

Immunopathological mechanisms of Modic changes

A multidimensional analysis of inflammatory evolution and key signaling pathways

Yongjun Tong^a, Xiangxi Kong^b, Fengdong Zhao^{b,*}

Abstract: Modic changes (MCs), characterized by magnetic resonance imaging signal alterations at vertebral endplates and adjacent bone marrow, are increasingly recognized as immune-driven lesions rather than mere structural degeneration. This review focuses on the pivotal roles of immune system and key immunological signaling in the initiation and progression of MCs. Within the Modic microenvironment, diverse immune cell populations—including monocytes, macrophages, mast cells, neutrophils, and lymphocytes—exhibit stage-specific infiltration patterns. In parallel, MCs are governed by a complex network of innate and adaptive immune signals. Endplate disruption and nucleus pulposus exposure break local immune privilege, activating inflammatory cascades that sustain cytokine and chemokine production, amplify immune cell recruitment, and promote chronic low-grade inflammation. Oxidative stress, metabolic disturbances, and potential microbial triggers such as *Cutibacterium acnes* further modulate these immune landscapes. The interplay of these mechanisms underscores MCs as dynamic immunoinflammatory processes, with distinct cellular and molecular profiles corresponding to their radiologic stages. Recognizing the immunological complexity of MCs underscores the need for future studies to delineate molecular signatures that could guide personalized treatment strategies and improve clinical outcomes.

Abbreviations: *C. acnes* = *cutibacterium acnes*, MCs = modic changes, MRI = magnetic resonance imaging, NP = nucleus pulposus.

Keywords: immunity, inflammation, intervertebral disc degeneration, lymphocytes, macrophages, Modic changes

1. Introduction

Modic changes (MCs) refer to signal abnormalities detected by magnetic resonance imaging (MRI) in the vertebral endplates and adjacent bone marrow, typically categorized into 3 types: type I (inflammatory, hypointense on T1-weighted and hyperintense on T2-weighted images), type II (fatty, hyperintense on T1 and iso- to slightly hyperintense on T2), and type III (sclerotic, hypointense on both

T1 and T2 sequences).^[1–3] Initially described as morphological markers of vertebral degeneration, MCs have since been recognized as dynamic lesions associated with distinct clinical and biological characteristics. Epidemiological studies report that MCs are present in approximately 18% to 58% of patients with chronic low back pain,^[4] and their presence strongly correlate with increased pain intensity, neurological dysfunction,^[5–7] and postoperative clinical outcomes and structural reconstruction.^[8,9]

Pathologically, MCs represent a progressive remodeling process at the bone–endplate–marrow interface, characterized by endplate disruption, bone marrow edema, fatty infiltration, and eventual sclerosis.^[10–12] These changes often coexist with intervertebral disc degeneration and are believed to reflect failed endplate repair or chronic inflammatory responses to disc-derived stimuli.^[11] Notably, MCs are not static entities but may undergo transformation between types, indicating a continuum of pathological evolution.^[13,14]

Emerging evidence supports a central role of the immune system in MC pathogenesis.^[15,16] Histological studies have demonstrated substantial infiltration of immune cells—including monocytes, macrophages, neutrophils, mast cells, and lymphocytes—within Modic lesions.^[15] Importantly, immune activation in MCs appears to be triggered by exposure of normally immune-privileged nucleus pulposus (NP)

YT and KX are co-first authors.

^a Department of Orthopedics, Zhejiang Hospital, Hangzhou, China,

^b Department of Orthopaedics, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China.

* Correspondence: Fengdong Zhao, Department of Orthopaedics, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, No. 3, Qingchun Rd East, Hangzhou, Zhejiang 310016, China (e-mail: zhaofengdong@zju.edu.cn).

Copyright © 2025 the Author(s). Published by Wolters Kluwer Health, Inc. on behalf of Higher Education Press. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Spine Research (2025) 1:2;37–49

Received: 7 July 2025 / Accepted: 4 August 2025

<http://dx.doi.org/10.1097/br9.0000000000000015>

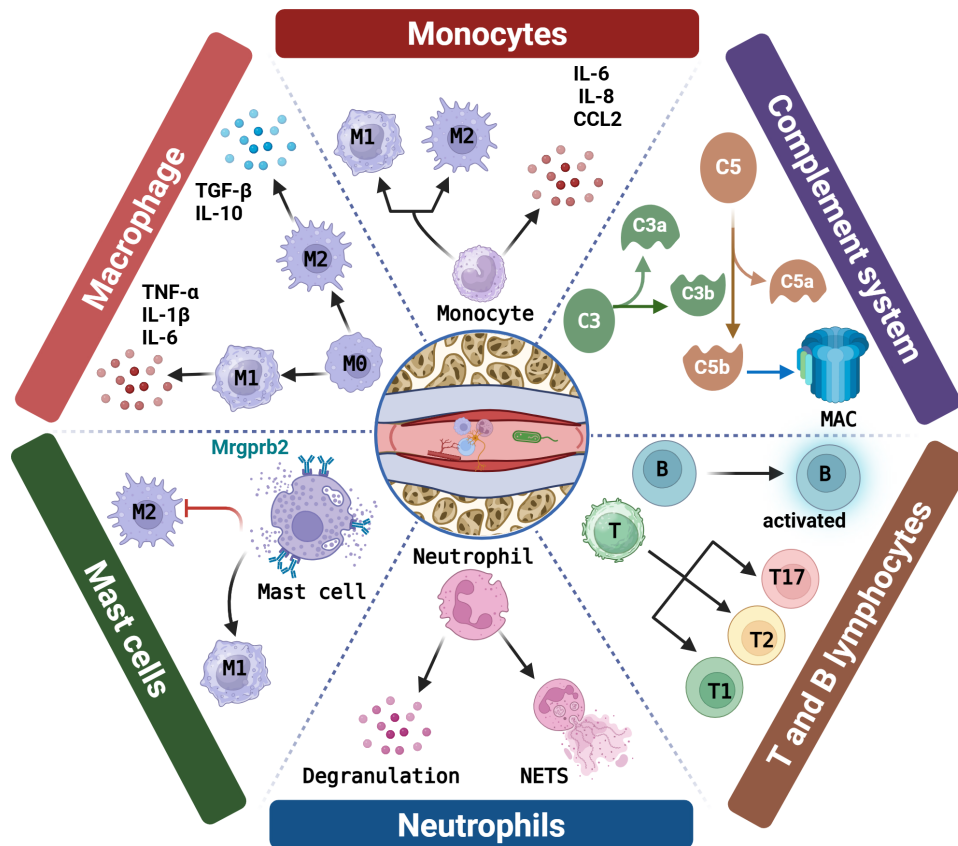


Figure 1. Involvement of immune system in MCs. MCs = modic changes.

tissue to the bone marrow compartment, leading to the release of damage-associated molecular patterns (DAMPs), activation of Toll-like receptors (TLRs), and initiation of inflammatory cascades.^[17] Moreover, microbial stimuli—particularly *Cutibacterium acnes*—have been implicated in modulating this immune landscape through innate receptors and complement activation.^[18,19]

Despite increasing recognition of MCs as immune-driven lesions, most existing reviews on MCs have primarily focused on imaging characteristics, associations with pain, and alterations in biomechanical properties.^[20,21]

The immunopathological mechanisms remain underexplored, particularly those involving immune cell recruitment, polarization, and crosstalk between innate and adaptive immunity. Accordingly, this review aims to address this gap by providing a systematic overview of recent advances in the understanding of cellular and molecular immunology of MCs and highlighting key immune signaling pathways and their potential roles in the progression and phenotypic transformation of MCs.

2. Involvement of immune system in MCs

MCs are characterized by specific MRI signal alterations within the vertebral endplates and adjacent bone marrow and are now widely regarded as manifestations of an inflammation-driven microenvironmental shift.^[22,23] Although MCs are radiologically classified into 3 subtypes—type I (inflammatory), type II (fatty), and type

III (sclerotic)—each type is accompanied by distinct patterns of immune cell infiltration and local tissue remodeling.^[15,24] Furthermore, dynamic transitions between these subtypes have been documented, reflecting the progressive nature of the underlying pathology.^[11,25,26]

Modic lesions have been shown histologically to harbor significant infiltration of various immune cells,^[15] including bone marrow-derived monocytes,^[27] macrophages,^[28] T lymphocytes,^[29] mast cells,^[30] and neutrophils^[31] (Fig. 1). Each Modic subtype exhibits unique immunological characteristics: type I lesions are marked by high expression of inflammatory mediators, enrichment of proinflammatory M1 macrophages, and prominent monocyte recruitment; type II is associated with fatty degeneration and relative suppression of inflammation; and type III is dominated by bone sclerosis with minimal inflammatory activity.^[15,21]

Collectively, these findings indicate that MCs represent a continuum of immune microenvironmental evolution, in which distinct immunological profiles and cellular compositions correspond to specific radiologic and histopathologic phenotypes. This lineage-specific immune landscape not only underpins the imaging and histologic classification of MCs but also provides potential biological targets for future immunomodulatory interventions.

