Modic changes: From potential molecular mechanisms to future research directions (Review)

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Abstract. Low back pain (LBP) is a leading cause of disability worldwide. Although not all patients with Modic changes (MCs) experience LBP, MC is often closely associated with LBP and disc degeneration. In clinical practice, the focus is usually on symptoms related to MC, which are hypothesized to be associated with LBP; however, the link between MC and nerve compression remains unclear. In cases of intervertebral disc herniation, nerve compression is often the definitive cause of symptoms. Recent advances have shed light on the pathophysiology of MC, partially elucidating its underlying mechanisms. The pathogenesis of MC involves complex bone marrow-disc interactions, resulting in bone marrow inflammation and edema. Over time, hematopoietic cells are gradually replaced by adipocytes, ultimately resulting in localized bone marrow sclerosis. This process creates a barrier between the intervertebral disc and the bone marrow, thereby enhancing the stability of the vertebral body. The latest understanding of the pathophysiology of MC suggests that chronic inflammation plays a significant role in its development and hypothesizes that the complement system may contribute to its pathological progression. However, this hypothesis requires further research to be confirmed. The present review we proposed a pathological model based on current research, encompassing the transition from Modic type 1 changes (MC1) to Modic type 2 changes (MC2). It discussed key cellular functions and their alterations in the pathogenesis of MC and outlined potential future research directions to further elucidate its mechanisms. Additionally, it reviewed the current clinical staging and pathogenesis of MC, recommended the development of an updated staging system and explored the prospects of integrating emerging artificial intelligence technologies.

Contents

1. Introduction
2. Occurrence and development of MCs
3. Involvement of the inflammatory system and the complement system
4. Clinical implications
5. Conclusion

1. Introduction

Low back pain (LBP) is one of the leading causes of disability worldwide and myelopathy associated with Modic changes (MCs) are considered highly specific for discogenic LBP. According to the signal intensity in magnetic resonance imaging (MRI), different types of MC can be classified (1). Modic type 1 changes (MC1) lesions are characterized by low signal intensity on T1-weighted MRI and high signal intensity on T2-weighted images. Conversely, Modic type 2 changes (MC2) lesions exhibit high signal intensity on T1-weighted images and low signal intensity on T2-weighted images. MC3) lesions demonstrate low signal intensity on both T1- and T2-weighted images. These signal intensities are thought to

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reflect underlying pathological processes: MC1 is typically associated with non-fatty inflammatory changes, MC2 with fatty degeneration and MC3 with sclerotic bone changes. Furthermore, these MC types are not static and may transition from one type to another over time, suggesting a dynamic interaction between the pathological progression of the vertebral endplate and bone marrow degeneration (1,2).

Currently, numerous clinical studies have been conducted to explore the pain association, prevalence and imaging manifestations of MCs (3-6). Meanwhile, significant progress has been made in understanding the pathological mechanisms of MC. Latest investigations propose that fibrosis is likely a key pathophysiological trait in MC1, while MC2 is thought to be linked to fibroinflammatory changes near the endplate, possibly involving the complement system (7,8). The present review aimed to synthesize the current understanding of the molecular and cellular properties inherent to MC, providing deeper insights into the disease mechanisms that drive these manifestations. Revealing these mechanisms will help elucidate the potential role of MC in LBP and deepen our understanding of MC pathophysiology.

2. Occurrence and development of MCs

The pathophysiology of MCs is multifactorial, including heavy physical load, autoimmune inflammation, endplate injury, *Cutibacterium acnes* infection, genetic susceptibility, diabetes and other metabolic conditions (9-13). MC is strongly associated with intervertebral disc degeneration (DD) and endplate rupture; however, the exact causal relationship between these phenomena remains uncertain, with some studies suggesting bidirectional effects (14). These factors contribute to morphological changes in the intervertebral disc and surrounding tissues. During embryonic development, nucleus pulposus (NP) cells become isolated from the circulatory system, leading to insufficient blood supply and an acidic environment that facilitates immune isolation and the accumulation of metabolic waste (15) (Fig. 1). When endplate damage occurs, NP immunogens may be exposed, resulting in the infiltration of M1 macrophages and triggering immune-mediated inflammatory responses (16). This destruction may also create pathways between the bone marrow and intervertebral discs, promoting osteoclast activity and impairing normal bone marrow function through inflammatory signals from the intervertebral discs (17-19). Additionally, microfractures of the endplate can lead to increased expression of type II collagen, catabolic enzymes and pro-inflammatory proteins, which in some cases may exacerbate DD (20,21).

However, not all cases of MC necessarily lead to DD. Some studies suggest that the degree of signal changes in vertebral endplates may be associated with an increased likelihood of DD, although the strength and potential mechanisms of this association are still under investigation (20,22). MC may exhibit high specificity (≥96%) in predicting DD, although its low sensitivity suggests that DD does not always result in MC (23).

