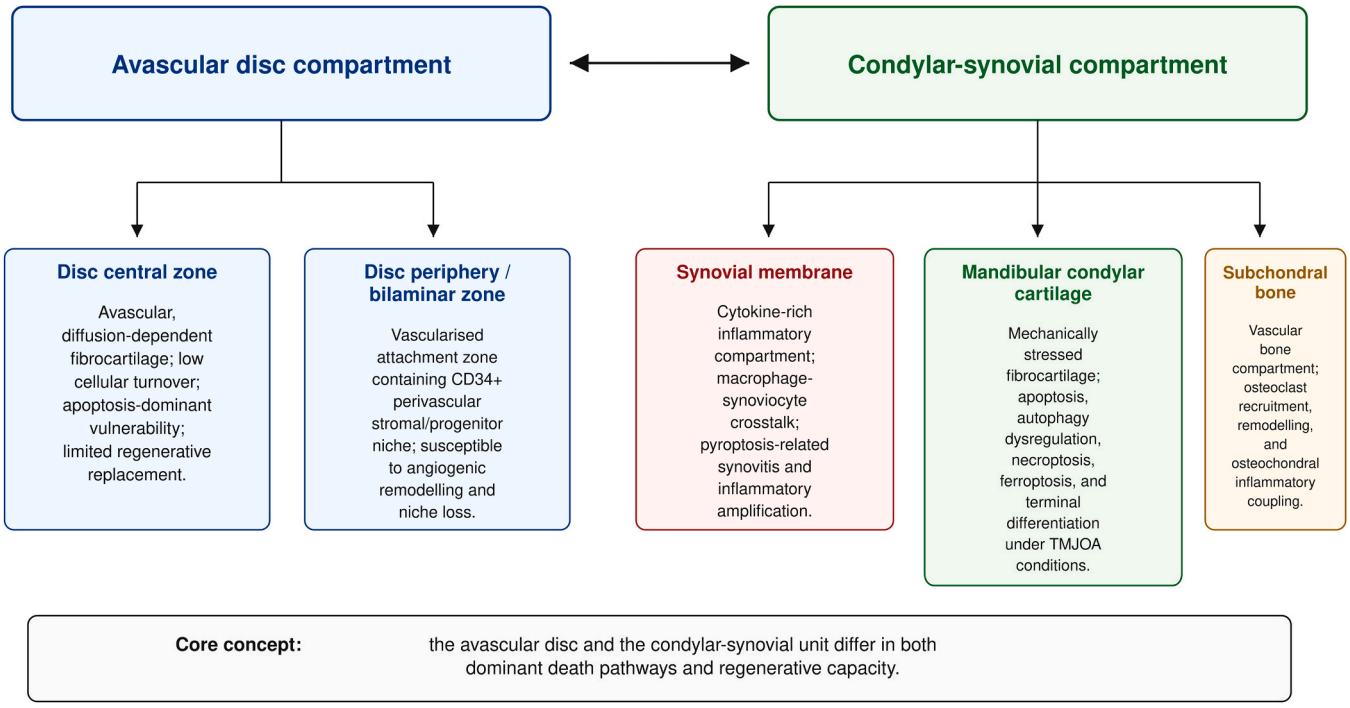



**Fig. 2. Temporomandibular joint (TMJ) compartments and differential vulnerability to regulated cell death.** Conceptual compartmentalisation of the temporomandibular joint (TMJ) according to vascularity, cellular turnover, dominant regulated cell-death vulnerability and regenerative capacity. Condylar cartilage itself is avascular; the adjacent synovium and subchondral bone are vascularised. The avascular disc compartment is separated from the condylar–synovial compartment because these regions differ substantially in oxygen and metabolite supply, inflammatory-cell access, progenitor-cell availability and reparative potential. The disc central zone is diffusion-dependent and has limited capacity for cellular replacement, making apoptosis of resident fibrocartilaginous and chondrocyte-like cells particularly repair-limiting. The disc periphery and bilaminar zone contain vascularised attachment tissue and CD34-positive perivascular stromal/progenitor elements, but this niche is vulnerable to angiogenic remodelling and death-programme-mediated depletion. In contrast, the synovial membrane, mandibular condylar cartilage and subchondral bone form a condylar–synovial unit in which inflammatory crosstalk, pyroptosis, autophagy dysregulation, necroptosis, ferroptosis, osteoclast recruitment and osteochondral remodelling may interact during temporomandibular joint osteoarthritis (TMJOA). The figure emphasises that compartment-specific vascularity and repair capacity determine which regulated cell-death pathways are most biologically consequential.

supporting a biomechanical-histological correspondence in which mechanical overload is a plausible upstream driver of caspase-3 activation across disc zones. ADDwR discs also exhibited a greater reduction in fibroblast-like cells and a higher proportion of chondrocyte-like cells than ADDwoR, consistent with more advanced adaptive phenotypic transformation in those areas under recurrent mechanical loading (Loreto et al., 2011).

### 4.4. *Vessel apoptosis: a self-limiting counter-process*

Normal TMJ discs are avascular except in the bilaminar zone and lateral/medial attachment margins (Loreto et al., 2010). Pathological angiogenesis accompanies disc degeneration – but to understand the vessel apoptosis described below as a counter-response, it is necessary first to establish the upstream angiogenic switch that drives vascular ingrowth in the diseased disc.

The VEGF (vascular endothelial growth factor) provides this signal. In healthy adult articular and fibrocartilaginous tissues, chondrocytes and fibrochondrocytes suppress VEGF expression to maintain the avascular status that characterises normal cartilage. Under pathological conditions – mechanical overload, hypoxia, and pro-inflammatory cytokines – disc cells undergo phenotypic change and acquire VEGF expression, constituting an angiogenic switch from a vascular-suppressive to a vascular-permissive microenvironment. This pattern has been documented in osteoarthritic human articular cartilage, where VEGF is detectable in chondrocytes and is significantly upregulated in severe disease, indicating that diseased chondrocytes may acquire a pro-angiogenic and partly hypertrophic-like phenotype (Murata et al., 2008; Pfander et al., 2001; Pufe et al., 2004). During normal endochondral ossification, hypertrophic chondrocytes at the cartilage–bone junction express VEGF to coordinate capillary invasion, cartilage resorption, and trabecular bone formation (Gerber et al., 1999); a comparable but pathological activation appears in osteoarthritic cartilage and degenerated disc. Mechanical overload directly contributes to this shift: in cartilage under excessive load, HIF-mediated signalling drives VEGF upregulation, providing a mechanotransduction link between abnormal biomechanics and angiogenic activation (Pufe et al., 2004).

CD34-positive endothelial microvessels represent the vascular response to this VEGF signal. The CD34 is a transmembrane glycoprotein expressed by vascular endothelial cells and is widely used in histopathology to highlight microvessels and quantify microvascular density (Fina et al., 1990; Sidney et al., 2014). CD34-positive luminal structures adjacent to, or penetrating, VEGF-positive disc cell zones mark the arrival or expansion of endothelial-lined microvessels in response to a permissive angiogenic microenvironment. Importantly, immunohistochemical analyses of the bilaminar zone in pathological TMJ disc specimens reveal a spatial association between VEGF-immunoreactive disc cells and CD34-immunoreactive endothelial microvessels in the same tissue region. Because separate immunostaining runs were performed (double staining was not conducted), this is characterised as a spatial association rather than cellular co-expression: VEGF immunopositivity identifies the pro-angiogenic disc cells generating the recruitment signal, while CD34 immunopositivity identifies the responding endothelial vascular structures. The two markers thus report different biological compartments – signal generator and signal recipient – within the same angiogenic axis. Chondrocytes or fibrochondrocytes do not themselves form blood vessels; rather, VEGF-positive disc cells activate endothelial recruitment and vascular ingrowth into a

matrix that would normally exclude vessels (Bonnet and Walsh, 2005; Gerber et al., 1999; Pfander et al., 2001). In the broader context of OA, a comparable vascular breach – channels crossing the tidemark, neurovascular invasion at the osteochondral junction, and osteophyte-associated angiogenesis – drives pain, subchondral bone remodelling, and disease progression (Bonnet and Walsh, 2005; Suri et al., 2007; Walsh et al., 2007).

In 15 TMJ discs displaced without reduction and 4 unaffected discs, TRAIL, DR5, and caspase-3 were co-expressed in the intima and media layers of newly formed vessels in the affected discs. This endothelial apoptosis has been interpreted as a self-limiting counter-process directed at inducing vessel regression, constituting an endogenous attempt to restrict the inflammatory vascular ingrowth that amplifies disc damage (Loreto et al., 2010). The complete sequence within Section 4.4 is therefore: VEGF + disc cells → CD34 + endothelial invasion (angiogenic switch) → TRAIL/DR5/caspase-3-driven endothelial apoptosis (self-limiting counter-response). The same TRAIL/DR5/caspase-3 apparatus thus operates in two spatially distinct compartments with opposite adaptive valences: CLC death worsens repair capacity while endothelial death attempts to limit angiogenesis-driven inflammation. This dual role of apoptosis in the TMJ disc, with repair-limiting CLC death on one side and potentially self-limiting endothelial death on the other, is summarised in Fig. 3 (Leonardi et al., 2011; Loreto et al., 2010, 2009).

### 4.5. *The intrinsic mitochondrial pathway*

Extrinsic TRAIL-driven apoptosis in the disc is accompanied by activation of the intrinsic mitochondrial pathway. In a cohort of 15 patients with ID and anterior disc displacement without reduction, compared with 6 unaffected discs, immunohistochemistry for Bax, Bcl-2, cytochrome c, and caspase-9 showed: complete absence of Bcl-2 immunopositivity in all pathological specimens; significantly greater cytochrome c and caspase-9 immunoreactivity in degenerated versus unaffected discs; and a significant correlation with the histopathological degeneration score (Spearman $\rho = 0.617$). These findings demonstrate that disc apoptosis occurs partly via the mitochondrial pathway (Caltabiano et al., 2013). The authors propose that convergence of extrinsic and intrinsic apoptosis, cross-linked via Bid cleavage by caspase-8, creates a self-amplifying loop that accelerates total disc cellularity loss (Caltabiano et al., 2013).

Nagai et al. (2003) extended the apoptosis narrative to the synovial compartment: in 47 arthroscopically obtained synovial specimens (31 ID, 11 OA, 5 condylar fractures), iNOS and Fas were detected primarily in synovial lining cells and subintimal macrophages; Fas expression was significantly higher in fractures than in OA, and single-stranded DNA (ssDNA, a direct marker of apoptosis) was significantly higher in OA than in ID. The positive correlation between iNOS and Fas/ssDNA expression indicated that nitric oxide-mediated oxidative stress and apoptosis co-evolve in the synovial lining as disc derangement progresses to OA (Nagai et al., 2003).

### 4.6. *Disc displacement and condylar chondrocyte apoptosis: the translational step*

Anterior disc displacement directly injures condylar chondrocytes through mechanical stress redistribution. In a rabbit surgical disc displacement model, apoptotic chondrocytes were abundant in articular cartilage from displaced joints, peaking at one to two weeks post-surgery and localised predominantly in the proliferative and hypertrophic zones, with a decrease in the total number of condylar chondrocytes by week two (Gu et al. 2002). At six weeks, the cartilage layer was thinner despite

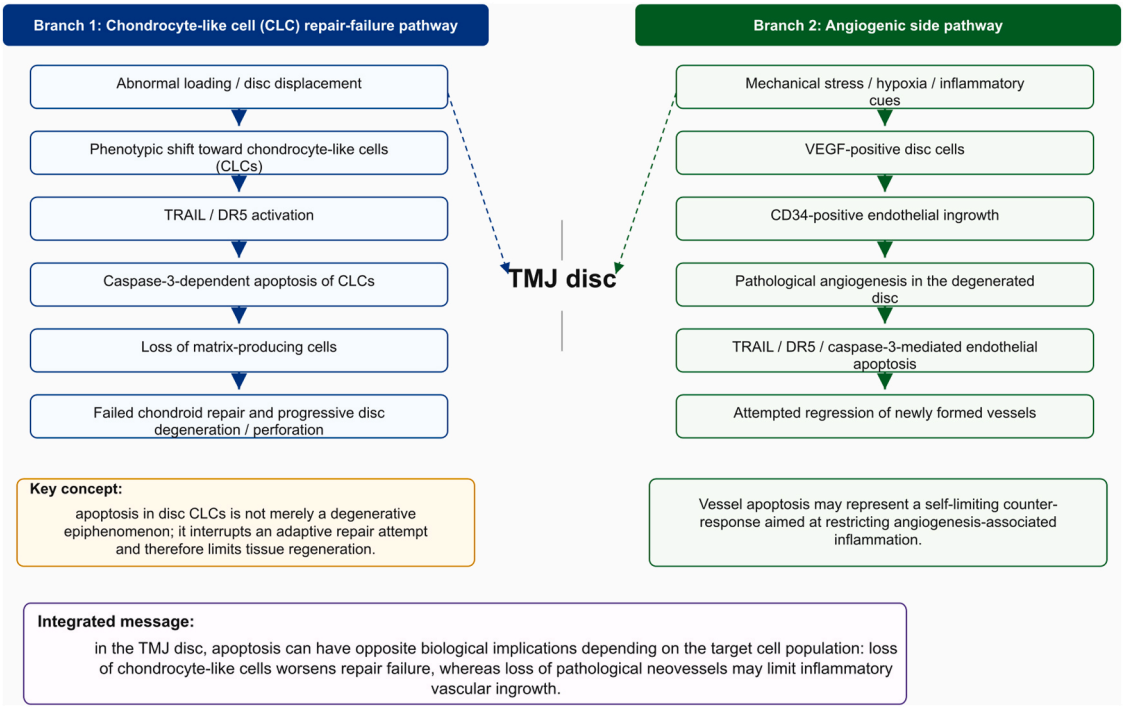



**Fig. 3. Cell death–repair failure axis in the TMJ disc.** Schematic representation of the two biologically distinct consequences of apoptosis in the degenerated temporomandibular joint disc. In the main repair-failure pathway, abnormal loading and disc displacement promote phenotypic transition of resident disc cells toward chondrocyte-like cells (CLCs). These CLCs express TRAIL and DR5 and undergo caspase-3-dependent apoptosis, reducing the population of matrix-producing cells and interrupting attempted chondroid repair. This sequence links internal derangement to progressive disc degeneration and, in advanced lesions, perforation. In the angiogenic side pathway, mechanical stress, hypoxia and inflammatory cues promote VEGF expression by disc cells, followed by CD34-positive endothelial ingrowth and pathological neovascularisation. TRAIL/DR5/caspase-3-mediated apoptosis of endothelial cells within newly formed vessels may represent a self-limiting counter-response aimed at restricting angiogenesis-associated inflammation. Thus, apoptosis has opposite biological implications depending on the target cell population: death of CLCs worsens repair failure, whereas death of pathological neovessels may limit inflammatory vascular ingrowth.

fewer apoptotic cells, indicating that early apoptotic loss is not compensated for by subsequent proliferation. This study established a direct causal link between disc displacement and condylar chondrocyte apoptosis, framing ADD not merely as a disc disease but as a trigger of condylar OA.