2.1. Monocytes: initiators of inflammation

Monocytes play a pivotal role in the early phases of inflammation. Upon recruitment to the site of injury,

they differentiate into either proinflammatory or anti-inflammatory macrophages, secrete cytokines, and perform phagocytic functions, thereby amplifying and regulating the inflammatory response. In addition, monocytes serve as antigen-presenting cells that bridge innate and adaptive immunity, making them essential initiators and modulators of immune responses.^[32]

Upon recruitment to injury sites, they differentiate into macrophages and modulate the local immune environment. Cross-sectional studies have shown that patients with chronic low back pain and MCs exhibit significantly elevated circulating monocyte counts compared with asymptomatic individuals, with a positive correlation between monocyte levels and MC presence.^[27] These findings suggest that monocytes not only reflect systemic inflammatory activity but may actively contribute to MC pathophysiology. Dudli et al. demonstrated that while NP cells alone do not elicit a strong inflammatory response from bone marrow-derived mononuclear cells (BMNCs), the presence of proinflammatory stimuli such as IL-1 α or lipopolysaccharide induces significant upregulation of IL-1, IL-6, IL-10, and TrkA, alongside T cell infiltration and MC1-like MRI changes *in vivo*.^[33] This suggests that NP exposure in an inflamed environment may trigger an autoimmune-like cascade, with monocytes playing a critical role in amplifying the response. Moreover, BMNCs exposed to conditioned medium from *Cutibacterium acnes* (*C. acnes*)—stimulated disc cells showed elevated IL-1, IL-6, IL-8, and CCL2 expression, indicating synergistic activation by microbial and disc-derived factors.^[34] These data highlight the potential of monocytes as both biomarkers and mediators in the initiation and progression of MCs.

2.2. Macrophage lineage polarization: its role in Modic type progression

Macrophages are central players in the innate immune system, essential for host defense, inflammation regulation, and tissue homeostasis maintenance.^[35] Their polarization into proinflammatory (M1) or anti-inflammatory/reparative (M2) phenotypes is shaped by the local microenvironment,^[36,37] and in MCs, this polarization appears closely tied to disease progression. Type I MCs represent an active inflammatory phase, featuring endplate disruption, bone marrow edema, and elevated proinflammatory cytokines. In this stage, macrophages predominantly adopt the M1 phenotype. Li et al.^[38] demonstrated that type I lesions show marked macrophage infiltration and a proinflammatory cytokine profile—far exceeding that of non-MC or type II cases. These M1 macrophages produce TNF- α , IL-1 β , and IL-6, which exacerbate nociception and tissue injury, contributing to the pain experienced in MC1.^[38,39] Further amplification occurs through the migration inhibitory factor (MIF)—CD74 axis, as Xiong et al.^[40] reported elevated MIF expression in MC1 endplates, promoting IL-6, IL-8, and PGE2 production and sustaining M1 activity. MIF was also elevated systemically in MC1/

MC2 patients, reinforcing its role in macrophage-driven inflammation.^[41]

As MCs evolve, a shift toward tissue repair and anti-inflammatory signaling emerges. In type II lesions, upregulation of osteoclast-related genes (*M-CSF1*, *RANKL*, *RUNX1/2*) and reduction of OSCAR expression suggest a postresorptive microenvironment modulated by macrophage–osteoclast interactions.^[42] Concurrently, M2 macrophages become more prominent, secreting TGF- β and IL-10, which support bone repair and fibrosis, reflecting the reparative nature of MC2.^[43–45] Djuric et al.^[46] noted that macrophages infiltrating disc herniations—particularly in patients with MCs—were largely M2 polarized (CD163⁺, CD209⁺) and the M1/M2 ratio remained stable despite higher total macrophage numbers, suggesting a phenotypic shift rather than expansion of inflammatory responses. Similarly, Li et al.^[38] observed reduced inflammatory severity and lack of M1 dominance in MC2, further indicating a transition from immune activation to resolution.

In late-stage Modic type III, sclerosis and subchondral bone thickening dominate. An *in vivo* model identified F4/80⁺ MAC-2⁻/low osteal macrophages (osteomacs) accumulating in sclerotic regions, where they promoted osteogenesis via oncostatin M (OSM)-induced STAT3/YAP1 signaling.^[28] This osteomac-driven bone formation highlights the final immunological phase of MCs, dominated by repair and matrix consolidation. Altogether, the macrophage phenotype shifts sequentially from M1-driven inflammation in MC1, to M2-mediated repair in MC2, and osteomac-facilitated sclerosis in MC3. These lineage-specific macrophage roles not only mirror histological changes across MC stages but also present potential therapeutic targets tailored to disease phase—ranging from anti-inflammatory to pro-repair and antisclerotic strategies.

Current evidence indicates that the polarization state of macrophages is intimately associated with the phenotypic subtype of MCs: type I is dominated by M1 macrophages, which drive inflammatory cytokine production, endplate disruption, and pain sensitization; type II is marked by an increase in M2 macrophages that mediate anti-inflammatory responses, tissue repair, and fatty replacement; type III features osteomac-driven bone formation contributing to sclerosis. These lineage-specific macrophage dynamics suggest a central role in the progression of Modic pathology and may serve as potential targets for tailored immunotherapies—ranging from anti-inflammatory strategies to pro-repair or antisclerotic interventions—depending on the lesion type.

2.3. Mast cells: noncanonical immune activation and amplification loop

Mast cells are tissue-resident immune cells of hematopoietic origin that mature in peripheral tissues and constitute a critical component of the innate immune system.^[47] While traditionally associated with allergic responses, mast cells have recently gained attention for their broader

roles in inflammation and tissue remodeling. Both the number and activation status of mast cells were significantly elevated in degenerated intervertebral discs compared with healthy controls, suggesting their involvement in disc degeneration.^[48] However, their role in the pathophysiology of MCs has long been underappreciated.

Recent evidence has revealed that mast cells are not only abundant within regions of disc degeneration but also exert crucial functions in the onset and progression of MCs through noncanonical activation pathways. Using both human tissue samples and murine models, Ji et al.^[30] systematically demonstrated that mast cell activation in Modic lesions does not occur via the classical IgE–FcεRI signaling cascade. Instead, it is driven by the Mas-related G protein-coupled receptor B2 (Mrgprb2) in response to bacterial metabolites, particularly those from *C. acnes*. Activation through Mrgprb2 leads to the release of histamine, tryptase, and various proinflammatory mediators.

This alternative activation route initiates multiple downstream inflammatory signaling cascades, including phosphoinositide 3-kinase–protein kinase B, mitogen-activated protein kinase, and c-Jun N-terminal kinase pathways. These molecular events promote degradation of the cartilage-endplate matrix, evidenced by increased expression of matrix metalloproteinase-13 (MMP13) and downregulation of cartilage-specific markers such as type II collagen (Col2) and SRY-box transcription factor 9 (SOX9). The structural integrity of the endplate is thereby compromised, contributing to the disruption of osteochondral continuity characteristic of Modic pathology.

Moreover, mast cells activated via the Mrgprb2 pathway release chemotactic factors that facilitate the recruitment of macrophages and skew their polarization toward the M1 phenotype. This enhances the production of potent proinflammatory cytokines such as TNF- α and IL-1 β , reinforcing a self-perpetuating inflammatory loop: mast cell activation \rightarrow cytokine release \rightarrow M1 macrophage polarization \rightarrow sustained inflammation. This loop represents a novel mechanism of immune amplification within the Modic microenvironment.

Functional experiments involving mast cell depletion and genetic knockout of Mrgprb2 further underscore the pathological role of mast cells in MCs. Both mast cell deficiency and Mrgprb2 deletion significantly attenuated Modic-associated tissue damage, whereas mast cell activation exacerbated vertebral endplate disruption and bone degradation. These findings highlight mast cells as crucial modulators of the immune microenvironment in MCs, acting through a nonclassical pathway that complements and intensifies local inflammation and tissue remodeling.

2.4. Neutrophils: early responders and potential amplifiers of inflammation

Neutrophils, as early responders in innate immunity, have increasingly been implicated in the pathogenesis of MCs, particularly during the inflammatory phase of type I lesions (MC1). Proteomic analyses revealed enrichment of neutrophil degranulation-related proteins—including

PLA2G2A, CHI3L1, and CLEC3A—in MC1 tissues, alongside activation of complement pathways, TLRs, and Fc γ receptor signaling.^[49] These findings suggest that neutrophil-derived enzymes and antimicrobial peptides may contribute to matrix breakdown and pain sensitization, amplifying chronic sterile inflammation. Mechanistic evidence from Heggli et al.^[50] further demonstrated elevated neutrophil-related chemokines and cytokines (IL-8, epithelial-derived neutrophil-activating peptide-78) in bone marrow aspirates of MC1 patients with high *C. acnes* genomic load, highlighting microbial burden as a driver of neutrophil activation.

Neutrophil involvement appears closely linked to complement activation. C1q and C5a, elevated in MC tissues, are known to recruit neutrophils, promoting degranulation and formation of neutrophil extracellular traps, which in turn amplify complement signaling—a self-perpetuating “complement–neutrophil loop”.^[16] This inflammatory microenvironment is supported by findings of increased CXCL5, GM-CSF, and IL-1 β in MC disc tissues,^[51] as well as histological confirmation of neutrophil infiltration and elevated IL-8 in *C. acnes*-positive specimens.^[31] A transcriptomic study by Vigeland et al.^[52] noted a sex-specific immune profile, with female MC1 patients showing higher neutrophil-related gene expression (CXCL8, MMP9, IL1R2), in contrast to male patients with T cell-dominated responses.