Histological comparisons between MC1 and MC2 have uncovered distinct tissue features and recent investigations have broadened our understanding to include the molecular and cellular dynamics within the bone marrow microenvironment. This has led to a clearer picture of the pathophysiological variations between these two types. Modic *et al* (1) observed that bone marrow biopsies from both MC1 and MC2 lesions are predominantly composed of fibrovascular granulation tissue. They proposed the hypothesis that MC2 could be a progression stage from MC1, characterized by an increased presence of adipocytes and the conversion of red marrow to yellow (1). However, this progression is not consistently linear, necessitating further research to clarify the relationship. Perilli *et al* (4) noted significant bone loss and active remodeling in MC1, whereas MC2 exhibited a decrease in bone formation. Conversely, MC3 is linked to a seemingly stable phase of bone remodeling, characterized by an increase in bone volume fraction and trabecular thickness (4). The interaction between the bone marrow in MC and the adjacent intervertebral discs, especially the fibrotic and pro-inflammatory cross-talk, is hypothesized to be pivotal in the pathophysiology of MC (24).

Studies have shed new light on the bone marrow environment of MC1. Heggli *et al* (8) observed an upregulation of fibroblast colony-forming units in MC1, an increase in levels of leptin receptor (LEPR)-positive bone marrow stromal cells (BMSCs) and a decrease in lipogenic differentiation ability. These findings suggest that changes in the bone marrow microenvironment could contribute to the fibrotic and inflammatory processes observed in MC1. Similar to MC1, MC2 exhibits inflammatory infiltration in the bone marrow; however, unlike MC1, this infiltration occurs without the involvement of lymphocytes or neutrophils, indicating a distinct inflammatory pathway in MC2 (25). This difference raises questions about the exact immune mechanisms involved, with some studies suggesting that pro-inflammatory adipokines may play a more significant role (26-28). Further investigation is warranted to elucidate cellular factors driving this inflammatory response. Conversely, inflammation in MC2 may be driven by pro-inflammatory adipokines derived from adipocytes, which could activate the complement system as an upstream regulator of inflammation (7). Over time, neutrophil markers observed during the acute/subacute repair phase were significantly downregulated, while the macrophage marker CD14 was found to be elevated in the bone marrow near the endplate (7). Based on these observations and previous reports, the present review hypothesized that neutrophils may be activated, matured and dysregulated in MC1, eventually being cleared by macrophages in MC2 (29,30) (Fig. 2).

Microfractures in the endplate may create pathways between the intervertebral disc and bone marrow, potentially leading to localized inflammation due to the presence of necrotic cells, degraded extracellular matrix (ECM) components and bacterial products. Some studies suggest that this may activate the complement system, although the exact mechanism remains to be fully elucidated (31-33). This activation may, in turn, trigger the toll-like receptors (TLRs), although the direct involvement of damage-associated molecular patterns (DAMPs) from the ECM in MC still requires confirmation (34). Activation of the complement system promotes the release of pro-inflammatory cytokines and may also contribute to fibrosis and angiogenesis (7,35-37). Although bone marrow lesions typically subside following acute endplate injury, chronic stimulation can lead to persistent inflammation and fibrosis, as seen in MC1 (38,39). Heggli *et al* (7) found