The rabbit study by Feng et al. (2002) is useful as an additional primary anchor for this sequence: surgically induced anterior disc displacement produced TUNEL-positive condylar chondrocytes most prominently at one to two weeks, with apoptotic cells concentrated in the proliferative and hypertrophic zones, followed by a remodelling phase at four to six weeks (Feng et al., 2002). This supports the interpretation that disc displacement can initiate a time-limited apoptotic burst before overt structural remodelling becomes dominant.

A clinically relevant molecular bridge from disc pathology to condylar apoptosis is provided by FSTL1 (follistatin-like protein 1). The FSTL1 is significantly elevated in the synovial fluid of temporomandibular disorders (TMD) patients with condylar bone resorption compared with those without; in condylar chondrocytes, FSTL1 overexpression disrupts mitochondrial morphology – reducing mitochondrial diameter and cross-sectional area and suppressing TIM23 and TOM20 mitochondrial membrane proteins – thereby inducing energy failure and mitophagy-dependent apoptosis. Targeted siRNA silencing of FSTL1 via intra-articular injection restored cartilage homeostasis markers and reduced apoptotic rates in the UAC rat TMJOA model (F. Li et al. 2025a).

### 4.7. BMSC exosomes as anti-apoptotic disc therapy

Bone marrow mesenchymal stem cell-derived exosomes (BMSC-Exos) represent a novel biological countermeasure against disc apoptosis. In TNF-α-treated TMJ disc chondrocytes and in a rat monoiodoacetate (MIA)-induced TMJOA model, BMSC-Exos attenuated the inhibitory effects on chondrocyte proliferation and chondrogenic potential and strongly suppressed TNF-α-induced apoptosis by increasing phosphorylation of PI3K/AKT pathway proteins. Intradiscal injection of BMSC-Exos alleviated disc degeneration and inflammation *in vivo* (Chen et al., 2025). This establishes a PI3K/AKT pro-survival axis as the disc's endogenous anti-apoptotic defence and BMSC-Exos as a carrier capable of reinforcing it.

## 5. Apoptosis in condylar cartilage

### 5.1. Zonal distribution and sex-related differences

Chondrocyte apoptosis in condylar cartilage under disordered occlusion follows a time- and sex-dependent pattern. In experimentally induced disordered occlusion (ECDO) in Sprague–Dawley rats, apoptotic chondrocytes increased significantly in the female 8- and 12-week subgroups and in the male 12-week subgroup. Female animals showed earlier and more extensive apoptosis, whereas male animals exhibited a significant decrease in chondrocyte proliferation in the 12-week subgroup. Histomorphological degradation was observed in all ECDO animals and correlated with the zonal distribution of apoptotic cells in the pre-hypertrophic and hypertrophic zones (Jiao et al., 2009). These sex differences in the timing and extent of apoptosis – with females showing earlier chondrocyte death – may partly explain the higher clinical prevalence of TMJOA in women.

### 5.2. iNOS and nitric oxide as mitochondrial apoptosis mediators

Nitric oxide (NO) produced by inducible nitric oxide synthase (iNOS) is a central mediator of mitochondria-dependent chondrocyte apoptosis in TMJOA. In unilateral anterior crossbite (UAC) rats and ATDC5 (a murine chondroprogenitor cell line) chondrocytes subjected to fluid flow shear stress (FFSS), iNOS expression was upregulated, accompanied by caspase-3 and caspase-9 immunostaining. These FFSS upregulated superoxide dismutase (SOD) and NO, reduced mitochondrial membrane potential (ΔΨm), and promoted cytochrome c release into the cytoplasm. All these changes were reversed by iNOS inhibitors, directly demonstrating that NO produced under mechanical load mediates mitochondrial damage and releases the intrinsic apoptotic cascade (Ren et al., 2019).

Tumour necrosis factor (TNF) is a further amplifier of this cascade. In UAC rats, TNF was significantly elevated in condylar chondrocytes and synovium from week 2, and local intra-articular injection of a TNF inhibitor at week 2 significantly reduced chondrocyte apoptosis (assessed by TUNEL), cleaved caspase-3, and Bax expression at week 4. In vitro, isolated condylar chondrocytes treated with TNF showed increased apoptosis by flow cytometry, and TNF inhibition abolished this effect (Yang et al., 2015). Together with the iNOS data, these findings position the TNF → NO → mitochondrial damage → caspase-9 → caspase-3 axis as a major apoptotic cascade in mechanically loaded condylar chondrocytes.

### 5.3. ERS pathway: Derlin-3 and the GRP78/CHOP/caspase-12 cascade

Endoplasmic reticulum stress (ERS) provides a second major upstream pathway for condylar chondrocyte apoptosis. Under FFSS in ATDC5 cells, the ERS-apoptosis pathway – characterised by upregulation of GRP78 (HSPA5), CHOP (DDIT3), ATF6, caspase-12, and cleaved caspase-3 – was induced. A key regulatory molecule is Derlin-3, an ER-associated degradation component whose expression in condylar cartilage increases at 1 and 3 weeks but decreases at 7 and 11 weeks after UAC induction (Liu et al., 2020). Derlin-3 thus operates as an endogenous brake on ERS-apoptosis coupling that is progressively lost as TMJOA advances – a mechanistic explanation for the increasing apoptotic burden observed at later disease stages.

The HIF transcription factors add a further layer of complexity to ERS-apoptosis regulation under the hypoxic microenvironment of condylar cartilage. In a UAC rat model over 2, 4, and 8 weeks, HIF-1α expression in condylar cartilage decreased progressively while HIF-2α increased, alongside rising ADAMTS5, MMP13, and cleaved caspase-3 at 8 weeks (Zhang et al., 2022). Complementary evidence from heterozygous HIF-1α-deficient mice showed thinner cartilage, reduced proteoglycan, and greater degeneration under mechanical stress than wild-type controls; mechanical stress in wild-type animals increased HIF-1α, VEGF, and caspase-3, with HIF-1α appearing to mediate a protective adaptive response (Mino-Oka et al., 2017). The synthesis of these data suggests that HIF-1α is chondroprotective while HIF-2α is pro-apoptotic, and that the loss of HIF-1α/gain of HIF-2α balance in progressive TMJOA shifts the hypoxic response from adaptive to destructive.

Mouth breathing exemplifies a non-occlusal aetiology for the same apoptotic cascades: in adolescent male rats, mouth breathing induced subchondral bone resorption, condylar cartilage thinning, and upregulation of TNF, Bax, cytochrome c, and cleaved caspase-3 in condylar cartilage, with apoptosis detectable in both the proliferative and hypertrophic layers. Both the extrinsic (TNF/caspase-8/caspase-3) and intrinsic (Bax/cytochrome c/caspase-9/caspase-3) pathways were activated simultaneously (Wang et al., 2023).

### 5.4. Epigenetic regulation: lncRNA HOTAIR

Long non-coding RNA HOTAIR (HOXC antisense RNA) links systemic inflammation and epigenetic regulation to apoptosis in condylar chondrocytes. The lncRNA HOTAIR was significantly upregulated in the synovial fluid of TMJ OA patients and of IL-1β-stimulated rabbit condylar chondrocytes. The HOTAIR knockdown reversed IL-1β-driven upregulation of MMP-1, MMP-3, and MMP-9, and significantly decreased the chondrocyte apoptosis rate induced by IL-1β, establishing HOTAIR as an epigenetic amplifier of both ECM catabolism and apoptosis in TMJOA (Zhang et al., 2016).

### 5.5. Chondrocyte apoptosis recruits osteoclasts: the CX3CL1/p38 axis

An important downstream consequence of condylar chondrocyte apoptosis is the active recruitment of osteoclast precursors (OCPs) to the subchondral zone, indicating that apoptosis can contribute actively to bone-resorptive signalling rather than representing only passive cell loss. In a TMJOA rat model, a temporal and spatial association between cartilage degradation and bone resorption was identified. Apoptotic chondrocytes – but not non-apoptotic chondrocytes – released CX3CL1 (fractalkine), a chemokine whose synthesis is regulated by p38 MAPK activation in dying cells. The CX3CL1–CX3CR1 axis recruited OCPs toward bone, and blockade of CX3CR1 or p38 (PH-797804) substantially reduced OCP chemotaxis and bone resorption. Pan-caspase inhibition (Z-VAD-FMK) also reduced OCP recruitment, confirming caspase dependence (Guo et al., 2022). This p38-CX3CL1 mechanistic axis reframes chondrocyte apoptosis from a cell-autonomous event to an intercellular signal with local osteochondral consequences.

### 5.6. Chondrocyte-derived exosomes and biomechanically driven cartilage calcification

Mechanically stressed condylar chondrocytes amplify TMJOA through a second non-cell-autonomous mechanism: enhanced exosome formation with pathologically altered pro-calcification cargo. In UAC rats over 4–12 weeks, TEM of degenerative condylar cartilage revealed a large number of exosome-like bilayer vesicles (50–150 nm) within the abnormal calcification matrix, accompanied by significantly elevated CD63 (exosome marker) positivity and progressive von Kossa-positive calcified zone expansion. The exosomal cargo was reciprocally dysregulated: matrix Gla protein (MGP, a direct calcification inhibitor that sequesters calcium–phosphate nucleation sites) was reduced in both chondrocytes and secreted exosomes, while tissue-nonspecific alkaline phosphatase (TNAP) and nucleotide pyrophosphatase/phosphodiesterase-1 (NPP1) – pro-calcification enzymes that together regulate inorganic phosphate (Pi) availability for basic calcium phosphate crystal formation – were significantly increased at all timepoints ($P < 0.01$). Under FFSS *in vitro*, primary condylar chondrocytes showed dose-dependent increases in exosome secretion (CD63 expression) and Alizarin red-positive calcified nodule formation; inhibition of exosome formation with GW4869 or supplementation of exogenous MGP and inhibition of TNAP/NPP1 (SBI-425; Ennp-1-IN-1) each significantly reduced calcification. The experimental sufficiency of these exosomes was demonstrated by local intra-articular injection of FFSS-stimulated chondrocyte exosomes into normal rat TMJs, which reproduced OA-like cartilage degeneration and calcification together with elevated TNFα, IL-1β, IL-6, and IL-18. Conversely, local GW4869 injection into UAC rats reduced calcification, degeneration, and cartilage inflammatory signalling. This exosome-dependent calcification cascade is mechanistically distinct from but temporally concurrent with the cell death programmes reviewed above: the same biomechanical stimuli that activate apoptosis, autophagy suppression, and necroptosis in condylar chondrocytes simultaneously drive exosome biogenesis, creating a parallel amplification loop – stressed chondrocytes → pathological exosomes → matrix calcification → inflammation → further chondrocyte stress – that accelerates osteochondral failure beyond what cell loss alone would predict (Q. Liu et al. 2022b).

### 5.7. Mechanical signalling in differentiation and terminal cell fate

Single-nucleus RNA sequencing of condylar cartilage from an overloading mouse model identified 11 distinct chondrocyte subtypes. Pseudotime trajectory and CellChat analyses converged on Acvr1b (the gene encoding activin receptor type IB / ALK4) and its downstream SMAD2/3 signalling as the key pathway driving terminal differentiation of condylar chondrocytes under overloading stress. Acvr1b inhibition *in vitro* reduced markers of terminal differentiation, positioning the activin/ALK4/SMAD axis as a novel therapeutic target for limiting overloading-driven chondrocyte fate commitment (Zhou et al., 2025). The mechanical signalling review by Liu et al. (2024) further maps how different magnitudes of mechanical stimulation selectively engage Wnt/β-catenin, TGF-β/BMP, FGF, and NF-κB pathways in TMJOA, with the appropriate magnitude window being critical: physiological loading is chondroprotective while excessive or insufficient loading promotes apoptotic and degenerative responses (Liu et al., 2024).