However, systemic neutrophil involvement remains debated. Özcan-Ekşi et al.^[27] found no significant difference in neutrophil-to-lymphocyte ratios (NLRs) between MC and non-MC groups, despite elevated NLR in general disc degeneration. Similarly, Rigal et al.,^[53] using anterior sampling, reported minimal neutrophil infiltration and no bacterial growth in most MC1 cases, suggesting that certain Modic lesions may follow a noninfectious, localized inflammatory trajectory independent of systemic neutrophil activation. These findings underscore the context-dependent role of neutrophils, likely significant in microbially influenced or high-inflammatory MC1 subtypes, but less prominent in sterile or late-phase lesions.

2.5. T and B lymphocytes: mediators of chronic inflammatory responses

MCs, particularly type I, involve not only innate but also adaptive immune responses, with accumulating evidence implicating T and B lymphocytes in their initiation and progression. Experimental models have demonstrated that NP exposure to the bone marrow triggers a complex antigen-specific immune reaction. In a rabbit model, subendplate implantation of autologous NP resulted in MC-like lesions with T cell infiltration and increased IL-4, IL-17, and IFN- γ expression, indicating Th1, Th2, and Th17 involvement.^[54] Geiss et al.^[29] further showed that NP-reactive CD4⁺ T cells predominantly secreted IL-4, suggesting a skewing toward a Th2-polarized, chronic inflammatory state. In vitro, NP cells were shown to possess immunogenicity and induce lymphocyte proliferation, but only in the presence of inflammatory stimuli

such as IL-1 α did this lead to activation of cytokines (IL-1, IL-6, IL-10) and neurotrophic factors like TrkA, promoting T cell recruitment and local inflammation.^[33]

In human studies, Heggli et al.^[50] observed that MC1 patients with low *C. acnes* burden exhibited significant upregulation of T and B cell-associated genes, particularly IL-13, alongside enrichment of pathways related to Th1/Th2/Th17 differentiation and B cell activation. Zhu et al.^[15] proposed that CXCL12 signaling in the bone marrow may promote B cell activation in this context, with C-X-C motif chemokine 12-positive (CXCL12⁺) leptin receptor-positive bone marrow stromal cells potentially sustaining chronic inflammation through interaction with T/B cells. These mechanisms suggest an autoimmune component in MC1 pathogenesis, independent of bacterial load.

Moreover, adaptive immunity may contribute to chronicity or tissue remodeling. Vigeland et al.^[55] reported that patients with high-shrt tau inversion recovery MC1 exhibited peripheral blood enrichment in interferon and B cell activation pathways, indicating that adaptive immune responses persist even in radiologically active lesions and may influence the fibrotic or reparative trajectory of MCs.

2.6. The complement system: a bridge and amplifier of inflammation in MCs

The complement system is a critical component of innate immune defense, consisting of 3 main activation pathways—classical, alternative, and lectin—as well as a network of regulatory proteins. Upon activation, the system initiates cleavage of C3 and C5, generating the potent chemoattractants C3a and C5a and culminating in the assembly of the membrane attack complex (MAC or terminal complement complex [TCC], C5b-9), which induces lysis of target cells.^[56] While complement plays an essential role in maintaining immune homeostasis, microbial defense, and clearance of apoptotic cells, dysregulated or excessive activation has been implicated in chronic inflammation, tissue destruction, and immune-mediated disorders.^[57]

Recent studies have proposed that the complement system may serve as both a driver and a maintainer of inflammation in MCs, particularly at the interface of vertebral endplates and bone marrow. According to Heggli et al.^[16] and Zhu et al.,^[15] multiple triggers—including endplate disruption, cell death, *C. acnes* infection, and immune complex formation—can initiate complement activation. The anaphylatoxins C3a and C5a further promote fibrosis, vascular and neural remodeling, and nociceptive sensitization through the induction of VEGF, TGF- β , and IL-1 β . In parallel, sublytic levels of TCCs may exacerbate cytokine release, contributing to endplate degradation and marrow remodeling.

Proteomic profiling revealed significant upregulation of complement components—including C1S, C1QB, C3, C4B, C6, C8B, and C9—in MC tissues, but not in non-MC controls.^[49] These findings point to active engagement of

both the classical and terminal complement cascades as hallmarks of the MC microenvironment. Furthermore, their analysis uncovered interaction networks linking complement activation to neutrophil degranulation, immunoglobulin complexes, and glutamate metabolism, implicating complement as a key mediator in both inflammation and pain amplification.

These observations were subsequently validated in a cadaveric study by Heggli et al.,^[23] who reported accumulation of C1QC, C5, C8A, C8B, C9, and complement factor B (CFB) in MC2 bone marrow. Expression levels were positively correlated with the degree of endplate structural damage. Combined with immunohistochemical analysis and endplate scoring, they proposed that fragmentation of the cartilaginous and bony endplates exposes extracellular matrix (ECM) proteins (e.g., FMOD, BGN, DCN), which can act as C1q ligands to trigger the classical complement pathway. This local activation may in turn lead to C3a/C5a-mediated angiogenesis, fibroblast activation, and inflammatory crosstalk between the endplate and bone marrow. An increased presence of TCC (C5b-9)-positive cells in both NP and endplate regions of degenerated discs, with their proportion positively correlated with the Pfirrmann grade of degeneration.^[58] The proportion of TCC-positive cells correlated with Pfirrmann grade. Notably, despite upregulation of the complement inhibitor CD59, TCC formation was not suppressed, indicating a failure of local regulatory mechanisms. The authors speculated that sublytic TCCs may contribute to sustained low-grade inflammation through mechanisms such as cell stress or activation of the NLRP3 inflammasome—creating a permissive milieu for the development of MCs.

An alternative perspective was provided by Djuric et al.,^[22] who identified a potential “dysfunctional activation” phenotype in MC tissue. They observed downregulation of CFB and C3 and upregulation of the complement inhibitor clustering, suggesting a possible breakdown in the activation cascade or an immunosuppressive response. Such a state may reflect “immune exhaustion” or a reparative anti-inflammatory phase, potentially explaining the fluctuating pain severity and variable response to immunomodulatory therapies in certain MC patients.

Nonetheless, not all evidence supports a significant role for complement in MC pathogenesis. A large-scale serum proteomics study by S Rajasekaran et al.^[49] found no differential expression of complement proteins such as C3, C4, or C5 in the peripheral blood of MC patients. This suggests that complement activation in MC may be highly localized to the vertebral endplate–bone marrow interface and not associated with systemic inflammatory responses.

2.7. Biomechanical disruption: a trigger for immune activation

While MCs have historically been attributed to mechanical factors such as abnormal loading, endplate microfractures,

and vertebral instability, accumulating evidence suggests that these biomechanical insults serve as upstream triggers for downstream immunological cascades. Structural failure of the cartilaginous or bony endplate facilitates the leakage of NP material into the adjacent bone marrow, thereby breaching its immune-privileged status.^[32] This exposure initiates a local immune response, characterized by activation of pattern recognition receptors such as TLRs, release of DAMPs, and subsequent recruitment of innate immune cells.^[17,33,59]

Experimental studies have demonstrated that mechanical endplate injury alone is sufficient to upregulate proinflammatory mediators such as TNF- α , IL-1 β , and IL-6 within the bone–disc interface.^[60,61] In animal models, annular puncture leads to endplate remodeling, bone marrow edema, and infiltration of macrophages and neutrophils—hallmarks of early-stage MC1.^[60,61] Moreover, breakdown products of ECM components, such as biglycan and fibromodulin, may serve as endogenous ligands for complement components and TLRs, thereby amplifying inflammatory cascades.^[16,17,23]

Thus, biomechanical stress and immune activation are tightly intertwined in the pathogenesis of MCs.^[11,33] The mechanical damage acts not only as an initiator of structural degeneration but also as a potent stimulator of innate and adaptive immune responses.^[16] This biomechanical–immunological coupling explains the chronicity and phenotypic progression of MCs and highlights the necessity of integrative treatment strategies that address both mechanical stabilization and immune modulation.^[11,16,33]

3. Key immunological signaling pathways

3.1. Innate immunity and proinflammatory activation

MCs, particularly type I, are increasingly recognized as a manifestation of innate immune dysregulation in discogenic chronic low back pain. The initiating event is thought to be the disruption of the vertebral endplate, which exposes the normally immune-privileged NP to the systemic immune system. This triggers the release of DAMPs (Fig. 2), such as HMGB1 and fragmented hyaluronic acid, which activate TLRs, especially TLR2 and TLR4. These receptors engage MyD88/TRIF signaling pathways, leading to nuclear factor kappa B (NF- κ B) activation and the production of proinflammatory cytokines, including IL-6, IL-1 β , and TNF- α .^[17,33,59,62–64] Degenerative NP cells themselves can amplify inflammation by releasing cytokines like IL-8 and CCL2, establishing MC lesions as self-sustaining inflammatory foci.^[34] Inflammasome signaling also plays a critical role: NLRP3, caspase-1, and IL-1 β are upregulated in MC1 endplates, contributing to matrix degradation via ADAMTS-5 and suppression of Col II and SOX9.^[65,66] TNF- α and IL-1 β create a feedback loop that enhances MMP and ADAMTS expression, reinforcing tissue destruction.^[67]