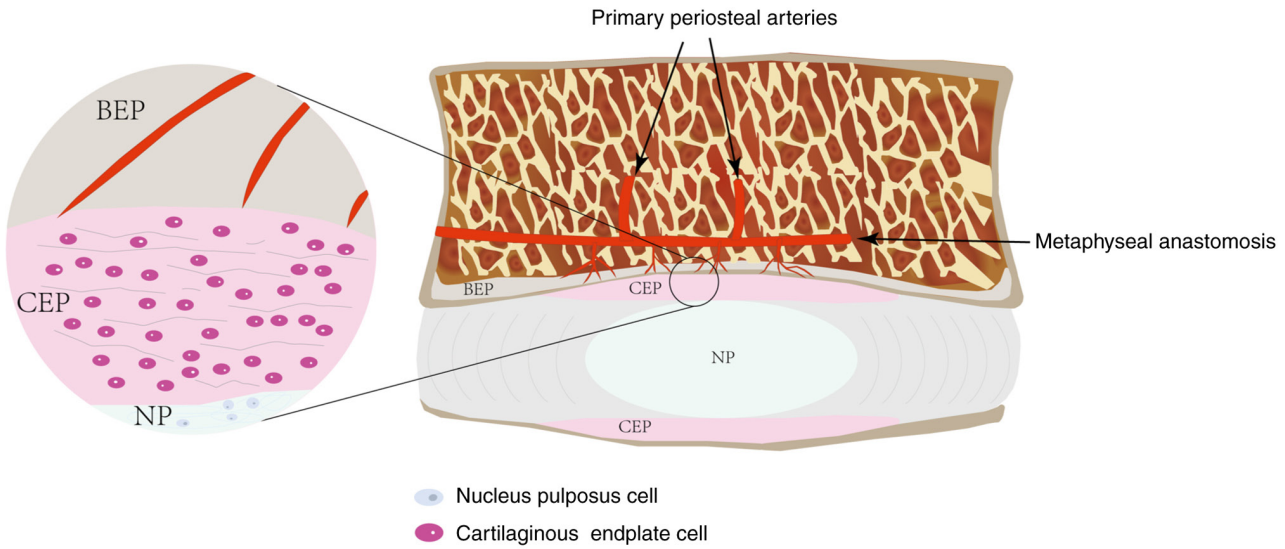


Figure 1. Healthy intervertebral discs and vertebrae in a 40-year-old female patient. The endplates remain intact, the disc height is within normal range and capillaries have not penetrated the cartilaginous endplates.

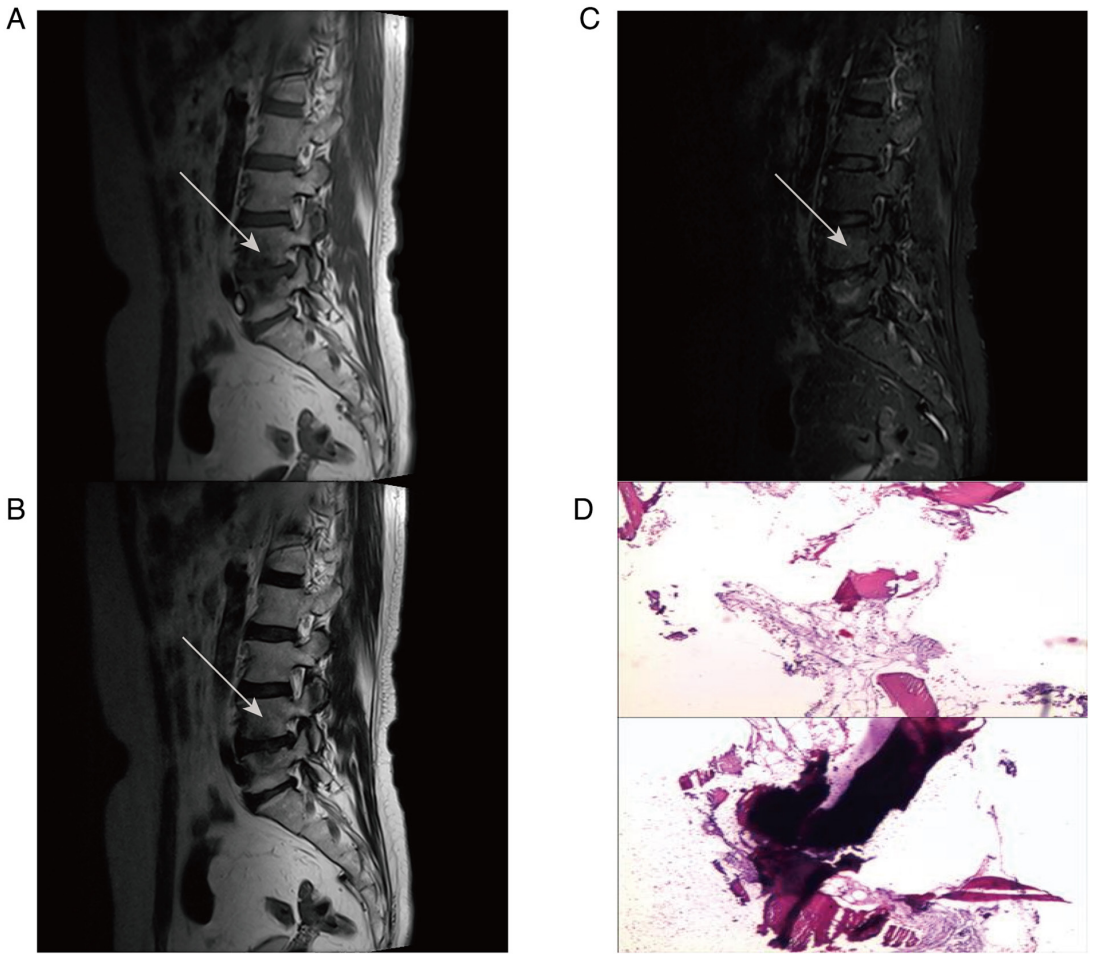


Figure 2. Typical imaging features of MC1 from a female patient who was 40 years old. (A) A T1-weighted image with localized low signal at the lower edge of L4. (B-C) T2-weighted and STIR sequences, respectively, highlighting localized high signal indicative of bone marrow edema. (D) A biopsy smear with fragmented bone tissue, minor adipose presence, and mild inflammatory infiltration. The biopsy site is marked by the white arrow. Magnification, x4xmagnification (above) and 10x magnification.