## 6. Autophagy: protective adaptation or cell-death pathway?

### 6.1. Autophagy as the first cellular response to mechanical overload

In the degenerative cartilage of the TMJ, autophagy is induced before apoptosis becomes prominent. In a rat model of biomechanical dental stimulation (4 molars displaced from original position), transmission electron microscopy detected autophagosomes, condensed chromatin, and abundant rough ER in experimental chondrocytes. The expression of Beclin1 and LC3 increased, while mTOR activity (assessed by p-mTOR and p-p70S6K) and MAP4K3 (mitogen-activated protein kinase kinase kinase kinase 3, an mTOR activator) decreased. The inversely proportional relationship between MAP4K3/mTOR activity and autophagy markers confirmed that mTOR inhibition is the principal mechanism coupling mechanical overload to autophagy induction (Zhang et al., 2013). This study established autophagy enhancement as an early protective response – not a death mechanism – in degenerative TMJ cartilage.

### 6.2. The ERN1–MTORC1–EIF2AK3 switch

As TMJOA progresses, the relationship between autophagy and apoptosis inverts. In UAC and FFSS models spanning 2–20 weeks, autophagy markers (Beclin1, LC3B-II, LAMP2) were elevated early and declined late; apoptosis markers (cleaved caspase-3) rose progressively. The molecular switch is governed by MTORC1 and its upstream regulators. In early injury, phosphorylated ERN1 (IRE1α) inhibits MTORC1 via AMPK (PRKAA1/2), promoting autophagic flux. As disease progresses, p-ERN1 signalling diminishes, releasing MTORC1 from inhibition. Activated MTORC1 then simultaneously suppresses autophagosome formation and, via phospho-EIF2AK3 (PERK), drives ERS-apoptosis through DDIT3 (CHOP) and CASP12 upregulation. p-EIF2AK3 additionally impairs autophagosome–lysosome fusion, eliminating the last autophagic defence. Chondrocyte-specific MTORC1 knockout in mice reproduced the pro-autophagy, anti-apoptosis phenotype; MTORC1 pharmacological activation worsened degeneration. Intra-articular rapamycin delivery rescued condylar cartilage through autophagy restoration and apoptosis suppression (Yang et al., 2020). The PDCD4 protein shows a parallel pattern: it suppresses autophagy and promotes apoptosis via Akt signalling in IL-1β-treated TMJ chondrocytes, further confirming that multiple molecular brakes on autophagy converge to push the chronically injured chondrocyte toward death (Liu et al., 2021a). An orchestrated review of initiation and progression of dental-stimulated TMJOA confirms: in insufficient matrix restoration, deep zone cells shift from autophagy to apoptosis and terminal differentiation, while superficial zone cells are prompted to differentiate and supply the cell loss in the deep zone, constituting the tissue's only remaining repair attempt (Liu et al., 2021b).

### 6.3. Migrasomes: a novel autophagy transfer system in TMJ synovium

A 2026 study identified migrasomes, vesicular organelles formed at retraction fibre tips of migrating cells, in synovial tissue and synovial fluid from patients with TMJOA. Single-cell transcriptomics and *in vitro* validation indicated infiltrating M1 macrophages as a major source of synovial migrasomes. Proteomic profiling showed enrichment in autophagy-related proteins, including LC3B and Beclin-1. After uptake

by osteoarthritic chondrocytes, M1 macrophage-derived migrasomes promoted autophagy activation, reduced catabolic changes and attenuated cartilage degeneration in a rat MIA-TMJOA model. The synovium-cartilage organoid model ("Mini-TMJ") supported synovium-to-cartilage migrasome transfer as a mechanism of intercellular autophagy support. These findings suggest that inflammatory macrophages may also generate vesicular cargo with chondroprotective activity under defined experimental conditions (Sa et al., 2026).

## 7. Pyroptosis and inflammasome-mediated synovitis

### 7.1. NLRP3/caspase-1/GSDMD in TMJOA synovium

Pyroptosis is a gasdermin-executed lytic death coupled to inflammasome activation. The NLRP3 oligomerises with apoptosis-associated speck-like protein containing a CARD (ASC) and pro-caspase-1 upon pathogen-associated molecular pattern (PAMP)/damage-associated molecular pattern (DAMP) sensing; active caspase-1 cleaves GSDMD and pro-IL-1β, with GSDMD-N-terminal fragments perforating the plasma membrane and releasing mature IL-1β and IL-18. In a complete Freund's adjuvant (CFA)-induced rat TMJOA model, NLRP3 mRNA and protein were upregulated in synovial tissue; caspase-1 inhibition by Ac-YVAD-cmk and NLRP3 inhibition by MCC950 both significantly suppressed pyroptosis in synovial tissue and reduced IL-1β secretion. In a macrophage-like synoviocyte (MLS) + fibroblast-like synoviocyte (FLS) co-culture model, LPS/ATP stimulation of MLS alone was insufficient to drive robust FLS pyroptosis; the macrophage component was required for robust FLS inflammasome activation. Ultrastructural evidence by TEM confirmed chromatin condensation, swollen mitochondria, dispersed trans-Golgi network, and plasma membrane pore formation in FLS – the morphological signature of pyroptosis. The NLRP3–caspase-1 axis thus operates through an obligatory macrophage-driven amplification mechanism in TMJ synovitis (Xin et al., 2022).

### 7.2. Chondrocyte pyroptosis with human tissue evidence

Human synovial-fluid data strengthen the case for pyroptosis in TMJOA. In synovial fluid and synovium from TMD patients, the pyroptotic biomarkers GSDMD, caspase-1 and IL-1β correlated positively with cartilage-degradation mediators and pro-inflammatory cytokines. In a mouse MIA-induced TMJOA model, alpha-kinase 1 (ALPK1)-deficient animals showed less synovitis, cartilage degeneration and chondrocyte pyroptosis than wild-type controls. In vitro, macrophage supernatants, rather than direct cytokine treatment alone, triggered ROS generation and NLRP3-dependent pyroptosis in primary TMJ chondrocytes and ATDC5 cells; metabolic disturbance preceded cell death. Inhibition of NLRP3 with MCC950 reduced both pyroptosis and metabolic disturbance by blocking caspase-1 activation and IL-1β secretion (Liu et al., 2023). Together with the MCC950/Ac-YVAD-cmk data (Xin et al., 2022), this study provides direct TMJ-specific evidence that pyroptosis contributes to cartilage degeneration in inflammatory TMJOA.

Reactive oxygen species (ROS) operate downstream of the NLRP3 inflammasome as effectors: in macrophages, hydrogen peroxide supplementation reversed the anti-inflammatory protection associated with MCC950, whereas N-acetylcysteine (NAC) reproduced MCC950-like effects, supporting a TLR4/NLRP3/ROS/IL-1β hierarchy (Liu, Li, Zhao, et al., 2023). In a separate CFA-induced murine TMJOA model, resatorvid downregulated the MyD88/NF-κB/NLRP3 cascade, reduced GSDMD expression and chondrocyte pyroptosis, and alleviated cartilage degeneration (Liu, Li, Feng, et al., 2023).

Taken together, these studies indicate that pyroptosis is no longer only an extrapolated mechanism in TMJOA. The best-supported evidence currently concerns synovium and condylar cartilage, whereas pyroptosis in the TMJ disc, especially in fibrochondrocytes and chondrocyte-like cells, remains uncharacterised.

## 8. Necroptosis and osteochondral inflammation

### 8.1. The RIPK3/MLKL necrosome in TMJOA

Necroptosis is initiated when apoptosis is blocked or overwhelmed: RIPK1 assembles with RIPK3 into the necrosome, RIPK3 phosphorylates MLKL (pMLKL), and oligomerised pMLKL forms plasma membrane pores causing osmotic lysis and release of DAMPs. In UAC-induced TMJOA rats, TEM revealed translucent cytosol, swollen organelles, and ruptured cell membranes in condylar chondrocytes at the early stage of cartilage degeneration. Both RIPK3 and pMLKL were upregulated by immunohistochemistry in the same cells. Intra-articular injection of RIPK3 or MLKL inhibitors, or genetic knockout of RIPK3/MLKL, significantly prevented cartilage degeneration (He et al., 2022), supporting necroptosis as a therapeutically modifiable mechanism of early condylar cartilage loss.

### 8.2. The TNFα–SDC4–TNFα vicious cycle

A self-amplifying necroptotic loop distinguishes TMJ necroptosis from simple DAMP release. Quantitative proteomics of DAMPs released by necroptotic condylar chondrocytes identified syndecan-4 (SDC4) and heat shock protein 90 as the principal signalling DAMPs. The SDC4, a heparan sulphate proteoglycan core protein, when released by necroptotic cells, significantly stimulated TNFα expression in cartilage and synovium; blocking SDC4 function with a specific antibody increased cartilage thickness and reduced synovial inflammation. The resulting TNFα → RIPK3/MLKL → necroptosis → SDC4 release → TNFα autocrine loop constitutes a feedforward cycle by which an initial necroptotic event propagates and sustains itself throughout the joint (He et al., 2022). The RIPK1 appears to regulate both limbs of this cycle: RIPK1 inhibition in TMJOA synoviocytes suppressed elevated inflammatory factors, NF-κB activation, and both apoptotic (caspase-8) and necroptotic (RIPK3/MLKL) cell death markers after TNF-α/cycloheximide stimulation. CFA-induced and disc perforation TMJOA models confirmed that RIPK1 inhibition protected articular cartilage against progressive degradation (Cao et al., 2024).

### 8.3. Temporal dynamics: apoptosis first, necroptosis later

A key mechanistic insight concerns the temporal sequence of death programme activation in mechanically stressed condylar cartilage. Under 60 g compressive mechanical force in a rat model, inflammation and apoptosis appeared throughout the entire cartilage layer on day 4 and persisted to day 7. Necroptosis was detectable only at the later time point (day 7) and was spatially concentrated in the transition layer rather than the full cartilage thickness. Lentiviral RIP1 silencing (Lenti-siRIP1) protected cartilage from thinning by simultaneously inhibiting sustained apoptosis at day 7 and late-stage necroptosis, confirming RIP1 as the shared upstream node coupling both programmes (Zhou et al., 2023). This temporal sequence – apoptosis as the immediate response, necroptosis as the amplified late event – has implications for treatment windows: anti-apoptotic intervention must precede, while anti-necroptotic intervention can follow, the onset of mechanical overload.

Earlier primary evidence from Zhang et al. (2017) already placed RIP1-dependent necroptosis within the mechanical-overload response of mandibular cartilage. In their compressive-force model, RIP1, RIP3 and caspase-8 increased after loading, and pharmacological inhibition of necroptosis with necrostatin-1 or apoptosis with Z-VAD partially restored cartilage thickness and chondrocyte number. Combined inhibition had a stronger protective effect, supporting the view that apoptosis and necroptosis are parallel, interacting responses to excessive mechanical force rather than mutually exclusive mechanisms (Zhang et al., 2017).

### 8.4. Epigenetic regulation: BRD4 and MLKL

The bromodomain protein BRD4 provides an epigenetic layer of necroptosis regulation in TMJOA. The BRD4 expression was notably upregulated in TMJ tissues under aberrant mechanical stress. Chromatin immunoprecipitation demonstrated BRD4 enrichment at the MLKL promoter region, and BRD4 expression showed a positive correlation with RIP3 and MLKL levels. Inhibition of BRD4 by JQ1 (intra-articular injection) significantly reduced chondrocyte necroptosis, downregulated TNF-α, RIP3, MLKL, and p-MLKL, and alleviated TMJOA-associated pathological changes (Huang et al., 2025). A narrative review of necroptosis in TMJOA contextualises these findings within the broader field: multiple small-molecule inhibitors of RIPK1, RIPK3, and MLKL have demonstrated efficacy in preclinical arthritis models, supporting the translational viability of this pathway (Zhao et al., 2025).

## 9. Ferroptosis, oxidative stress, and lipid peroxidation in TMJOA

### 9.1. Molecular machinery

Ferroptosis is iron-dependent cell death defined by accumulation of lipid hydroperoxides from peroxidation of polyunsaturated fatty acid (PUFA)-containing membrane phospholipids. The central antioxidant brake is the system Xc−/GSH/GPX4 axis: system Xc− imports cystine in exchange for glutamate; cystine is reduced to cysteine and condensed into glutathione (GSH); GPX4 uses GSH as a co-factor to reduce lipid hydroperoxides to non-toxic lipid alcohols. Depletion of GSH or GPX4 – through p53-mediated SLC7A11 suppression, inflammatory cytokine-driven iron accumulation, or direct GPX4 inhibition – unmasks lipid peroxide accumulation and ferroptotic cell death. The ACSL4 amplifies ferroptosis by esterifying PUFAs into membrane phospholipids. GPX4-independent parallel defences include FSP1/CoQ10, DHODH, and GCH1/BH4 (Zhang et al., 2025).