Bone marrow edema, a hallmark of MC1, reflects this acute inflammatory phase. Animal studies have shown that TNF- α knockout reduces T2-weighted hyperintensity

on MRI, implicating TNF- α in early disease stages.^[60] MC1 tissues exhibit high levels of TNF-positive cells and nerve sprouting, with PGP9.5-positive nerve fibers more abundant in MC1 than in MC2 or controls.^[68] Clinically, MC1 often presents with inflammatory pain features and shows transient responsiveness to corticosteroids.^[69] Macrophage MIF is also upregulated in MC1 endplates and blood. Through CD74 signaling, MIF induces IL-6, IL-8, and PGE2 production, which can be inhibited by ISO-1.^[40,41] This pathway may be shared between infectious and noninfectious MCs, as MIF is similarly elevated in *C. acnes*–induced models.^[70] Complement activation further contributes to inflammation. Elevated levels of C1q, C3, C5, and TCCs have been observed in MC1/2, driving neutrophil infiltration, osteoclastogenesis, and angiogenesis via TGF- β and VEGF signaling.^[16,49]

The role of infection—particularly *C. acnes*—in MC1 remains controversial. Injection of the bacterium into vertebrae in animal models induces Modic-like MRI changes and upregulates TNF- α , IL-1 β , and IFN- γ .^[71] Human MC1 discs positive for *C. acnes* exhibit higher levels of IL-8, MIP-1 α , MCP-1, and neutrophil infiltration, suggesting a chemokine-driven innate immune response.^[31] Transcriptomic studies have distinguished bacterial and nonbacterial MC1 subtypes: the former characterized by neutrophil degranulation and elevated IL-8/MIP-1 β , the latter by T/B cell–dominated responses.^[50] Systemic immune activation has also been observed. Patients with MC-related back pain display elevated monocyte/basophil counts and erythrocyte sedimentation rate, as well as proteomic enrichment of immunoglobulins, complement, and NF- κ B-related proteins in disc tissue.^[27,49]

Emerging mechanisms add further complexity to MC pathophysiology. Galectin-3, which regulates endplate homeostasis, declines progressively from MC I to III, and correlates with aggrecan and CCL3 expression. Its inhibition reduces endplate cell survival, suggesting a protective role.^[72] TRP ion channels (e.g., TRPV4, TRPC6) correlate with IL-6/IL-15 and may link inflammation to pain via cellular mechanosensing.^[73] Oxidative stress, indicated by elevated 8-iso-prostaglandin F $_{2\alpha}$ and Raftlin levels, may amplify membrane-bound immune signaling.^[74] HIF-1 α /Notch1 signaling has also been implicated in endplate remodeling and inflammatory activation in early MC1/2 lesions.^[75] Despite these insights, clinical translation remains challenging. A multicenter randomized controlled trial showed no benefit of infliximab in MC1 patients, suggesting that TNF- α –driven inflammation may be secondary rather than causal.^[76,77] Moreover, peripheral cytokine profiles failed to predict response to antibiotics, highlighting the focal and heterogeneous nature of Modic inflammation.^[78]

3.2. Adaptive immunity (T/B cell crosstalk)

The adaptive immune system is increasingly implicated in the pathogenesis of MCs, particularly type I lesions.

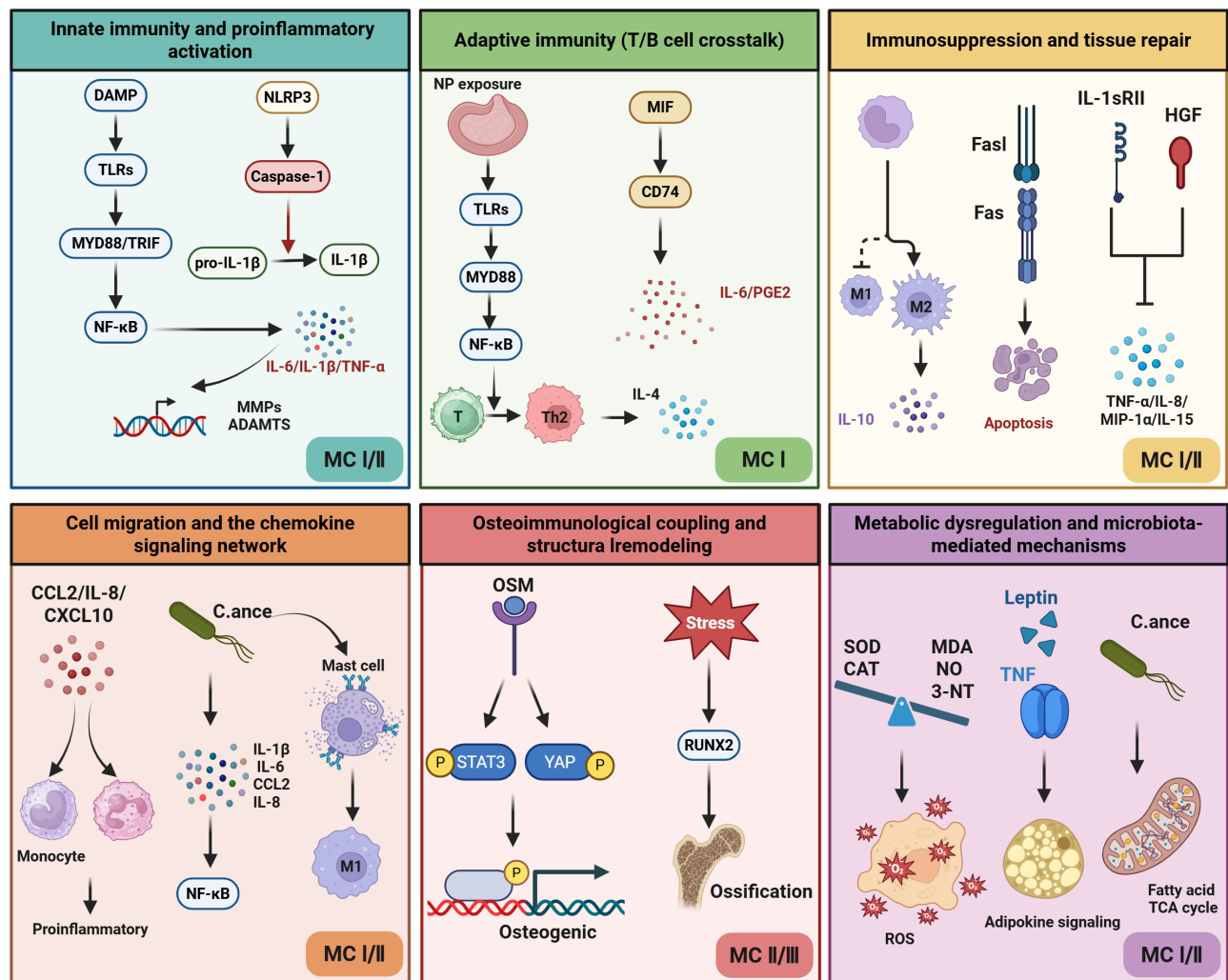


Figure 2. Key signaling pathways in immune regulation. MC = Modic change.

Under normal conditions, the NP of intervertebral discs is immune-privileged; however, endplate disruption exposes NP components to the bone marrow, where they may be misrecognized as neo-antigens. This can initiate a T cell-mediated autoimmune response, contributing to bone marrow edema and pain. In animal models, subendplate implantation of autologous NP tissue induced MRI changes resembling MC1, with concurrent elevation of IL-4, IL-17, and IFN- γ , and histological features of NP- and chondrocyte-like cell proliferation, reflecting activation of adaptive immunity.^[54,62] Notably, porcine studies revealed that chronic NP exposure skews CD4⁺ T cells toward a Th2 phenotype, marked by IL-4 production and negligible IFN- γ , suggesting an atypical immune profile resembling allergic responses.^[29] This Th2 bias may be linked to IgE-mediated mechanisms observed in some patients with recurrent disc herniation, potentially contributing to chronic pain sensitization.

Experimental models further support this immune-activating potential of NP tissue. Co-culture systems showed that NP cells prolong BMNC survival and enhance cytokine production under inflammatory conditions, particularly following IL-1 α stimulation. *In vivo*,

implantation of lipopolysaccharide-preconditioned NP tissue triggered MC1-like MRI signals, endplate damage, and CD3⁺ T cell infiltration—consistent with a role for NP as an immune-activating foci via TLR2/4–MyD88–NF- κ B pathways^[33] (Fig. 2). Complementing this, systemic immunologic changes have also been reported. Transcriptomic profiling of peripheral blood in MC1 patients identified 37 differentially expressed genes enriched in interferon response and mitochondrial metabolism, including IFI27, RSAD2, and RAVR2—markers of immune activation.^[55] Downregulation of genes linked to pain resolution, such as GLYTL2, further supports the systemic immune component of MC-related symptoms.