### 9.2. Ferroptosis in TMJ-specific evidence

Based on published primary data, GPX4 expression is significantly reduced in TMJOA tissues and synovial fluid. Proteomic analysis of synovial fluid from patients with TMJ anterior disc displacement and OA identified upregulation of FGFR1, FBLN2, and GRB2, implicating ferroptotic signalling specifically in the ADD-with-OA microenvironment. In rat TMJOA models (UAC, occlusal disorder, MIA, IL-1β), ferroptosis markers (elevated p53, elevated ACSL4, decreased GPX4) were confirmed. Liproxstatin-1 (Lip-1), a ferroptosis inhibitor, suppressed condylar chondrocyte ferroptosis, restored mitochondrial function, reduced ROS and lipid peroxidation, and preserved cartilage matrix in these models (Zhang et al., 2025).

### 9.3. The HIF-1α/TFRC axis: direct mechanistic evidence from human TMJOA

A mechanistic chain connecting synovial inflammation to iron-driven ferroptosis in condylar chondrocytes has been proposed and experimentally supported. In TMJOA patients, synovial fluid aspirated before hyaluronic acid lavage contained markedly elevated IL-1β, ROS, $Fe^{3+}$, and $Fe^{2+}$ compared with post-lavage values – providing direct human biofluid support for iron overload as a feature of TMJOA (Chen et al., 2024). The RNA sequencing of IL-1β-treated TMJ chondrocytes identified a gene ontology shift toward iron homeostasis and oxidative stress-related cell death. In UAC rats, condylar cartilage demonstrated reduced COL2A1, decreased chondrocyte number, GPX4 downregulation, and elevation of 4-hydroxynonenal (4-HNE) – a specific end-product of PUFA lipid peroxidation and a recognised ferroptosis-associated lipid peroxidation marker – all reversed by intra-articular ferrostatin-1 (Fer-1).

The upstream regulatory hierarchy operates as follows: IL-1β → HIF-1α transcriptional upregulation → TFRC (transferrin receptor 1) induction → $Fe^{2+}$ entry into chondrocytes → Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \cdot OH$) → propagating lipid radical chain → ferroptotic death. The directionality was pharmacologically confirmed: HIF-1α inhibition downregulated IL-1β-induced TFRC expression, whereas TFRC inhibition did not alter HIF-1α levels, placing HIF-1α upstream of TFRC in this experimental setting. Both HIF-1α and TFRC inhibition independently rescued IL-1β-induced mitochondrial membrane potential loss and restored mitochondrial structure. Downstream, both HIF-1α and TFRC inhibition reduced IL-1β-stimulated MMP13 and rescued COL2A1 expression in chondrocytes (Chen et al., 2024). The HIF-1α/TFRC/iron/4-HNE/GPX4↓ axis thus constitutes the primary inflammation-to-ferroptosis transduction pathway in TMJOA condylar chondrocytes.

This also clarifies the dual-role paradox of HIF-1α in the TMJ: HIF-1α is chondroprotective against apoptosis under mechanical stress (Mino-Oka et al., 2017) but pro-ferroptotic via TFRC-driven iron loading under inflammatory conditions (Chen et al., 2024) – the same transcription factor having divergent consequences depending on the dominant upstream stimulus.

### 9.4. The Nrf2/ARE anti-ferroptotic defence: curcumin as an experimental activator

The principal endogenous cellular defence against ferroptosis beyond GPX4 operates through the Nrf2/antioxidant response element (ARE) transcriptional programme. Nrf2 drives expression of HO-1, SOD2, NQO-1, and GCLC – the rate-limiting enzyme for GSH synthesis – supporting the GSH/GPX4 anti-ferroptotic system. In IL-1β-stimulated human TMJ chondrocytes, curcumin (CUR), the principal bioactive polyphenol of Curcuma longa, activated Nrf2 (and its phosphorylated form p-Nrf2) and upregulated all four Nrf2 downstream antioxidants (HO-1, SOD2, NQO-1, GCLC) at both mRNA and protein levels. The CUR concomitantly suppressed IL-1β-induced iNOS, COX-2, IL-6, MMP-1, MMP-3, MMP-9, MMP-13, ADAMTS-4, and ADAMTS-5, and reduced ROS generation, while restoring COL2A1 and ACAN mRNA expression (Jiang et al., 2020). Because the Nrf2/ARE programme drives GCLC-mediated GSH synthesis upstream of GPX4, curcumin's mechanism positions it as an anti-ferroptotic agent operable at the GSH supply level – complementing radical-trapping ferroptosis inhibitors such as liproxstatin-1 and ferrostatin-1, and providing a plant-derived therapeutic with demonstrated intra-articular tolerability in TMJOA.

A polymer nanoparticle platform extends this polyphenol anti-ferroptotic strategy into a sustained intra-articular delivery system with superior pharmacokinetics. Poly(p-coumaric acid) nanoparticles (PCA NPs), synthesised by polycondensation of p-coumaric acid (p-CA, a naturally occurring phytophenolic acid) and stabilised with DSPE-PEG2k into ~118 nm spherical particles, exhibit concentration-dependent DPPH and ABTS radical-scavenging activity significantly exceeding that of hyaluronic acid (HA) at all tested concentrations. In IL-1β- and erastin-stimulated condylar chondrocytes, PCA NPs restored GPX4 and SLC7A11 expression, suppressed ACSL4 and p53 upregulation, reduced $Fe^{2+}$ accumulation (FerroOrange probe), diminished lipid ROS and MDA, restored mitochondrial network morphology and membrane potential (JC-1 staining), and elevated intracellular GSH and SOD activity. In vivo transcriptomic analysis of MIA-induced TMJOA rat condylar cartilage by KEGG GSEA confirmed ferroptosis as the primary pathway modulated by PCA NP treatment alongside oxidative phosphorylation and oxidative stress pathways. At 8 weeks post-injection, PCA NPs significantly outperformed HA in BV/TV recovery, Mankin score improvement, MMP13/iNOS suppression, and collagen II restoration. Importantly, Cy5-labelled PCA NPs retained detectable fluorescence in the TMJ for at least 7 days post-injection – significantly longer than free Cy5 or p-CA-Cy5 (both nearly absent by day 5) – a pharmacokinetic advantage confirmed by SEM to reflect adherence to the fibrocartilage matrix surface. This drug-free nanoparticle platform

combines: sustained joint retention exceeding HA, direct ferroptosis inhibition through GPX4/SLC7A11 axis restoration, anti-inflammatory blockade of iNOS/TNFα/MMP pathways, and a natural polyphenol safety profile – making PCA NPs a multi-functional, disease-modifying candidate that operates simultaneously at the Nrf2/ferroptosis and inflammatory axes of TMJOA (Guo et al., 2024).

### 9.5. Inflammatory amplification: pyroptosis–ferroptosis loop

The inflammatory milieu creates a pyroptosis-to-ferroptosis amplification loop: IL-1β – the canonical GSDMD pore-release product – activates HIF-1α/TFRC to drive iron overload, elevates lipid peroxidation, and downregulates GSH, directly inducing ferroptotic conditions in neighbouring chondrocytes. Conversely, ferroptosis-associated lipid peroxidation products (including 4-HNE) can activate NLRP3 inflammasome assembly, reinforcing pyroptosis (Chen et al., 2024; Zhang et al., 2025). This IL-1β → HIF-1α/TFRC → $Fe^{2+}$/ROS/4-HNE → GPX4↓ → ferroptosis → lipid peroxides → NLRP3 → IL-1β cycle constitutes a self-sustaining inflammatory death amplification loop that is specifically accessible to therapeutic interruption at multiple nodes: NLRP3 can be inhibited by MCC950; HIF-1α and TFRC can be blocked to reduce iron influx; the Nrf2/ARE transcriptional programme can be activated by curcumin to restore glutathione supply; and lipid peroxidation can be suppressed by liproxstatin-1 or ferrostatin-1.

## 10. Cellular senescence, mitophagy failure, and the progenitor-cell niche

### 10.1. Senescence in TMJOA

Cellular senescence – permanent cell-cycle arrest accompanied by the senescence-associated secretory phenotype (SASP) – is a state that bridges ageing-associated metabolic decline and OA pathogenesis. Key biomarkers include p16 (CDKN2A), p21 (CDKN1A), p53, SA-β-galactosidase, and Lamin A/C. The cyclin-dependent kinase inhibitor p21 carries a dual role in TMJOA: beyond its canonical senescence-associated cell cycle arrest, p21 exerts an immunoregulatory function in the condylar cartilage. In p21-knockout mice subjected to a TMJ loading protocol, condylar OA was significantly exacerbated compared with wild-type, with greater inflammatory infiltrate and cartilage loss. This suggests that p21 limits the immune-mediated component of condylar degeneration, and that p21 loss removes an important brake on cartilage destruction (Khurel-Ochir et al., 2021).

### 10.2. Sympathetic innervation and mitochondrial dynamics

The sympathetic nervous system provides a recently identified upstream regulator of mitochondrial dynamics and potential senescence in TMJOA chondrocytes. Activation of the α2-adrenergic receptor (Adra2) by norepinephrine in primary condylar chondrocytes upregulated MMP-3, downregulated aggrecan, and simultaneously increased mitochondriogenesis, the number of mitochondria, mitochondrial fusion and fission, and mitophagy. α2-Adrenergic receptor antagonism (yohimbine) attenuated these catabolic and mitochondrial changes, establishing a sympathetic → α2-Adra2 → mitochondrial dynamics → catabolism axis in TMJ chondrocytes that may link pain-related sympathetic tone to cartilage degeneration (He et al., 2024). This represents a novel neuro-osteochondral pathway with therapeutic implications in pain-associated TMJOA.

### 10.3. Single-cell transcriptomics: terminal differentiation trajectories

Single-nucleus RNA sequencing of overloaded condylar cartilage identified 11 distinct cell types (Zhou et al., 2025). Pseudotime trajectory analysis revealed Acvr1b (ALK4 / activin receptor type 1B) and its SMAD2/3 downstream signalling as the key driver of terminal chondrocyte differentiation under mechanical overload. CellChat intercellular communication analysis confirmed Acvr1b-mediated cell fate commitment. These scRNA-seq data provide the highest-resolution view currently available of the cellular heterogeneity underlying condylar cartilage degeneration and identify cell subtypes at differential risk for apoptosis and terminal differentiation. Earlier scRNA-seq work on OA cartilage had identified regulatory chondrocytes (RegC) and fibrochondrocytes as the principal necroptotic subtypes (MLKL/RIPK1/RIPK3-enriched), while homeostatic chondrocytes (HomC) showed lower necroptosis scores, establishing subtype specificity for death programme engagement.

### 10.4. The perivascular progenitor niche: the repair counterpoint to cell death

The conceptual integration of cell death with repair capacity requires consideration of a putative perivascular repair reservoir in the disc periphery. The normal TMJ disc is nearly avascular; only its peripheral zone – the bilaminar zone and lateral/medial margins – contains vascularisation and associated perivascular stromal cells. These CD34 + perivascular stromal cells share morphological and phenotypic features with pericyte-associated MSC precursors described in fibrocartilaginous tissues and have been proposed as constituents of a perivascular progenitor niche in the TMJ disc periphery.

Loss or dysfunction of perivascular stromal cells could reduce the disc's already limited repair capacity. However, direct evidence that CD34-positive stromal cells in the TMJ disc are selectively depleted through TRAIL/DR5-mediated apoptosis or inflammation-associated ferroptosis is currently lacking. Their susceptibility to individual death programmes and their functional contribution to disc repair therefore remain hypotheses requiring targeted investigation. Conversely, the superficial zone of the condylar cartilage, which retains progenitor-like qualities including the capacity to proliferate and differentiate toward the deep zone (Liu et al., 2021b), represents the condyle's analogous repair reservoir – similarly vulnerable to SASP-driven paracrine senescence, ferroptosis, and necroptosis-associated DAMPs.

MSC-centred TMJOA reviews reinforce this repair-centred interpretation. Cui et al. (2017) and Zhao and Xie (2021) both emphasised that conventional management rarely restores degraded cartilage or subchondral bone, whereas MSC-based strategies may act through chondrogenic differentiation, trophic support, immunomodulation, exosomes and scaffold-assisted fibrocartilage regeneration (Cui et al., 2017; Zhao & Xie, 2021). In the present review, these data are used not as proof that the disc niche can already be therapeutically rebuilt, but as support for treating progenitor-cell preservation as a biologically relevant counterpart to regulated cell death.

MIA-induced TMJOA in female rats showed activation of the toll-like receptor pathway, oestrogen metabolism, oxidative stress, and altered energy metabolism as convergent drivers of condylar OA, with oestrogen-related pathways contributing to the higher prevalence in women (Liu et al., 2025). Together with the sex differences in apoptosis timing (Jiao et al., 2009), these data highlight female oestrogen biology as an important modulator of death programme vulnerability in the TMJ.

The perivascular origin of CD34 + stromal cells in the disc periphery also intersects with the vascular endothelial growth factor (VEGF) signalling network that governs osteogenic repair capacity in the condylar compartment. During endochondral ossification, VEGFA functions as the central mediator coupling hypertrophic cartilage remodelling, vascular invasion, and bone deposition: hypertrophic chondrocytes at the chondro-osseous junction secrete VEGF, which promotes endothelial ingrowth while simultaneously recruiting osteoblast-lineage precursors from the perichondrium into the primary ossification centre (Gerber et al., 1999; Maes et al., 2010). HIF-1α, essential for chondrocyte growth arrest and survival under hypoxic conditions (Schipani et al., 2001), amplifies VEGF production and thereby couples angiogenesis to

osteogenesis (Wang et al., 2007). Lineage-tracing studies have established that a proportion of hypertrophic chondrocytes survive the cartilage-to-bone transition and transdifferentiate into osteoblasts and osteocytes during both development and fracture repair (Yang et al., 2014; Zhou et al., 2014) – a process requiring VEGFA to maintain the vascular microenvironment that supports precursor recruitment and mineralisation. Beyond its paracrine roles, intracellular VEGF directly regulates mesenchymal stem cell fate: loss of intracellular VEGF shifts the RUNX2/PPARγ2 balance toward adipogenesis and away from osteoblastogenesis, demonstrating that VEGF acts within skeletal progenitors as well as through extracellular vascular mechanisms (Liu et al., 2012). By extrapolation from skeletal biology, disruption of a perivascular repair niche could impair regenerative support in TMJOA. Whether CD34-positive stromal cells in the disc undergo pathway-specific depletion, or contribute directly to VEGF-dependent condylar repair, remains unproven.

## 11. Crosstalk between cell death pathways

Programmed cell death pathways are not isolated linear cascades but form an interconnected network in which shared molecular switches, compensatory responses, and integrated multi-programme states determine cellular fate (Bedoui et al., 2020; Eskander et al., 2025; Kist & Vucic, 2021). Three linked questions organise the crosstalk literature: which molecules serve as shared switches between pathways; do cells engage genuinely integrated death states that cannot be attributed to any single programme; and where do current mechanistic models fall short (Sorokin et al., 2025)? The discussion below applies these general principles to the TMJ context with specific reference to primary TMJ data where available.

### 11.1. Shared molecular switches

Caspase-8 is the master switch between extrinsic apoptosis and necroptosis. When active, caspase-8 cleaves RIPK1 and RIPK3, preventing necrosome assembly and directing the cell towards apoptotic death. When caspase-8 activity is blocked – by viral inhibitors, by cFLIP upregulation, or by sustained biomechanical overload that depletes initiator caspases – RIPK1 and RIPK3 are free to assemble the necrosome and activate MLKL (Kutumova et al., 2025; Yuan & Ofengeim, 2024). In the TMJ, this switch is not theoretical: the temporal sequence in mechanically compressed condylar cartilage – apoptosis on day 4 across the whole cartilage layer, necroptosis on day 7 confined to the transition zone – represents the biological manifestation of this competition under sustained stress, as caspase-8 capacity is outpaced by progressive load (Zhou et al., 2023).

Caspase-3 bridges apoptosis and secondary pyroptosis through GSDME (gasdermin E) cleavage. Although canonical pyroptosis depends on caspase-1-mediated GSDMD cleavage, active caspase-3 can cleave GSDME to generate a pore-forming N-terminal fragment, converting an apoptotic stimulus into a lytic, pyroptotic-like outcome. Conversely, caspase-3 can inactivate GSDMD by cleaving it at a non-canonical site, attenuating pyroptosis when apoptosis is the dominant mode of death (Wang & Kanneganti, 2021). The net outcome – lytic pyroptosis or non-lytic apoptosis – depends on which caspase substrates are engaged first and at what stoichiometry. In the TMJ synovium, where macrophage-driven IL-1β release through GSDMD pores and FLS apoptosis coexist (Xin et al., 2022), caspase-3/GSDME crossover is biologically plausible and mechanistically unexplored.

The BCL-2 family proteins, Beclin-1, $Ca^{2+}$, and p53 link apoptosis and autophagy, making stress responses rheostatic rather than binary (Kutumova et al., 2025). The BCL-2 binds and sequesters Beclin-1, preventing autophagosome nucleation; pro-apoptotic BH3-only proteins release Beclin-1 by displacing it from BCL-2, simultaneously initiating autophagy and promoting BAX/BAK-mediated cytochrome c release. In TMJ models, an early autophagy-dominant phase coincides with p-ERN1-mediated suppression of MTORC1, whereas later apoptotic dominance coincides with restored MTORC1 activity (Yang et al., 2020; Zhang et al., 2013).

The MTORC1 operates at the apex of the autophagy–apoptosis switch: MTORC1 activation suppresses autophagic flux and simultaneously drives EIF2AK3-mediated ERS-apoptosis; conversely, MTORC1 inhibition by intra-articular rapamycin restores autophagy and suppresses apoptosis, and loss of autophagic protection sensitises chondrocytes to ferroptosis and necroptosis through ROS accumulation (Li et al., 2021; Yang et al., 2020).

### 11.2. TMJ-specific molecular hubs

NF-κB/ROS bridge pyroptosis, ferroptosis, and senescence in the condylar and synovial compartments. IL-1β released through GSDMD pores activates NF-κB, upregulates TFRC and HIF-1α (iron accumulation), and suppresses GPX4, directly imposing ferroptotic conditions in neighbouring chondrocytes (Chen et al., 2024). Ferroptosis-associated lipid peroxidation products – particularly 4-HNE – can activate NLRP3 inflammasome assembly, establishing a pyroptosis → ferroptosis → pyroptosis amplification cycle (Chen et al., 2024; Zhang et al., 2025). The same ROS excess generated by failed mitophagy promotes HIF-2α upregulation, caspase-3 activation, and SASP secretion, thereby linking the mitophagy/senescence arm to all inflammatory death programmes (Zhang et al., 2022).

The SDC4–TNFα vicious cycle (He et al., 2022) exemplifies how necroptotic DAMPs re-enter the network as inflammatory inputs: syndecan-4 released by necroptotic chondrocytes stimulates TNFα expression in cartilage and synovium, thereby activating RIPK1 and re-initiating the apoptosis–necroptosis competition in neighbouring cells. The cycle is thus self-amplifying and can only be broken upstream (RIPK1/RIPK3/SDC4 inhibition) rather than by targeting a single downstream effector.

### 11.3. PANoptosis-compatible convergence of cell-death programmes

PANoptosis is an inflammatory cell-death state in which pyroptotic, apoptotic and necroptotic machinery are engaged in an integrated network that cannot be fully explained by any single pathway (Gullett et al., 2022; Wang & Kanneganti, 2021). The operational criterion is functional redundancy (Fig. 4): disruption of one arm alone, such as caspase-1, RIPK3 or Bax/Bak, does not completely prevent cell death, whereas combined disruption of pyroptotic and apoptosis-necroptosis modules provides greater protection (Gullett et al., 2022). Infection models show that cells can switch death routes when one arm is inhibited or pathogen-modified (Bedoui et al., 2020; Snyder & Oberst, 2021). In non-TMJ disease contexts, including neurological disorders and cancer, PANoptosis may remove damaged or malignant cells while also amplifying bystander inflammation (Guo et al., 2025; P. Li et al., 2025b; J. Liu et al., 2022a).

In the TMJ, direct evidence of PANoptosis has not been reported, but several prerequisites are present. Condylar chondrocytes under UAC or MIA models show activation of caspase-3 (apoptotic), RIPK3/MLKL (necroptotic) and GSDMD/caspase-1 (pyroptotic) pathways under TNFα- and IL-1β-rich conditions; the SDC4-TNFα loop may sustain cytokine levels sufficient to engage more than one module. PANoptotic assessment, as operationally defined by Gullett et al. (2022), would require combined pathway knockdown or inhibition to test whether blocking one pathway is insufficient to prevent cell death (Gullett et al., 2022). This is a feasible next step for TMJ models, particularly in synoviocyte and macrophage-FLS co-culture systems (Xin et al., 2022).

### 11.4. Evidence architecture and knowledge gaps in the TMJ crosstalk context

Mapping the general cell death crosstalk literature onto the TMJ

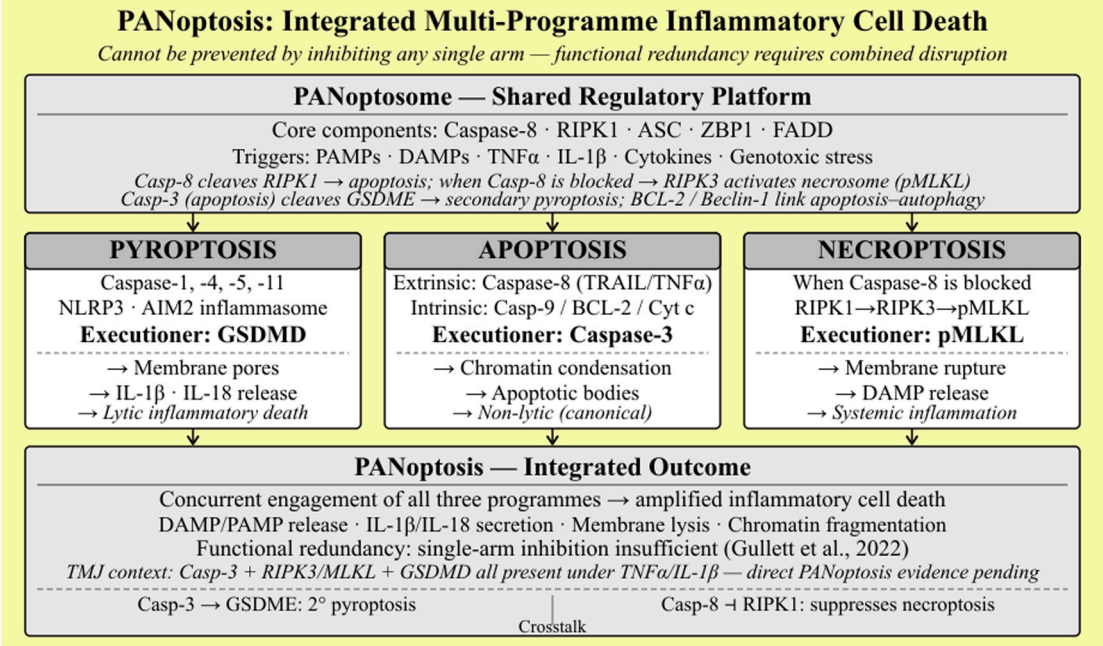



**Fig. 4. PANoptosis as an integrated inflammatory cell-death platform.** The diagram summarises PANoptosis as a coordinated, multi-programme form of regulated cell death in which pyroptosis, apoptosis and necroptosis are not activated as isolated pathways, but through a shared regulatory platform, the PANoptosome. Upstream inflammatory, damage-associated, and stress signals, including pathogen-associated molecular patterns (PAMPs), damage-associated molecular patterns (DAMPs), tumour necrosis factor-α (TNFα), interleukin-1β (IL-1β), cytokine signalling, and genotoxic stress, converge on core molecular components such as caspase-8, RIPK1, ASC, ZBP1, and FADD. These signals may engage pyroptotic execution via inflammasome-associated caspases and gasdermin D (GSDMD), apoptotic execution via caspase-3, and necroptotic execution via the RIPK1-RIPK3-phosphorylated MLKL axis. The lower panel indicates the integrated outcome, in which membrane permeabilisation or rupture, cytokine release, chromatin fragmentation and DAMP/PAMP release amplify tissue inflammation. In the temporomandibular joint (TMJ), the coexistence of caspase-3, RIPK3/MLKL and GSDMD expression under TNFα/IL-1β-rich conditions may support a PANoptosis-compatible environment. However, direct evidence for a complete PANoptotic complex in TMJ tissues remains to be demonstrated. Abbreviations: ASC, apoptosis-associated speck-like protein containing a CARD; DAMP, damage-associated molecular pattern; FADD, Fas-associated death domain protein; GSDMD, gasdermin D; IL, interleukin; MLKL, mixed-lineage kinase domain-like protein; PAMP, pathogen-associated molecular pattern; RIPK, receptor-interacting serine/threonine-protein kinase; TMJ, temporomandibular joint; TNFα, tumour necrosis factor-α; ZBP1, Z-DNA-binding protein 1.

reveals a consistent gradient in the maturity of evidence. Apoptosis–necroptosis–pyroptosis crosstalk has the largest combined evidence base – genetic (RIPK1/3 knockout, caspase-8 deletion studies), mechanistic (necrosome/inflammasome biochemistry), and some integrated modelling – but clinical translation in the TMJ context remains limited to small animal studies without biomarker validation in human tissue (Qian et al., 2024; Sorokin et al., 2025). Autophagy crosstalk with apoptosis has strong mechanistic support (ERN1–MTORC1–EIF2AK3 axis) (Yang et al., 2020) and preclinical therapeutic leverage (rapamycin), but models do not yet incorporate autophagy–ferroptosis or autophagy–necroptosis interactions specifically in TMJ tissue.

Ferroptosis integration is the clearest gap in the evidence for crosstalk. Although the pyroptosis → ferroptosis link via IL-1β/HIF-1α/TFRC is mechanistically supported (Chen et al., 2024), ferroptosis is largely excluded from quantitative multi-pathway models because cross-pathway biochemical connections to the RIPK1/caspase-8 axis and to the GSDMD system remain incompletely characterised (Kutumova et al., 2025). A TMJ-specific computational model integrating MTORC1, RIPK1, NF-κB, and the HIF-1α/TFRC/GPX4 ferroptosis arm would be a useful advance and tractable, given the density of quantitative *in vitro* and *in vivo* data now available in the field.

A second gap is translation from network biology to clinical biomarkers. Cancer and inflammatory disease research consistently argues that adaptive rewiring across death programmes makes single-pathway therapeutic targeting insufficient, yet context-specific biomarkers able to identify which death mode dominates at a given TMJOA stage remain absent (Guo et al., 2026; Qian et al., 2024). Synovial fluid proteomics already contains pyroptotic biomarkers (Liu, Li, Zhao, et al., 2023) and ferroptosis indicators ($Fe^{2+}$ overload) (Chen et al., 2024); adding necroptotic (pMLKL, SDC4) and autophagic (LC3B, SQSTM1) markers to a multi-programme panel would provide the stage-specific fingerprint needed to match therapeutic intervention to disease phase.