While T cell mechanisms dominate current research, there is emerging evidence that B cells may also contribute. The MIF–CD74 axis, known to activate monocytes and support antigen presentation, is upregulated in MC1 endplates. CD74, as a key chaperone of MHC-II molecules, likely promotes T–B cell interactions and facilitates adaptive immune activation. Additionally, this axis drives IL-6 and PGE2 production, linking innate signals to humoral responses.^[40] Although direct evidence of B cell activation within MC lesions remains limited, these findings suggest

that humoral immunity may be an under-recognized factor in MC1 pathophysiology.

3.3. Immunosuppression and tissue repair

As MCs evolve chronically, there is a notable immunological shift from proinflammatory destruction toward immune suppression and tissue repair. This transition is characterized by a downregulation of proinflammatory mediators, a phenotypic shift in immune cells toward tolerance or reparative activity, and concurrent tissue-level adaptations such as fibrosis, ECM remodeling, and limited neurovascular regeneration. Compared with the acute inflammatory phase of type I MC, intermediate and late stages—particularly in types I and II—exhibit a low-grade, reparative phenotype shaped by macrophage polarization, stem cell activity, and upregulated anti-inflammatory cytokines.^[79,80] Macrophages play a central role in this process. Immunohistochemical studies reveal that although CD68⁺ macrophages are more abundant in MC-positive (MC⁺) endplates, the expression of M2 markers (e.g., CD163, CD209) dominates, while proinflammatory M1 markers are comparatively limited, indicating a primary role in tissue remodeling and debris clearance rather than immune activation.^[39] Supporting this, macrophage density has been associated with spontaneous disc resorption, even in type II MC patients, implying active participation of M2-like macrophages in remodeling via IL-10-mediated effects.^[46]

Anti-inflammatory and angiostatic cytokine patterns further underscore this reparative shift. Serum profiling studies demonstrate that declining trends in TNF- α , IL-8, MIP-1 α , and IL-15 in MC patients, along with significant upregulation of immunosuppressive mediators such as IL-1sRII and hepatocyte growth factor (HGF). IL-1sRII, in particular, may serve as a biomarker for MC-related immunosuppression.^[79] Concomitantly, downregulation of angiogenic factors including VEGF-C, Tie2, and VCAM-1 suggests a metabolically quiescent or “silent” immune environment. At the tissue level, programmed cell death mechanisms also contribute to structural remodeling. Increased Fas receptor (FasR) expression and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL)-positive apoptosis in MC I/II endplates implicate the Fas–FasL axis in cell turnover, independent of disc degeneration severity, hinting at its role in age-related rather than acutely inflammatory changes.^[81] Bone marrow mesenchymal stem cells further support tissue reconstruction. CD90⁺ bone marrow mesenchymal stem cells are enriched in MC I/II marrow and strongly correlate with fibrotic markers (FN1, α -SMA, COL1), suggesting that these cells actively guide the transition from edema to fibrosis.^[80]

Late-stage MC, particularly type II, is increasingly recognized as a fibrosing inflammatory condition. Cadaveric analysis revealed dense accumulation of complement proteins (C1Q, C5, C9), matrix components (FN1, BGN, DCN), and neurovascular regulators (VEGFR1, SEM3A,

POSTN) at sites of endplate disruption, establishing MC II as a complement-mediated fibrotic state rather than mere fatty replacement.^[23] Animal studies corroborate these findings: rabbit models of MC show long-term coexistence of inflammatory and reparative markers (IL-4, IL-17, IFN- γ), chondrocyte-like proliferation, and matrix remodeling 12–20 weeks postinjury.^[54] Similarly, NP-exposed T cells display IL-4-driven Th2 polarization, reinforcing the concept of adaptive immune deviation toward anti-inflammatory states during chronic MC progression.^[29]

3.4. Cell migration and the chemokine signaling network

Chemokines are integral to the pathogenesis of MCs, orchestrating immune cell recruitment, inflammatory amplification, and structural remodeling at the vertebral endplate. In type I MCs, a cytokine-rich microenvironment characterized by elevated CCL2, IL-8, and CXCL10 promotes monocyte and neutrophil infiltration through sustained proinflammatory cascades.^[60] Early-stage animal models identified TNF- α as a central initiator of bone marrow edema, with TNFR1/2 knockout suppressing MRI hyperintensity, whereas anti-TNF agents had a limited effect in later stages, suggesting a temporal role in inflammation priming.^[60] Human disc samples from MC patients show elevated GM-CSF, ENA-78, and IL-1 β expression, with trends toward increased TNF- α , indicating persistent immune activation even in the fatty degeneration phenotype of Modic type II.^[51]

Microbial stimuli, particularly *C. acnes*, act as potent inducers of chemokine expression. Disc and marrow cells exposed to *C. acnes* exhibit increased IL-1 β , IL-6, CCL2, and IL-8 expression, triggering inflammatory signaling in bone marrow mononuclear cells and enhancing neutrophil infiltration.^[31,34] This bacteria–chemokine axis is thought to disrupt local immune tolerance, facilitating a chronic inflammatory milieu. Mechanistically, chemokine signaling is reinforced by lipid raft scaffolding proteins such as Raftlin, which, along with oxidative stress marker 8-iso-PGF2 α , is elevated in MC serum. These factors enhance NF- κ B activity and stabilize receptor clustering at the membrane, amplifying immune responses.^[74]

Recent studies have revealed dynamic shifts in chemokine profiles in response to microbial modulation. Longitudinal data from the AIM study demonstrated reductions in CXCL10, CXCL11, and CXCL13 with concurrent increases in GM-CSF and therapy-related declines in IL-6, suggesting chemokine plasticity during disease course and treatment.^[82] Functional analysis showed CXCL9–11 operating in either proinflammatory or anti-inflammatory modules depending on TNF or IL-10 dominance, respectively.^[82] Additionally, *C. acnes* activates mast cells through Mrgprb2-dependent pathways, inducing MMP13, inhibiting cartilage matrix markers, and promoting M1 macrophage polarization while suppressing M2 responses—a pathway distinct from classical

allergic inflammation.^[30] These insights have driven therapeutic innovations, such as nitric oxide (NO)-releasing nanoplatforms targeting chemotactic and inflammatory signaling, which demonstrated efficacy in delaying disc degeneration and preserving endplate integrity in preclinical models.^[70]

Clinically, the expression of chemokines such as CXCL13, CCL19, and CCL27 correlates with pain improvement, indicating their utility as biomarkers for monitoring disease activity and therapeutic response.^[82] Together, these findings underscore that chemokine-mediated immune migration in MC is not merely a passive byproduct of degeneration, but a dynamic, targetable driver of disease progression.

3.5. Osteoimmunological coupling and structural remodeling

The concept of osteoimmunological coupling—denoting the reciprocal interaction between immune activity and skeletal remodeling—has become central to understanding the pathophysiology of MCs. Mounting evidence suggests that the vertebral endplate and adjacent marrow operate as a functional unit where inflammation, apoptosis, matrix degradation, and bone turnover intersect. This immuno-skeletal interface governs the transition from the edematous phenotype of type I MC to fatty degeneration in type II, and ultimately to the sclerotic transformation characteristic of type III.

At the cellular level, bone marrow stromal cells within MC1 lesions exhibit a fibrogenic phenotype marked by elevated COL1A1, FN1, and ACTA2 expression, alongside increased fibronectin adhesion. This program appears reversible by fibroblast growth factor 2 (FGF2), which raises concerns about the masking effect of FGF2-containing media in *ex vivo* studies of native MC1 cells.^[83] Concomitantly, structural degradation occurs via apoptosis and matrix catabolism. Upregulation of the Fas–FasL axis and terminal deoxynucleotidyl transferase dUTP nick end labeling-positive cells in MC I/II endplates implicates programmed cell death in cartilage-endplate breakdown.^[81] This is exacerbated by matrix metalloproteinases such as ADAMTS-5, -7, and -12, which suppress chondrogenic markers (Col II, Sox9) and accelerate aggrecan degradation under TNF- α /NF- κ B stimulation.^[66,84]

Histomorphological analyses confirm subtype-specific remodeling patterns. Type I MCs exhibit increased osteoid surface/bone surface, indicative of active remodeling, while type II shows reduced osteogenesis, and type III features trabecular thickening and elevated bone mineral density.^[24] These observations are genetically supported by associations of IL1A and MMP3 polymorphisms with type II MC, and VDR and MMP20 variants with broader MC phenotypes.^[85,86]

Immune cells contribute directly to structural transformation. Osteal macrophages in MC II/III regions express high levels of OSM, which activates STAT3/YAP1 signaling and promotes osteogenic differentiation (Runx2, ALP). OSM neutralization attenuates sclerosis,

underscoring its role in immune-driven ossification.^[28] Similarly, NLRP3 inflammasome activation in MC I/II endplates drives IL-1 β production and enhances matrix degradation, while circulating collagen breakdown products (e.g., PRO-C3, C4M) may serve as fibrosis-linked biomarkers.^[65,87]

Importantly, these osteoadaptive responses appear early in disease evolution. Annular puncture in animal models induces endplate thickening, trabecular hypertrophy, osteophyte formation, and matrix mineralization even before MCs become radiographically evident.^[61] Clinical imaging also reveals that type II lesions can present with significant sclerosis, challenging the view of this subtype as purely fatty.^[88]