The ageing and degenerating TMJ therefore exhibits a convergent multi-pathway death network: mitophagy failure elevates ROS, driving simultaneous apoptosis, ferroptosis, and NLRP3 pyroptosis (Yang et al., 2020; Zhang et al., 2013); GSDMD-released IL-1β amplifies ferroptosis via HIF-1α/TFRC (Chen et al., 2024); necroptotic SDC4 sustains the TNFα loop (He et al., 2022); and SASP cytokines prime the synovium for macrophage-driven FLS pyroptosis amplification (Liu, Li, Zhao, et al., 2023; Xin et al., 2022) – all superimposed on a progenitor pool already depleted by disc ID-associated apoptosis (Leonardi et al., 2011; Loreto et al., 2009). This convergent pathology is the reason why multi-pathway crosstalk should inform the framework for both mechanistic understanding and therapeutic design in TMJOA.

## 12. Therapeutic implications

Apoptosis in the disc can be counteracted by anti-TRAIL antibodies or TRAIL decoy receptor upregulation (to block the CLC apoptosis), TNF inhibition, iNOS inhibitors, and BMSC-derived exosomes delivered intradiscally (Chen et al., 2025; Leonardi et al., 2011; Loreto et al., 2009; Ren et al., 2019; Yang et al., 2015). The PI3K/AKT axis activated by BMSC-Exos provides a pharmacologically actionable survival pathway for disc chondrocytes (Chen et al., 2025).

Autophagy restoration via MTORC1 inhibition (intra-articular rapamycin) (Yang et al., 2020) and M1 macrophage-derived migrasome delivery (restoring autophagic flux in OA chondrocytes) (Sa et al., 2026) represent mechanistically distinct strategies for autophagy rescue.

Pyroptosis suppression through NLRP3 inhibition (MCC950), caspase-1 blockade (Ac-YVAD-cmk), TLR4 antagonism (resatorvid), and ALPK1 pathway blockade has been tested in TMJ-specific experimental models (Liu, Li, Feng, et al., 2023; Liu, Li, Zhao, et al., 2023; Xin et al., 2022). Reactive oxygen species (ROS) scavenging with NAC provides a downstream complementary approach.

Necroptosis inhibition targets multiple nodes: RIPK1 inhibition, RIPK3/MLKL inhibition, SDC4 antibody blockade, and BRD4 inhibition (JQ1) (Cao et al., 2024; He et al., 2022; Huang et al., 2025; Zhou et al., 2023). Temporal considerations apply: anti-RIP1 lentiviral delivery must precede day 7 to capture both apoptotic and necroptotic windows (Zhou et al., 2023).

Ferroptosis inhibition operates at multiple nodes of the HIF-1α/TFRC/iron/GPX4 axis: suppression of lipid peroxidation by liproxstatin-1 and ferrostatin-1 (both reported in UAC rat TMJOA); Nrf2/ARE activation via curcumin (intra-articular injection reported in CFA rat TMJOA), which drives GCLC-mediated GSH supply upstream of GPX4; iron chelation (deferoxamine); HIF-1α inhibition to reduce TFRC induction; and direct TFRC blockade (Chen et al., 2024; Jiang et al., 2020; Zhang et al., 2025). The NLRP3 blockade simultaneously reduces ferroptotic susceptibility by curtailing IL-1β-mediated upregulation of HIF-1α/TFRC, illustrating the shared therapeutic leverage of pyroptosis and ferroptosis inhibition (Chen et al., 2024; Zhang et al., 2025).

Experimental evidence supports α2-adrenergic receptor antagonism to attenuate sympathetic signalling-associated mitochondrial dysregulation and identifies p21-mediated immunoregulation as protective against condylar cartilage degeneration (He et al., 2024; Khurel-Ochir et al., 2021). Acvr1b/ALK4 inhibition to limit terminal differentiation (Zhou et al., 2025) represents an emerging strategy that targets cell fate commitment rather than death itself.

Disc repair requires addressing the progenitor niche. BMSC-Exos delivered intradiscally preserved disc chondrocyte viability via PI3K/AKT (Chen et al., 2025). Scaffolds seeded with CD34 + perivascular stromal cells from the disc periphery, combined with anti-apoptotic coatings (TRAIL blockade) and anti-ferroptotic coatings (GPX4 augmentation), represent a conceptually sound tissue-engineering approach that has not yet been tested (Cui et al., 2017; Loreto et al., 2009; Zhang et al., 2025; Zhao & Xie, 2021).

This therapeutic framing should remain conservative. The broader regenerative literature supports platelet-rich plasma (PRP), HA and MSC-based interventions as potentially structure-modifying or repair-supportive in TMJOA, but results remain heterogeneous and often model-dependent (Cardoneanu et al., 2022; Zhao & Xie, 2021). Therefore, anti-death interventions should be presented as complementary to, not replacements for, regenerative strategies directed at cartilage, disc and subchondral bone repair.

## 13. Gaps and future directions

The evidence landscape identifies several specific gaps that can be addressed experimentally.

Pyroptosis, previously considered a "research gap" in primary TMJ studies, is now documented by two direct primary studies (Liu, Li, Zhao, et al., 2023; Xin et al., 2022), one of which includes human synovial fluid data. However, both studies focus on the condylar cartilage and synovium; pyroptosis in the disc fibrochondrocyte is entirely uncharacterised.

Disc-specific data are currently unavailable for autophagy, necroptosis, and ferroptosis. Whether autophagy in disc CLCs is protective or biphasic, whether RIPK3/MLKL is activated in disc fibrochondrocytes, and whether the GPX4/system Xc− axis is expressed and functional in disc peripheral cells are entirely open questions.

Necroptosis has substantial interventional evidence among the emerging pathways, with blockade of the RIPK1, RIPK3, MLKL, SDC4, and BRD4 pathways showing preclinical TMJOA benefit. However, human tissue validation for RIPK3 or pMLKL expression in condylar cartilage biopsies or synovial fluid remains limited. Such translational data would substantially strengthen the evidential rank.

The functional characterisation of CD34 + perivascular stromal cells in the TMJ disc periphery – clonogenicity, chondrogenic differentiation potential, phenotypic distinction from endothelial cells and pericytes, response to death-inducing stimuli – remains at the descriptive stage. Functional studies of this niche population would help convert the cell death-to-repair-capacity framework from conceptual to mechanistic.

The paracrine cross-talk between dying disc cells and condylar chondrocytes – mediated by apoptotic vesicles (apoVs), migrasomes, and exosomes in synovial fluid – has not been directly mapped in TMJ-specific models. Given that Chen et al. (2025) demonstrate BMSC-Exos can protect disc cells and that Sa et al., 2026 demonstrate macrophage migrasomes restore autophagic flux in condylar chondrocytes (Chen et al., 2025; Sa et al., 2026), the possibility of disc-cell-derived vesicles similarly signalling to the condyle is mechanistically plausible and experimentally approachable.

## 14. Conclusions

Cell death in the temporomandibular joint is a multi-compartment, multi-mechanism, temporally dynamic, and repair-coupled phenomenon. In the TMJ disc, apoptosis via TRAIL/DR5 (Leonardi et al., 2011; Loreto et al., 2009) and the mitochondrial Bax/cytochrome c/caspase-9 pathway (Caltabiano et al., 2013) defines the cell death landscape of internal derangement. The repair-limiting framing of chondrocyte-like cell apoptosis (Loreto et al., 2009) and the protective potential of BMSC exosomes (Chen et al., 2025) together demarcate the biological question as cell death versus repair capacity rather than death mechanism per se.

In condylar cartilage, autophagy – initially protective, later suppressed through the MTORC1/ERN1/EIF2AK3 switch (Yang et al., 2020; Zhang et al., 2013) – is the mechanism whose failure enables apoptosis, and subsequently necroptosis (He et al., 2022; Zhou et al., 2023), pyroptosis (Liu, Li, Zhao, et al., 2023; Xin et al., 2022), and ferroptosis (Zhang et al., 2025) to gain dominance. All four are mechanistically interconnected through MTORC1, NF-κB, ROS, and the IL-1β amplification loop. Chondrocyte apoptosis has local osteochondral consequences beyond cartilage loss, actively recruiting osteoclast precursors via p38-CX3CL1 signalling (Guo et al., 2022), thereby driving subchondral bone resorption.

The most productive frame for future investigation is not "which pathway causes the most cell death?" but "which pathway most selectively eliminates the progenitor pools without which repair is impossible?" – in both the disc periphery and the condylar superficial zone. Answering this question will define the next generation of disease-modifying targets for TMJOA, targets amenable to intra-articular delivery in one of the most anatomically accessible joints in the body.

## List of abbreviations

4-HNE: 4-hydroxynonenal
ACSL4: acyl-CoA synthetase long-chain family member 4
ADD: anterior disc displacement
ADDwR: anterior disc displacement with reduction
ADDwoR: anterior disc displacement without reduction
ALPK1: alpha-kinase 1
AMPK: AMP-activated protein kinase (PRKAA1/2)
ARE: antioxidant response element
ASC: apoptosis-associated speck-like protein containing a CARD
ATDC5: AT805 teratocarcinoma-derived murine chondroprogenitor cell line
ATF6: activating transcription factor 6
Bax: BCL-2-associated X protein
BCL-2: B-cell lymphoma 2
Beclin-1: beclin 1 autophagy-related protein

BMSC: bone marrow mesenchymal stem cell
BMSC-Exos: BMSC-derived exosomes
BRD4: bromodomain-containing protein 4
CARD: caspase activation and recruitment domain
CD34: cluster of differentiation 34
CD63: cluster of differentiation 63
CFA: complete Freund's adjuvant
CHOP/DDIT3: C/EBP homologous protein
CLCs: chondrocyte-like cells
COL2A1: collagen type II alpha 1 chain
CUR: curcumin
DAMP: damage-associated molecular pattern
Derlin-3/DERL3: ER-associated degradation component 3
DR5: death receptor 5
ECM: extracellular matrix
ECDO: experimentally created disordered occlusion
EIF2AK3/PERK: eukaryotic translation initiation factor 2 alpha kinase 3
ERN1/IRE1α: endoplasmic reticulum to nucleus signalling 1
ERS: endoplasmic reticulum stress
FADD: Fas-associated death domain protein
FFSS: fluid flow shear stress
FLS: fibroblast-like synoviocyte
FSP1: ferroptosis suppressor protein 1
FSTL1: follistatin-like protein 1
GCH1: GTP cyclohydrolase 1
GPX4: glutathione peroxidase 4
GRP78/HSPA5: glucose-regulated protein 78
GSH: glutathione
GSDMD: gasdermin D
GSDME: gasdermin E
HA: hyaluronic acid
HIF-1α: hypoxia-inducible factor 1-alpha
HIF-2α: hypoxia-inducible factor 2-alpha
HO-1: haem oxygenase 1
ID: internal derangement
IL-1β: interleukin-1β
IL-6: interleukin-6
IL-18: interleukin-18
iNOS: inducible nitric oxide synthase
JQ1: BRD4 bromodomain inhibitor
LAMP2: lysosomal-associated membrane protein 2
LC3: microtubule-associated protein 1 light chain 3
lncRNA: long non-coding RNA
LPS: lipopolysaccharide
MDA: malondialdehyde
MIA: monoiodoacetate
MLS: macrophage-like synoviocyte
MLKL: mixed lineage kinase domain-like protein
MMP: matrix metalloproteinase
MSC: mesenchymal stem cell
MTORC1: mechanistic target of rapamycin complex 1
NAC: N-acetylcysteine
NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells
NLRP3: NLR family pyrin domain-containing protein 3
NO: nitric oxide
NQO-1: NAD(P)H quinone dehydrogenase 1
Nrf2: nuclear factor erythroid 2-related factor 2
OA: osteoarthritis
p62/SQSTM1: sequestosome 1
PANoptosis: integrated inflammatory cell death combining Pyroptosis, Apoptosis, and Necroptosis
PAMP: pathogen-associated molecular pattern
PDA: posterior disc attachment
PI3K: phosphatidylinositol 3-kinase
PINK1: PTEN-induced kinase 1
pMLKL: phosphorylated MLKL
PUFA: polyunsaturated fatty acid
RCD: regulated cell death
RIPK1: receptor-interacting serine/threonine-protein kinase 1
RIPK3: receptor-interacting serine/threonine-protein kinase 3
ROS: reactive oxygen species
SA-β-gal: senescence-associated β-galactosidase
SASP: senescence-associated secretory phenotype
SDC4: syndecan-4
SLC7A11: solute carrier family 7 member 11 (system $Xc^-$ catalytic subunit)
SOD: superoxide dismutase
ssDNA: single-stranded DNA
TFRC: transferrin receptor
TLR4: toll-like receptor 4
TMD: temporomandibular disorders
TMJ: temporomandibular joint
TMJOA: temporomandibular joint osteoarthritis
TNFα: tumour necrosis factor-alpha
TRAIL: tumour necrosis factor-related apoptosis-inducing ligand
UAC: unilateral anterior crossbite
VEGF: vascular endothelial growth factor
ZBP1: Z-DNA-binding protein 1

## Ethics approval

This is a narrative review article. No original human or animal studies were conducted and no ethics approval was required. All data derive from previously published studies cited in the reference list.

## Funding

This research received no specific grant from public, commercial, or not-for-profit funding agencies.

## CRediT authorship contribution statement

**Mugurel Constantin Rusu:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

## Declaration of Generative AI and AI-assisted technologies in the manuscript preparation process

During the preparation of this work, the author used Claude (Anthropic) for manuscript editing support, structural organisation of the review sections, reference auditing, and drafting of ancillary submission documents. The author reviewed and edited all output as needed and takes full responsibility for the content of the published article.

## Declaration of Competing Interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

No new data were generated or analysed in this review. Data sharing is not applicable.

## References


Bedoui, S., Herold, M. J., & Strasser, A. (2020). Emerging connectivity of programmed cell death pathways and its physiological implications. *Nature Reviews Molecular Cell Biology, 21*(11), 678–695. https://doi.org/10.1038/s41580-020-0270-8

Bonnet, C. S., & Walsh, D. A. (2005). Osteoarthritis, angiogenesis and inflammation. *Rheumatology (Oxford), 44*(1), 7–16. https://doi.org/10.1093/rheumatology/keh344

Caltabiano, R., Leonardi, R., Musumeci, G., Bartoloni, G., Rusu, M. C., Almeida, L. E., & Loreto, C. (2013). Apoptosis in temporomandibular joint disc with internal derangement involves mitochondrial-dependent pathways. An in vivo study. *Acta Odontologica Scandinavica, 71*(3-4), 577–583. https://doi.org/10.3109/00016357.2012.700060

Cao, X., Peng, S., Yan, Y., Li, J., Zhou, J., Dai, H., & Xu, J. (2024). Alleviation of temporomandibular joint osteoarthritis by targeting RIPK1-mediated inflammatory signalling. *Journal of Cellular and Molecular Medicine, 28*(5), Article e17929. https://doi.org/10.1111/jcmm.17929

Cardoneanu, A., Macovei, L. A., Burlui, A. M., Mihai, I. R., Bratoiu, I., Rezus, I. I., … Rezus, E. (2022). Temporomandibular joint osteoarthritis: Pathogenic mechanisms involving the cartilage and subchondral bone, and potential therapeutic strategies for joint regeneration. *International Journal of Molecular Sciences, 24*(1). https://doi.org/10.3390/ijms24010171

Chen, B. Y., Pathak, J. L., Lin, H. Y., Guo, W. Q., Chen, W. J., Luo, G., & Liu, C. (2024). Inflammation triggers chondrocyte ferroptosis in TMJOA via HIF-1alpha/TFRC. *Journal of Dental Research, 103*(7), 712–722. https://doi.org/10.1177/00220345241242389

Chen, W., Huang, F., Chen, B., Lin, H., Luo, G., Zhang, W., … Liu, C. (2025). BMSC derived exosomes attenuate apoptosis of temporomandibular joint disc chondrocytes in TMJOA via PI3K/AKT pathway. *Stem Cell Reviews and Reports, 21*(2), 491–508. https://doi.org/10.1007/s12015-024-10810-7

Cui, D., Li, H., Xu, X., Ye, L., Zhou, X., Zheng, L., & Zhou, Y. (2017). Mesenchymal stem cells for cartilage regeneration of TMJ osteoarthritis. *Stem Cells International, 2017*, Article 5979741. https://doi.org/10.1155/2017/5979741

Eskander, G., Abdelhamid, S. G., Wahdan, S. A., & Radwan, S. M. (2025). Insights on the crosstalk among different cell death mechanisms. *Cell Death Discovery, 11*(1), 56. https://doi.org/10.1038/s41420-025-02328-9

Feng, J., Gu, Z., Cao, Z., Takanori, S., Hu, J., & Peng, J. (2002). Chondrocyte apoptosis in rabbit temporomandibular joint after anterior disc displacement. *Zhonghua Kou Qiang Yi Xue Za Zhi, 37*(3), 200–202.

Fina, L., Molgaard, H. V., Robertson, D., Bradley, N. J., Monaghan, P., Delia, D., … Greaves, M. F. (1990). Expression of the CD34 gene in vascular endothelial cells. *Blood, 75*(12), 2417–2426.

Galanti, C., Musumeci, G., Valentino, J., Giunta, S., & Castorina, S. (2013). A role for apoptosis in temporomandibular joint disc degeneration. A contemporary review. *Italian Journal of Anatomy and Embryology, 118*(1), 151–158.

Gerber, H. P., Vu, T. H., Ryan, A. M., Kowalski, J., Werb, Z., & Ferrara, N. (1999). VEGF couples hypertrophic cartilage remodeling, ossification and angiogenesis during endochondral bone formation. *Nature Medicine, 5*(6), 623–628. https://doi.org/10.1038/9467

Gu, Z., Shibata, T., Cao, Z., Feng, J., & Hu, J. (2002). Chondrocyte apoptosis in temporomandibular joints with disc displacement. *Journal of Oral and Maxillofacial Surgery, 60*(9), 1026–1031; discussion 1031. https://doi.org/10.1053/joms.2002.34414

Gullett, J. M., Tweedell, R. E., & Kanneganti, T. D. (2022). It's All in the PAN: Crosstalk, plasticity, redundancies, switches, and interconnectedness encompassed by PANoptosis underlying the totality of cell death-associated biological effects. *Cells, 11*(9). https://doi.org/10.3390/cells11091495

Guo, D., Guo, Y., Zhu, C., Liao, Y., Lin, Z., Zhang, H., … Zou, Z. (2026). Programmed cell death network in cancer drug resistance: A framework for therapeutic intervention. *Drug Resistance Updates, 86*, Article 101387. https://doi.org/10.1016/j.drup.2026.101387

Guo, J., Su, K., Wang, L., Feng, B., You, X., Deng, M., … Xia, J. (2024). Poly(p-coumaric acid) nanoparticles alleviate temporomandibular joint osteoarthritis by inhibiting chondrocyte ferroptosis. *Bioactive Materials, 40*, 212–226. https://doi.org/10.1016/j.bioactmat.2024.06.007

Guo, Y. N., Cui, S. J., Tian, Y. J., Zhao, N. R., Zhang, Y. D., Gan, Y. H., … Wang, X. D. (2022). Chondrocyte apoptosis in temporomandibular joint osteoarthritis promotes bone resorption by enhancing chemotaxis of osteoclast precursors. *Osteoarthritis Cartilage, 30*(8), 1140–1153. https://doi.org/10.1016/j.joca.2022.04.002

Guo, Z., Liu, Y., Chen, D., Sun, Y., Li, D., Meng, Y., … Chen, X. (2025). Targeting regulated cell death: Apoptosis, necroptosis, pyroptosis, ferroptosis, and cuproptosis in anticancer immunity. *Journal of Translational Internal Medicine, 13*(1), 10–32. https://doi.org/10.1515/jtim-2025-0004

Haskin, C. L., Milam, S. B., & Cameron, I. L. (1995). Pathogenesis of degenerative joint disease in the human temporomandibular joint. *Critical Reviews in Oral Biology & Medicine, 6*(3), 248–277. https://doi.org/10.1177/10454411950060030601

He, F., Ma, Y., Li, S., Ren, H., Liu, Q., Chen, X., … Yu, S. (2022). Necroptotic TNFalpha-Syndecan 4-TNFalpha vicious cycle as a therapeutic target for preventing temporomandibular joint osteoarthritis. *Journal of Bone and Mineral Research, 37*(5), 1044–1055. https://doi.org/10.1002/jbmr.4542

He, J., Qin, W., Zhang, Y., Yan, J., Han, X., Gao, J., … Jiao, K. (2024). Upregulated mitochondrial dynamics is responsible for the procatabolic changes of chondrocyte induced by alpha2-adrenergic signal activation. *Cartilage, 15*(4), 440–452. https://doi.org/10.1177/19476035231189841

Huang, Z., Han, M., Ren, J., Zhang, C., Ren, Y., Zhang, J., … Li, H. (2025). BRD4 inhibition ameliorates aberrant mechanical stress-induced temporomandibular joint osteoarthritis through modulating MLKL and necroptosis. *International Journal of Biological Macromolecules, 319*(Pt 2), Article 145486. https://doi.org/10.1016/j.ijbiomac.2025.145486

Jiang, C., Luo, P., Li, X., Liu, P., Li, Y., & Xu, J. (2020). Nrf2/ARE is a key pathway for curcumin-mediated protection of TMJ chondrocytes from oxidative stress and inflammation. *Cell Stress Chaperones, 25*(3), 395–406. https://doi.org/10.1007/s12192-020-01079-z

Jiao, K., Wang, M. Q., Niu, L. N., Dai, J., Yu, S. B., Liu, X. D., & Wang, G. W. (2009). Death and proliferation of chondrocytes in the degraded mandibular condylar cartilage of rats induced by experimentally created disordered occlusion. *Apoptosis, 14*(1), 22–30. https://doi.org/10.1007/s10495-008-0279-5

Khurel-Ochir, T., Izawa, T., Iwasa, A., Kano, F., Yamamoto, A., & Tanaka, E. (2021). The immunoregulatory role of p21 in the development of the temporomandibular joint-osteoarthritis. *Clinical and Experimental Dental Research, 7*(3), 313–322. https://doi.org/10.1002/cre2.404

Kist, M., & Vucic, D. (2021). Cell death pathways: Intricate connections and disease implications. *The EMBO Journal, 40*(5), Article e106700. https://doi.org/10.15252/embj.2020106700

Kutumova, E., Akberdin, I., Lavrik, I., & Kolpakov, F. (2025). Mathematical modeling of cell death and survival: Toward an integrated computational framework for multi-decision regulatory dynamics. *Cells, 14*(22). https://doi.org/10.3390/cells14221792

Leonardi, R., Almeida, L. E., Rusu, M., Sicurezza, E., Palazzo, G., & Loreto, C. (2011). Tumor necrosis factor-related apoptosis-inducing ligand expression correlates to temporomandibular joint disk degeneration. *Journal of Craniofacial Surgery, 22*(2), 504–508. https://doi.org/10.1097/SCS.0b013e3182087394

Li, B., Guan, G., Mei, L., Jiao, K., & Li, H. (2021). Pathological mechanism of chondrocytes and the surrounding environment during osteoarthritis of temporomandibular joint. *Journal of Cellular and Molecular Medicine, 25*(11), 4902–4911. https://doi.org/10.1111/jcmm.16514

Li, F., Qian, W., Wang, J., & Gao, M. (2025a). FSTL1 can be a promising target in TMJ osteoarthritis via regulating chondrocyte mitophagy and apoptosis. *Journal of Craniofacial Surgery, 36*(4), 1401–1407. https://doi.org/10.1097/SCS.0000000000010906

Li, P., Gao, Y., Tao, Z., Mu, Z., Du, S., & Zhao, X. (2025b). PANoptosis: Cross-talk among apoptosis, necroptosis, and pyroptosis in neurological disorders. *Journal of Inflammation Research, 18*, 8131–8140. https://doi.org/10.2147/JIR.S526158

Liu, J., Hong, M., Li, Y., Chen, D., Wu, Y., & Hu, Y. (2022a). Programmed cell death tunes tumor immunity. *Frontiers in Immunology, 13*, Article 847345. https://doi.org/10.3389/fimmu.2022.847345

Liu, J., Yang, H., Zhang, H., Liu, Q., Zhou, P., He, F., … Wang, M. (2020). Biomechanically reduced expression of Derlin-3 is linked to the apoptosis of chondrocytes in the mandibular condylar cartilage via the endoplasmic reticulum stress pathway. *Archives of Oral Biology, 118*, Article 104843. https://doi.org/10.1016/j.archoralbio.2020.104843

Liu, Li, Feng, Yaping, Hu, Shiyu, Li, Huimin, Li, Yanyan, Ke, Jin, & Long, Xing (2021a). PDCD4 suppresses autophagy and promotes apoptosis via Akt in chondrocytes of temporomandibular joint osteoarthritis. *Oral Diseases, 27*(3), 547–558. https://doi.org/10.1111/odi.13559

Liu, Q., Wang, R., Hou, S., He, F., Ma, Y., Ye, T., … Zhang, M. (2022b). Chondrocyte-derived exosomes promote cartilage calcification in temporomandibular joint osteoarthritis. *Arthritis Research & Therapy, 24*(1), 44. https://doi.org/10.1186/s13075-022-02738-5

Liu, Q., Yang, H., Zhang, M., Zhang, J., Lu, L., Yu, S., … Wang, M. (2021b). Initiation and progression of dental-stimulated temporomandibular joints osteoarthritis. *Osteoarthritis Cartilage, 29*(5), 633–642. https://doi.org/10.1016/j.joca.2020.12.016

Liu, S., Wu, C., Yao, Y., Dong, X., & Xu, L. (2025). Single monoiodoacetic acid injection reveals toll-like receptor, oestrogen, oxidative stress, and altered energy metabolism as key drivers of temporomandibular joint osteoarthritis in female rats. *Archives of Oral Biology, 174*, Article 106233. https://doi.org/10.1016/j.archoralbio.2025.106233

Liu, X., Li, H., Feng, Y., Guo, H., Li, Y., Ke, J., & Long, X. (2023). Resatorvid alleviates experimental inflammatory TMJOA by restraining chondrocyte pyroptosis and synovial inflammation. *Arthritis Research & Therapy, 25*(1), 230. https://doi.org/10.1186/s13075-023-03214-4

Liu, X., Li, Y., Zhao, J., Hu, Z., Fang, W., Ke, J., … Long, X. (2023). Pyroptosis of chondrocytes activated by synovial inflammation accelerates TMJ osteoarthritis cartilage degeneration via ROS/NLRP3 signaling. *International Immunopharmacology, 124*(Pt A), Article 110781. https://doi.org/10.1016/j.intimp.2023.110781

Liu, Y., Berendsen, A. D., Jia, S., Lotinun, S., Baron, R., Ferrara, N., & Olsen, B. R. (2012). Intracellular VEGF regulates the balance between osteoblast and adipocyte differentiation. *Journal of Clinical Investigation, 122*(9), 3101–3113. https://doi.org/10.1172/JCI61209

Liu, Y., Jia, F., Li, K., Liang, C., Lin, X., Geng, W., & Li, Y. (2024). Critical signaling molecules in the temporomandibular joint osteoarthritis under different magnitudes of mechanical stimulation. *Frontiers in Pharmacology, 15*, Article 1419494. https://doi.org/10.3389/fphar.2024.1419494

Loreto, C., Almeida, L. E., Migliore, M. R., Caltabiano, M., & Leonardi, R. (2010). TRAIL, DR5 and caspase 3-dependent apoptosis in vessels of diseased human temporomandibular joint disc. An immunohistochemical study. *European Journal of Histochemistry, 54*(3), Article e40.