Additional contributors include loss of lubricin and dysregulated lipid metabolism. Lubricin deficiency, worsened by *C. acnes* infection, potentiates TLR2–NF- κ B signaling and matrix breakdown,^[89] while lipid accumulation correlates with increased MMP-1, ADAMTS-5, and reduced aggrecan expression.^[90] Furthermore, mechanical disruption of endplates induces BMP-2 expression, suggesting that biomechanical stress alone can trigger ossification pathways and promote late-stage sclerosis.^[91]

3.6. Metabolic dysregulation and microbiota-mediated mechanisms

Beyond mechanical stress and inflammation, MCs—particularly type I and II—are increasingly understood within a broader pathophysiological framework involving oxidative stress, metabolic dysregulation, and microbial signaling. In MC1, redox imbalance plays a central role, with elevated systemic levels of oxidative/nitrosative markers such as malondialdehyde, NO, and 3-nitrotyrosine, coupled with decreased antioxidant enzymes like superoxide dismutase and catalase, suggesting that persistent oxidative stress contributes to marrow hyperemia and endplate damage.^[92] In MC2 lesions, adipokine signaling from hypertrophic yellow marrow, including leptin and TNF superfamily members, has been proposed to sustain low-grade paracrine inflammation across the disc–endplate interface.^[93] Lubricin deficiency further exacerbates this process; its loss in MC1 is associated with IL-1 β -driven upregulation of MMP-1 and ADAMTS-5, activating TLR2–NF- κ B signaling and promoting early matrix degradation.^[89]

Microbial factors, particularly *C. acnes*, have also been implicated in MC pathogenesis. *In vitro* and animal studies show that *C. acnes* induce Modic-like changes only in an inflamed milieu, supporting a dual-hit hypothesis.^[33,34] Clinical reports confirm frequent *C. acnes* detection in MC1 tissues using polymerase chain reaction and culture methods,^[94,95] and endplate injection of the bacterium has successfully reproduced MC2-like MRI changes in animal models.^[71] However, conflicting evidence suggests possible contamination during surgical sampling.^[96] Recent microbiome analyses have expanded this perspective, revealing endplate microbial dysbiosis and altered fatty acid and tricarboxylic acid cycle metabolites in

MC patients.^[97] Parallel gut microbiome studies show decreased short-chain fatty acid-producing bacteria and increased C-reactive protein and FABP5, implying a gut-endplate–marrow axis linking systemic inflammation to MC development.^[98]

Metabolic byproducts also impact structural integrity. Advanced glycation end products may alter collagen properties in the endplate via hydrogen bonding and biomechanical remodeling.^[99] Systemically, a “hyporesponsive” inflammatory phenotype with suppressed TNF- α and IL-8 but elevated IL-1sRII and HGF has been observed in MC patients, indicating adaptive immune modulation rather than persistent high-grade inflammation.^[79] Moreover, an association between MC2 and vascular calcification suggests that compromised nutrient supply may link systemic metabolic imbalance to local degenerative changes.^[100]

4. Conclusions

MCs, a distinct radiographic phenotype within degenerative spinal disorders, represent a dynamic immunopathological process that transcends the traditional “mechanical degeneration–structural failure” paradigm. This review characterizes MCs as a progressive, phase-specific disorder of the bone–endplate–marrow interface, shaped by the interplay of innate and adaptive immune responses, fluctuating inflammatory states, and converging molecular pathways—including complement activation, DAMP–TLR signaling, lipid raft–mediated cascades, and chemokine-driven recruitment.

In the initial inflammatory phase, endplate disruption and NP exposure break immune privilege and activate DAMP–TLR–NF- κ B pathways, inducing infiltration by macrophages, neutrophils, and mast cells. This results in robust secretion of proinflammatory cytokines such as IL-1 β , TNF- α , and IL-6—hallmarks of type I MC. Complement activation, particularly via C3a, C5a, and MAC, amplifies matrix degradation and nociceptive sensitization. As inflammation evolves, reparative mechanisms emerge. Type II MC reflects an immunosuppressive and fibrotic shift marked by M2 macrophages, Th2 cells, CD90+ MSCs, and increased IL-10, HGF, and IL-1sRII. In type III MC, vertebral sclerosis and endplate ossification are driven by bone-resident macrophages and osteogenic mediators such as OSM and BMP-2.

Throughout this continuum, chemokines like IL-8, MCP-1, and CXCL10 coordinate immune cell migration and may serve as biomarkers of disease activity and therapeutic response. Additional modulators—Raftlin, oxidative stress metabolites, and Notch/HIF signaling—link MCs to broader metabolic dysfunction. In a subset of patients, low-virulence pathogens like *C. acnes* may contribute to an “infectious-type Modic,” potentially responsive to targeted antimicrobial therapy.

MCs should thus be redefined as a multiphase immunometabolic disorder. Future studies must clarify the molecular and immunological signatures of MC subtypes to

support the development of personalized, mechanism-based interventions beyond descriptive imaging.

Acknowledgments

Not applicable.

Ethical statement

Not applicable.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Funding source

Not applicable.

Data availability statement

Not applicable.

Author contributions

YJT AND XXK drafted the manuscript. FDZ supervised and critically revised the manuscript.

References

- [1] Modic MT, Masaryk TJ, Ross JS, Carter JR. Imaging of degenerative disk disease. *Radiology*. 1988;168:177–86.
- [2] Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. *Radiology*. 1988;166(1 Pt 1):193–9.
- [3] de Roos A, Kressel H, Spritzer C, Dalinka M. MR imaging of marrow changes adjacent to end plates in degenerative lumbar disk disease. *AJR Am J Roentgenol*. 1987;149:531–4.
- [4] Wei B, Wu H. Study of the distribution of lumbar Modic changes in patients with low back pain and correlation with lumbar degeneration diseases. *J Pain Res*. 2023;16:3725–33.
- [5] Yang X, Karis DSA, Vleggeert-Lankamp CLA. Association between Modic changes, disc degeneration, and neck pain in the cervical spine: a systematic review of literature. *Spine J*. 2020;20:754–64.
- [6] Kjaer P, Korsholm L, Bendix T, Sorensen JS, Leboeuf-Yde C. Modic changes and their associations with clinical findings. *Eur Spine J*. 2006;15:1312–9.
- [7] van der Graaf JW, Kroeze RJ, Buckens CFM, Lessmann N, van Hooff ML. MRI image features with an evident relation to low back pain: a narrative review. *Eur Spine J*. 2023;32:1830–41.
- [8] Ziegler DS, Carreon L, Andersen MO, Jensen RK. The association between preoperative MRI findings and surgical revision within three years after surgery for lumbar disc herniation. *Spine (Phila Pa 1976)*. 2019;44:818–25.
- [9] Shuai W, Xiao Y, Zhang Z, Liu L, Song Y, Yang X. Postoperative sclerotic Modic changes after transforaminal lumbar interbody fusion: whether it is different between nano-hydroxyapatite/polyamide 66 and polyetheretherketone cage? *World Neurosurg*. 2025;197:123846.
- [10] Rajasekaran S, Ramachandran K, K S SVA, Kanna RM, Shetty AP. From Modic to disc endplate bone marrow complex - the natural course and clinical implication of vertebral endplate changes. *Global Spine J*. 2025;15:196–209.

- [11] Dudli S, Fields AJ, Samartzis D, Karppinen J, Lotz JC. Pathobiology of Modic changes. *Eur Spine J.* 2016;25:3723–34.
- [12] Liu H, Gan Y, He B, et al. mNGS technique was used to analyze the microbiome structure of intervertebral disc tissue in 99 patients with degenerative disc disease. *Eur Spine J.* 2025;34:1709–21.
- [13] Kuisma M, Karppinen J, Niinimäki J, et al. A three-year follow-up of lumbar spine endplate (Modic) changes. *Spine (Phila Pa 1976).* 2006;31:1714–8.
- [14] Mitra D, Cassar-Pullicino VN, McCall IW. Longitudinal study of vertebral type-1 end-plate changes on MR of the lumbar spine. *Eur Radiol.* 2004;14:1574–81.
- [15] Zhu W, Yang Z, Zhou S, et al. Modic changes: from potential molecular mechanisms to future research directions (Review). *Mol Med Rep.* 2025;31:90.
- [16] Heggli I, Teixeira GQ, Iatridis JC, Neidlinger-Wilke C, Dudli S. The role of the complement system in disc degeneration and Modic changes. *JOR Spine.* 2024;7:e1312.
- [17] Piccinini AM, Midwood KS. DAMPening inflammation by modulating TLR signalling. *Mediators Inflamm.* 2010;2010:672395.
- [18] Khalil JG, Gandhi SD, Park DK, Fischgrund JS. Cutibacterium acnes in spine pathology: pathophysiology, diagnosis, and management. *J Am Acad Orthop Surg.* 2019;27:e633–40.
- [19] Lan W, Wang X, Tu X, Hu X, Lu H. Different phylotypes of Cutibacterium acnes cause different Modic changes in intervertebral disc degeneration. *PLoS One.* 2022;17:e0270982.
- [20] Crump KB, Alminnawi A, Bermudez-Lekerika P, et al. Cartilaginous endplates: a comprehensive review on a neglected structure in intervertebral disc research. *JOR Spine.* 2023;6:e1294.
- [21] Viswanathan VK, Shetty AP, Rajasekaran S. Modic changes - an evidence-based, narrative review on its patho-physiology, clinical significance and role in chronic low back pain. *J Clin Orthop Trauma.* 2020;11:761–9.
- [22] Djuric N, Rajasekaran S, Tangavel C, et al. Influence of endplate avulsion and Modic changes on the inflammation profile of herniated discs: a proteomic and bioinformatic approach. *Eur Spine J.* 2022;31:389–99.
- [23] Heggli I, Laux CJ, Mengis T, et al. Modic type 2 changes are fibroinflammatory changes with complement system involvement adjacent to degenerated vertebral endplates. *JOR Spine.* 2023;6:e1237.
- [24] Perilli E, Parkinson IH, Truong LH, Chong KC, Fazzalari NL, Osti OL. Modic (endplate) changes in the lumbar spine: bone micro-architecture and remodelling. *Eur Spine J.* 2015;24:1926–34.
- [25] Tamai H, Teraguchi M, Hashizume H, et al. A prospective, 3-year longitudinal study of Modic changes of the lumbar spine in a population-based cohort: the Wakayama Spine study. *Spine (Phila Pa 1976).* 2022;47:490–7.
- [26] Bostelmann R, Petridis A, Fischer K, Vajkoczy P, Bostelmann T, Barth M. New insights into the natural course and clinical relevance of Modic changes over 2 years following lumbar limited discectomy: analysis of prospective collected data. *Eur Spine J.* 2019;28:2551–61.
- [27] Özcan-Ekşi EE, Berikol G, Ekşi MS. Potential blood markers as screening tools for subjects with low back pain: an age- and gender-matched cross-sectional analysis. *Curr Med Res Opin.* 2024;40:77–85.
- [28] Wang J, Zheng Z, Huang B, et al. Osteal tissue macrophages are involved in endplate osteosclerosis through the OSM-STAT3/YAP1 signaling axis in Modic changes. *J Immunol.* 2020;205:968–80.
- [29] Geiss A, Larsson K, Junevik K, Rydevik B, Olmarker K. Autologous nucleus pulposus primes T cells to develop into interleukin-4-producing effector cells: an experimental study on the autoimmune properties of nucleus pulposus. *J Orthop Res.* 2009;27:97–103.
- [30] Ji Z, Li J, Tao S, et al. Mrgprb2-mediated mast cell activation exacerbates Modic changes by regulating immune niches. *Exp Mol Med.* 2024;56:1178–92.
- [31] Yuan Y, Chen Y, Zhou Z, et al. Association between chronic inflammation and latent infection of Propionibacterium acnes in non-pyogenic degenerated intervertebral discs: a pilot study. *Eur Spine J.* 2018;27:2506–17.
- [32] Shi C, Pamer EG. Monocyte recruitment during infection and inflammation. *Nat Rev Immunol.* 2011;11:762–74.
- [33] Dudli S, Liebenberg E, Magnitsky S, Lu B, Lauricella M, Lotz JC. Modic type 1 change is an autoimmune response that requires a proinflammatory milieu provided by the ‘Modic disc’. *Spine J.* 2018;18:831–44.
- [34] Dudli S, Miller S, Demir-Deviren S, Lotz JC. Inflammatory response of disc cells against Propionibacterium acnes depends on the presence of lumbar Modic changes. *Eur Spine J.* 2018;27:1013–20.
- [35] Shapouri-Moghaddam A, Mohammadian S, Vazini H, et al. Macrophage plasticity, polarization, and function in health and disease. *J Cell Physiol.* 2018;233:6425–40.
- [36] Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M. The chemokine system in diverse forms of macrophage activation and polarization. *Trends Immunol.* 2004;25:677–86.
- [37] Murray PJ, Wynn TA. Protective and pathogenic functions of macrophage subsets. *Nat Rev Immunol.* 2011;11:723–37.
- [38] Li W, Djuric N, Mink C, Vleggeert-Lankamp CLA. Inflammation and macrophage polarization are associated with Modic change type in lumbar radiculopathy. *Brain Spine.* 2025;5:104249.
- [39] Djuric N, Lafeber GCM, Li W, van Duinen SG, Vleggeert-Lankamp CLA. Exploring macrophage differentiation and its relation to Modic changes in human herniated disc tissue. *Brain Spine.* 2022;2:101698.
- [40] Xiong C, Huang B, Cun Y, Aghdasi BG, Zhou Y. Migration inhibitory factor enhances inflammation via CD74 in cartilage end plates with Modic type 1 changes on MRI. *Clin Orthop Relat Res.* 2014;472:1943–54.
- [41] Gjefsen E, Gerwin K, Goll G, et al. Macrophage migration inhibitory factor: a potential biomarker for chronic low back pain in patients with Modic changes. *RMD Open.* 2021;7(2):e001726.
- [42] Torkki M, Majuri ML, Wolff H, et al. Osteoclast activators are elevated in intervertebral disks with Modic changes among patients operated for herniated nucleus pulposus. *Eur Spine J.* 2016;25:207–16.
- [43] Dou Y, Zhang Y, Liu Y, et al. Role of macrophage in intervertebral disc degeneration. *Bone Res.* 2025;13:15.
- [44] Yokozeki Y, Kawakubo A, Miyagi M, et al. Reduced TGF-beta expression and CD206-positive resident macrophages in the intervertebral discs of aged mice. *Biomed Res Int.* 2021;2021:7988320.
- [45] Kawakubo A, Miyagi M, Yokozeki Y, et al. Origin of M2 Mvarphi and its macrophage polarization by TGF-beta in a mice intervertebral injury model. *Int J Immunopathol Pharmacol.* 2022;36:3946320221103792.
- [46] Djuric N, Yang X, El Barzouhi A, et al. Lumbar disc extrusions reduce faster than bulging discs due to an active role of macrophages in sciatica. *Acta Neurochir (Wien).* 2020;162:79–85.
- [47] da Silva EZ, Jamur MC, Oliver C. Mast cell function: a new vision of an old cell. *J Histochem Cytochem.* 2014;62:698–738.
- [48] Wiet MG, Piscioneri A, Khan SN, Ballinger MN, Hoyland JA, Purmessur D. Mast cell-intervertebral disc cell interactions