Loreto, C., Almeida, L. E., Trevilatto, P., & Leonardi, R. (2011). Apoptosis in displaced temporomandibular joint disc with and without reduction: An immunohistochemical study. *Journal of Oral Pathology & Medicine, 40*(1), 103–110. https://doi.org/10.1111/j.1600-0714.2010.00920.x

Loreto, C., Musumeci, G., & Leonardi, R. (2009). Chondrocyte-like apoptosis in temporomandibular joint disc internal derangement as a repair-limiting mechanism. An in vivo study. *Histology and Histopathology, 24*(3), 293–298.

Lu, K., Ma, F., Yi, D., Yu, H., Tong, L., & Chen, D. (2022). Molecular signaling in temporomandibular joint osteoarthritis. *Journal of Orthopaedic Translation, 32*, 21–27. https://doi.org/10.1016/j.jot.2021.07.001

Maes, C., Kobayashi, T., Selig, M. K., Torrekens, S., Roth, S. I., Mackem, S., … Kronenberg, H. M. (2010). Osteoblast precursors, but not mature osteoblasts, move into developing and fractured bones along with invading blood vessels. *Developmental Cell, 19*(2), 329–344. https://doi.org/10.1016/j.devcel.2010.07.010

Mino-Oka, A., Izawa, T., Shinohara, T., Mori, H., Yasue, A., Tomita, S., & Tanaka, E. (2017). Roles of hypoxia inducible factor-1alpha in the temporomandibular joint. *Archives of Oral Biology, 73*, 274–281. https://doi.org/10.1016/j.archoralbio.2016.10.028

Murata, M., Yudoh, K., & Masuko, K. (2008). The potential role of vascular endothelial growth factor (VEGF) in cartilage: How the angiogenic factor could be involved in the pathogenesis of osteoarthritis? *Osteoarthritis Cartilage, 16*(3), 279–286. https://doi.org/10.1016/j.joca.2007.09.003

Nagai, H., Kumamoto, H., Fukuda, M., & Takahashi, T. (2003). Inducible nitric oxide synthase and apoptosis-related factors in the synovial tissues of temporomandibular joints with internal derangement and osteoarthritis. *Journal of Oral and Maxillofacial Surgery, 61*(7), 801–807. https://doi.org/10.1016/s0278-2391(03)00155-1

Pfander, D., Kortje, D., Zimmermann, R., Weseloh, G., Kirsch, T., Gesslein, M., … Swoboda, B. (2001). Vascular endothelial growth factor in articular cartilage of healthy and osteoarthritic human knee joints. *Annals of the Rheumatic Diseases, 60*(11), 1070–1073. https://doi.org/10.1136/ard.60.11.1070

Pufe, T., Lemke, A., Kurz, B., Petersen, W., Tillmann, B., Grodzinsky, A. J., & Mentlein, R. (2004). Mechanical overload induces VEGF in cartilage discs via hypoxia-inducible factor. *American Journal of Pathology, 164*(1), 185–192. https://doi.org/10.1016/S0002-9440(10)63109-4

Qian, S., Long, Y., Tan, G., Li, X., Xiang, B., Tao, Y., & Zhang, X. (2024). Programmed cell death: molecular mechanisms, biological functions, diseases, and therapeutic targets. *MedComm (2020), 5*(12), Article e70024. https://doi.org/10.1002/mco2.70024

Ren, H., Yang, H., Xie, M., Wen, Y., Liu, Q., Li, X., & Wang, M. (2019). Chondrocyte apoptosis in rat mandibular condyles induced by dental occlusion due to mitochondrial damage caused by nitric oxide. *Archives of Oral Biology, 101*, 108–121. https://doi.org/10.1016/j.archoralbio.2019.03.006

Sa, G., Zou, Z., Zhou, H., Sa, G., Zhou, J., Tu, H., … Yang, X. (2026). M1 macrophage-derived migrasomes ameliorate temporomandibular joint osteoarthritis via autophagy. *Journal of Nanobiotechnology, 24*(1). https://doi.org/10.1186/s12951-026-04248-x

Schipani, E., Ryan, H. E., Didrickson, S., Kobayashi, T., Knight, M., & Johnson, R. S. (2001). Hypoxia in cartilage: HIF-1alpha is essential for chondrocyte growth arrest and survival. *Genes & Development, 15*(21), 2865–2876. https://doi.org/10.1101/gad.934301

Sidney, L. E., Branch, M. J., Dunphy, S. E., Dua, H. S., & Hopkinson, A. (2014). Concise review: Evidence for CD34 as a common marker for diverse progenitors. *Stem Cells, 32*(6), 1380–1389. https://doi.org/10.1002/stem.1661

Snyder, A. G., & Oberst, A. (2021). The antisocial network: Cross talk between cell death programs in host defense. *Annual Review of Immunology, 39*, 77–101. https://doi.org/10.1146/annurev-immunol-112019-072301

Sorokin, O., Hause, F., Wedler, A., Alakhras, T., Bauchspiess, T., Dietrich, A., … Uversky, V. N. (2025). Comprehensive analysis of regulated cell death pathways: Intrinsic disorder, protein-protein interactions, and cross-pathway communication. *Apoptosis, 30*(9-10), 2110–2162. https://doi.org/10.1007/s10495-025-02161-6

Suri, S., Gill, S. E., Massena de Camin, S., Wilson, D., McWilliams, D. F., & Walsh, D. A. (2007). Neurovascular invasion at the osteochondral junction and in osteophytes in osteoarthritis. *Annals of the Rheumatic Diseases, 66*(11), 1423–1428. https://doi.org/10.1136/ard.2006.063354

Walsh, D. A., Bonnet, C. S., Turner, E. L., Wilson, D., Situ, M., & McWilliams, D. F. (2007). Angiogenesis in the synovium and at the osteochondral junction in osteoarthritis. *Osteoarthritis Cartilage, 15*(7), 743–751. https://doi.org/10.1016/j.joca.2007.01.020

Wang, Y., & Kanneganti, T. D. (2021). From pyroptosis, apoptosis and necroptosis to PANoptosis: A mechanistic compendium of programmed cell death pathways. *Computational and Structural Biotechnology Journal, 19*, 4641–4657. https://doi.org/10.1016/j.csbj.2021.07.038

Wang, Y., Liu, Z., Ma, G., Xu, Y., & Li, Y. (2023). Mouth breathing induces condylar remodelling and chondrocyte apoptosis via both the extrinsic and mitochondrial pathways in male adolescent rats. *Tissue Cell, 83*, Article 102146. https://doi.org/10.1016/j.tice.2023.102146

Wang, Y., Wan, C., Deng, L., Liu, X., Cao, X., Gilbert, S. R., … Clemens, T. L. (2007). The hypoxia-inducible factor alpha pathway couples angiogenesis to osteogenesis during skeletal development. *Journal of Clinical Investigation, 117*(6), 1616–1626. https://doi.org/10.1172/JCI31581

Xin, Y., Wang, W., Mao, E., Yang, H., & Li, S. (2022). Targeting NLRP3 inflammasome alleviates synovitis by reducing pyroptosis in rats with experimental temporomandibular joint osteoarthritis. *Mediators of Inflammation, 2022*, Article 2581151. https://doi.org/10.1155/2022/2581151

Yang, H., Wen, Y., Zhang, M., Liu, Q., Zhang, H., Zhang, J., … Wang, M. (2020). MTORC1 coordinates the autophagy and apoptosis signaling in articular chondrocytes in osteoarthritic temporomandibular joint. *Autophagy, 16*(2), 271–288. https://doi.org/10.1080/15548627.2019.1606647

Yang, H., Zhang, M., Wang, X., Zhang, H., Zhang, J., Jing, L., … Wang, M. (2015). TNF accelerates death of mandibular condyle chondrocytes in rats with biomechanical stimulation-induced temporomandibular joint disease. *PLoS One, 10*(11), Article e0141774. https://doi.org/10.1371/journal.pone.0141774

Yang, L., Tsang, K. Y., Tang, H. C., Chan, D., & Cheah, K. S. (2014). Hypertrophic chondrocytes can become osteoblasts and osteocytes in endochondral bone formation. *Proceedings of the National Academy of Sciences of the United States of America, 111*(33), 12097–12102. https://doi.org/10.1073/pnas.1302703111

Yuan, J., & Ofengeim, D. (2024). A guide to cell death pathways. *Nature Reviews Molecular Cell Biology, 25*(5), 379–395. https://doi.org/10.1038/s41580-023-00689-6

Zhang, C., Lin, S., Li, T., Jiang, Y., Huang, Z., Wen, J., … Li, H. (2017). Mechanical force-mediated pathological cartilage thinning is regulated by necroptosis and apoptosis. *Osteoarthritis Cartilage, 25*(8), 1324–1334. https://doi.org/10.1016/j.joca.2017.03.018

Zhang, C., Wang, P., Jiang, P., Lv, Y., Dong, C., Dai, X., … Wang, Z. (2016). Upregulation of lncRNA HOTAIR contributes to IL-1beta-induced MMP overexpression and chondrocytes apoptosis in temporomandibular joint osteoarthritis. *Gene, 586*(2), 248–253. https://doi.org/10.1016/j.gene.2016.04.016

Zhang, J., Hu, Y., Wang, Z., Wu, X., Yang, C., & Yang, H. (2022). Hypoxia-inducible factor expression is related to apoptosis and cartilage degradation in temporomandibular joint osteoarthritis. *BMC Musculoskeletal Disorders, 23*(1), 583. https://doi.org/10.1186/s12891-022-05544-x

Zhang, M., Zhang, J., Lu, L., Qiu, Z. Y., Zhang, X., Yu, S. B., … Wang, M. Q. (2013). Enhancement of chondrocyte autophagy is an early response in the degenerative cartilage of the temporomandibular joint to biomechanical dental stimulation. *Apoptosis, 18*(4), 423–434. https://doi.org/10.1007/s10495-013-0811-0

Zhang, Y., Zhang, D., Liao, X., Xu, Q., Bu, L., Zheng, J., … Yang, C. (2025). Novel insights into the role of ferroptosis in temporomandibular joint osteoarthritis and knee osteoarthritis. *International Journal of Medical Sciences, 22*(9), 2119–2131. https://doi.org/10.7150/ijms.107057

Zhao, M., Song, L., Liu, Z., Li, Y., & Wang, Y. (2025). Necroptosis and its role in the pathogenesis and treatment of temporomandibular joint osteoarthritis: A narrative review. *Archives of Oral Biology, 176*, Article 106300. https://doi.org/10.1016/j.archoralbio.2025.106300

Zhao, Y., & Xie, L. (2021). An update on mesenchymal stem cell-centered therapies in temporomandibular joint osteoarthritis. *Stem Cells International, 2021*, Article 6619527. https://doi.org/10.1155/2021/6619527

Zhou, D., Jiang, Y., Li, Y., Zeng, H., Li, X., He, Y., … Zhou, Y. (2025). Mechanistic insights into overloading-induced terminal differentiation of TMJ condylar cartilage at the single cell level. *Smart Med, 4*(3), Article e70011. https://doi.org/10.1002/smmd.70011

Zhou, X., von der Mark, K., Henry, S., Norton, W., Adams, H., & de Crombrugghe, B. (2014). Chondrocytes transdifferentiate into osteoblasts in endochondral bone during development, postnatal growth and fracture healing in mice. *PLoS Genet, 10*(12), Article e1004820. https://doi.org/10.1371/journal.pgen.1004820

Zhou, Y., Lin, S., Huang, Z., Zhang, C., Wang, H., Li, B., & Li, H. (2023). Receptor-interacting protein 1 inhibition prevents mechanical stress-induced temporomandibular joint osteoarthritis by regulating apoptosis and later-stage necroptosis of chondrocytes. *Archives of Oral Biology, 147*, Article 105612. https://doi.org/10.1016/j.archoralbio.2022.105612