- regulate inflammation, catabolism and angiogenesis in discogenic back pain. *Sci Rep.* 2017;7:12492.
- [49] Rajasekaran S, Soundararajan DCR, Nayagam SM, et al. Modic changes are associated with activation of intense inflammatory and host defense response pathways - molecular insights from proteomic analysis of human intervertebral discs. *Spine J.* 2022;22:19–38.
- [50] Heggli I, Mengis T, Laux CJ, et al. Low back pain patients with Modic type 1 changes exhibit distinct bacterial and non-bacterial subtypes. *Osteoarthr Cartil Open.* 2024;6:100434.
- [51] Schroeder GD, Markova DZ, Koerner JD, et al. Are Modic changes associated with intervertebral disc cytokine profiles? *Spine J.* 2017;17:129–34.
- [52] Vigeland MD, Flåm ST, Vigeland MD, et al; The Aim Study Group. Gene expression correlates with disability and pain intensity in patients with chronic low back pain and Modic changes in a sex-specific manner. *Int J Mol Sci.* 2025;26(2):800.
- [53] Rigal J, Thelen T, Byrne F, et al. Prospective study using anterior approach did not show association between Modic 1 changes and low grade infection in lumbar spine. *Eur Spine J.* 2016;25:1000–5.
- [54] Han C, Wang T, Jiang HQ, et al. An animal model of Modic changes by embedding autogenous nucleus pulposus inside subchondral bone of lumbar vertebrae. *Sci Rep.* 2016;6:35102.
- [55] Vigeland MD, Flåm ST, Vigeland MD, et al; AIM Study Group. Correlation between gene expression and MRI STIR signals in patients with chronic low back pain and Modic changes indicates immune involvement. *Sci Rep.* 2022;12:215.
- [56] Mastellos DC, Hajishengallis G, Lambris JD. A guide to complement biology, pathology and therapeutic opportunity. *Nat Rev Immunol.* 2024;24:118–41.
- [57] Kemper C, Ferreira VP, Paz JT, Holers VM, Lionakis MS, Alexander JJ. Complement: the road less traveled. *J Immunol.* 2023;210:119–25.
- [58] Teixeira GQ, Yong Z, Goncalves RM, et al. Terminal complement complex formation is associated with intervertebral disc degeneration. *Eur Spine J.* 2021;30:217–26.
- [59] Klawitter M, Hakozaiki M, Kobayashi H, et al. Expression and regulation of toll-like receptors (TLRs) in human intervertebral disc cells. *Eur Spine J.* 2014;23:1878–91.
- [60] Papuga MO, Kwok E, You Z, et al. TNF is required for the induction but not the maintenance of compression-induced BME signals in murine tail vertebrae: limitations of anti-TNF therapy for degenerative disc disease. *J Orthop Res.* 2011;29:1367–74.
- [61] Maertz T, Newton M, Marek AA, Planalp M, Baker K. Dynamic adaptation of vertebral endplate and trabecular bone following annular injury in a rat model of degenerative disc disease. *Spine J.* 2018;18:2091–101.
- [62] Ma XL, Ma JX, Wang T, Tian P, Han C. Possible role of auto-immune reaction in Modic type I changes. *Med Hypotheses.* 2011;76:692–4.
- [63] Akgun MY, Akyol S, Ozlen F, et al. Role of the MyD88 dependent pathway in degenerative disc disease. *Turk Neurosurg.* 2023;33:1005–11.
- [64] Alizada O, Akyol S, Ozlen F, et al. Can TRIF/TICAM-1 dependent pathway be target pathway in lumbar intervertebral disc degeneration? *Turk Neurosurg.* 2023;33:804–10.
- [65] Tang P, Zhu R, Ji WP, et al. The NLRP3/Caspase-1/Interleukin-1 β axis is active in human lumbar cartilaginous endplate degeneration. *Clin Orthop Relat Res.* 2016;474:1818–26.
- [66] Chen S, Huang Y, Zhou ZJ, et al. Upregulation of tumor necrosis factor α and ADAMTS-5, but not ADAMTS-4, in human intervertebral cartilage endplate with Modic changes. *Spine (Phila Pa 1976).* 2014;39:E817–25.
- [67] Zhang JF, Wang GL, Zhou ZJ, Fang XQ, Chen S, Fan SW. Expression of matrix metalloproteinases, tissue inhibitors of metalloproteinases, and interleukins in vertebral cartilage endplate. *Orthop Surg.* 2018;10:306–11.
- [68] Ohtori S, Inoue G, Ito T, et al. Tumor necrosis factor-immunoreactive cells and PGP 9.5-immunoreactive nerve fibers in vertebral endplates of patients with discogenic low back pain and Modic type 1 or type 2 changes on MRI. *Spine (Phila Pa 1976).* 2006;31:1026–31.
- [69] Bailly F, Maigne JY, Genevay S, et al. Inflammatory pain pattern and pain with lumbar extension associated with Modic 1 changes on MRI: a prospective case-control study of 120 patients. *Eur Spine J.* 2014;23:493–7.
- [70] Tao S, Shen Z, Chen J, et al. Red light-mediated photoredox catalysis triggers nitric oxide release for treatment of Cutibacterium acne induced intervertebral disc degeneration. *ACS Nano.* 2022;16:20376–88.
- [71] Shan Z, Zhang X, Li S, Yu T, Mamuti M, Zhao F. The influence of direct inoculation of Propionibacterium acnes on Modic changes in the spine: evidence from a rabbit model. *J Bone Joint Surg Am.* 2017;99:472–81.
- [72] Li J, Han N, Liu Z, et al. Role of galectin-3 in intervertebral disc degeneration: an experimental study. *BMC Musculoskelet Disord.* 2024;25:249.
- [73] Sadowska A, Touli E, Hitzl W, et al. Inflammaging in cervical and lumbar degenerated intervertebral discs: analysis of pro-inflammatory cytokine and TRP channel expression. *Eur Spine J.* 2018;27:564–77.
- [74] Demirhan I, Oner E, Yuksel Z, Yuksel M, Belge Kurutas E. Raftlin and 8-iso-prostaglandin F2 α levels and gene network analysis in patients with Modic changes. *Eur Spine J.* 2023;32:2368–76.
- [75] Xiong Z, Ding J, Zhou J, Yao S, Zheng J, Guo X. Correlation between the HIF-1 α /Notch signaling pathway and Modic changes in nucleus pulposus cells isolated from patients with low back pain. *BMC Musculoskelet Disord.* 2020;21:500.
- [76] Gjefsen E, Bråten LC, Ponzi E, et al. Efficacy of a tumor necrosis factor inhibitor in chronic low-back pain with Modic type 1 changes: a randomized controlled trial. *Arthritis Rheumatol.* 2025;77(5):615–23.
- [77] Hanberg JS, Ermann J, Katz JN. Modic changes and tumor necrosis factor inhibition: is the door shut? *Arthritis Rheumatol.* 2025;77(5):503–505.
- [78] Bråten LCH, Gjefsen E, Gervin K, et al; AIM-Study Group. Cytokine patterns as predictors of antibiotic treatment effect in chronic low back pain with Modic changes: subgroup analyses of a randomized trial (AIM Study). *J Pain Res.* 2023;16:1713–24.
- [79] Karppinen J, Koivisto K, Ketola J, et al. Serum biomarkers for Modic changes in patients with chronic low back pain. *Eur Spine J.* 2021;30:1018–27.
- [80] Dudli S, Karol A, Giudici L, et al. CD90-positive stromal cells associate with inflammatory and fibrotic changes in Modic changes. *Osteoarthr Cartil Open.* 2022;4:100287.
- [81] Wang F, Jiang JM, Deng CH, Wang FL, Fu ZZ, Zhang ZF. Expression of Fas receptor and apoptosis in vertebral endplates with degenerative disc diseases categorized as Modic type I or II. *Injury.* 2011;42(8):790–95.
- [82] Gjefsen E, Gervin K, Bråten LCH, et al. Longitudinal changes of serum cytokines in patients with chronic low back pain and Modic changes. *Osteoarthritis Cartilage.* Apr 2023;31(4):543–47.
- [83] Heggli I, Blache U, Herger N, et al. FGF2 overrides key pro-fibrotic features of bone marrow stromal cells isolated from Modic type 1 change patients. *Eur Cell Mater.* 2022;44:101–14.

- [84] Zhang Q, Huang M, Wang X, Xu X, Ni M, Wang Y. Negative effects of ADAMTS-7 and ADAMTS-12 on endplate cartilage differentiation. *J Orthop Res.* 2012;30:1238–43.
- [85] Karppinen J, Daavittila I, Solovieva S, et al. Genetic factors are associated with Modic changes in endplates of lumbar vertebral bodies. *Spine (Phila Pa 1976).* 2008;33:1236–41.
- [86] Kanna RM, Shanmuganathan R, Rajagopalan VR, et al. Prevalence, patterns, and genetic association analysis of Modic vertebral endplate changes. *Asian Spine J.* 2017;11(4):594–600.
- [87] Dudli S, Ballatori A, Bay-Jensen AC, et al. Serum biomarkers for connective tissue and basement membrane remodeling are associated with vertebral endplate bone marrow lesions as seen on MRI (Modic changes). *Int J Mol Sci.* 2020;21(11).
- [88] Sun C, Wang H, Jiang J, Lu F, Ma X, Xia X. The pathology of type II Modic changes: fat deposition or osteosclerosis? A study using CT scan. *Biomed Res Int.* 2018;2018:6853720.
- [89] Liu J, Wei X, Huang B, et al. Lubricin expression in the lumbar endplate and its association with Modic changes. *J Orthop Translat.* 2020;22:124–31.
- [90] Li C, Li D, Yao X, Sun S, Ren B, Han Y. Expression of lipid metabolism and cartilage degeneration-related factors in lumbar vertebral endplate Modic changes. *Jt Dis Relat Surg.* 2025;36:39–46.
- [91] Imran S, Latif R, Ahmad I, Ilyas MS, Aziz A, Zehra U. Vertebral endplate defects induced mechanical alterations and disc calcification. *Global Spine J.* 2025;15:1564–71.
- [92] Belge Kurutas E, Senoglu M, Yuksel KZ, Unsal V, Altun I. Oxidative/nitrosative stress in patients with Modic changes: preliminary controlled study. *Spine (Phila Pa 1976).* 2015;40:1101–7.
- [93] Vrselja Z, Curic G. Vertebral marrow adipose tissue adipokines as a possible cause of intervertebral disc inflammation. *Joint Bone Spine.* 2018;85:143–6.
- [94] Aghazadeh J, Salehpour F, Ziaei E, et al. Modic changes in the adjacent vertebrae due to disc material infection with *Propionibacterium acnes* in patients with lumbar disc herniation. *Eur Spine J.* 2017;26:3129–34.
- [95] Najafi S, Mahmoudi P, Bassampour SA, Shekarchi B, Soleimani M, Mohammadimehr M. Molecular detection of *Propionibacterium acnes* in biopsy samples of intervertebral disc with Modic changes in patients undergoing herniated disc surgery. *Iran J Microbiol.* 2020;12:516–21.
- [96] Fritzell P, Welinder-Olsson C, Jönsson B, et al. Bacteria: back pain, leg pain and Modic sign—a surgical multicentre comparative study. *Eur Spine J.* 2019;28:2981–89.
- [97] Nian S, Tang S, Shen S, et al. Landscape of the lumbar cartilaginous end plate microbiota and metabolites in patients with Modic changes. *J Bone Joint Surg Am.* 2024;106:1866–75.
- [98] Rajasekaran S, Vasudevan G, Tangavel C, et al. Does the gut microbiome influence disc health and disease? The interplay between dysbiosis, pathobionts, and disc inflammation: a pilot study. *Spine J.* 2024;24:1952–63.
- [99] Nash A, Noh SY, Birch HL, de Leeuw NH. Lysine-arginine advanced glycation end-product cross-links and the effect on collagen structure: a molecular dynamics study. *Proteins.* 2021;89:521–30.
- [100] Mengis T, Bernhard L, Nüesch A, et al. The expression of toll-like receptors in cartilage endplate cells: a role of toll-like receptor 2 in pro-inflammatory and pro-catabolic gene expression. *Cells.* 2024;13(7).