that within MC2, the boundaries of endplate damage appeared to be regressing, implying that chronic inflammation might cause these defects to propagate towards the periphery. The mechanical load on the edge of the endplate defect is higher

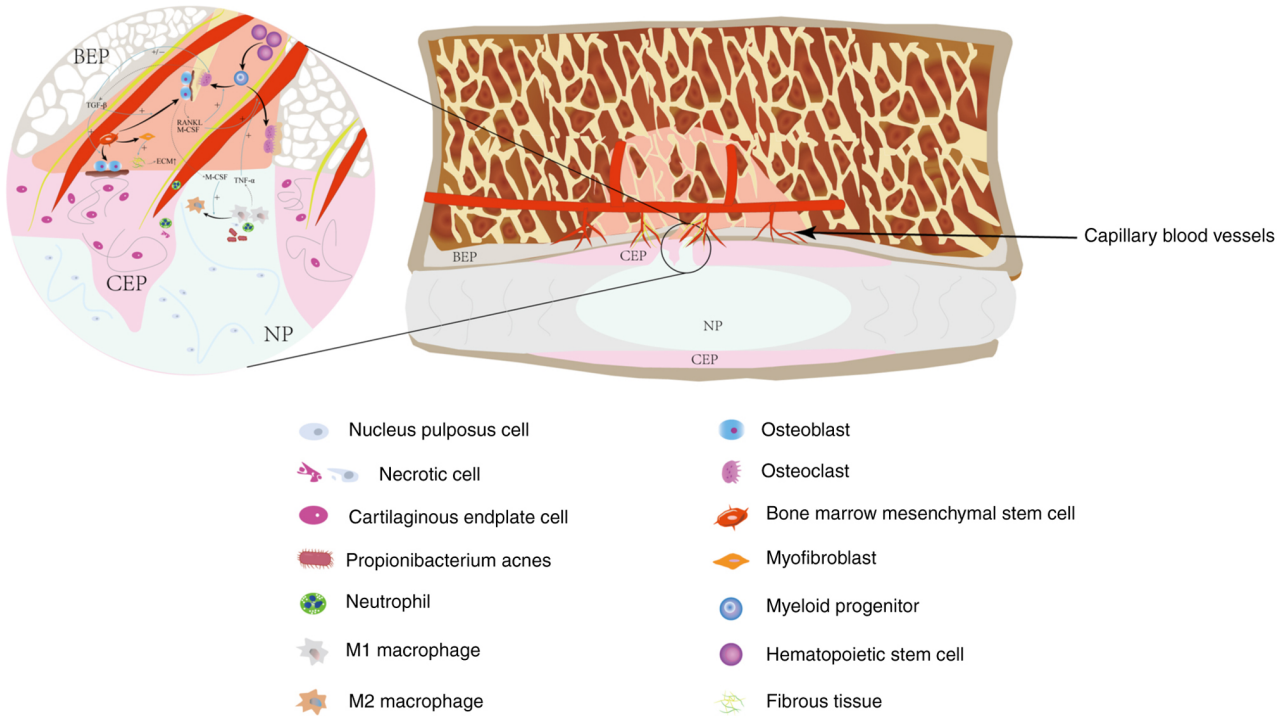


Figure 3. The observed pathological changes in MC1. Notable features include endplate damage, a reduction in disc height and potential neurovascular ingrowth into the injured area. Studies have suggested that BMSCs may differentiate into either osteoblasts or myofibroblasts; however, the distinct roles of these pathways in the high bone turnover and fibrotic characteristics of MC1 require further exploration. Inflammation is associated with the differentiation of hematopoietic stem cells into osteoclasts, which can result in the formation of porous bone endplates and thinning of bone trabeculae. Although *Cutibacterium acnes* infection or cellular death is hypothesized to attract neutrophils and macrophages, the precise mechanisms through which these immune cells impact the inflammatory progression in MC1 remain to be fully elucidated. MC1, Modic type 1 changes; BMSCs, bone marrow stromal cells; BEP, bone endplate; CEP, cartilage endplate; NP, Nucleus pulposus.

and the involvement of the complement system might drive this process (7,14). Therefore, it was hypothesized that unresolved biomechanical factors leading to MC could result in expanding endplate damage, leading to a coexistence of acute inflammatory injury and chronic repair in the affected region. This suggests that as endplate damage worsens, complex dual repair reactions will occur (Figs. 3 and 4).

In MC1, BMSCs located in the perivascular region exhibit a significant increase in C-X-C motif chemokine 12 (CXCL12) and LEPR levels, promoting the formation of a hematopoietic niche and enhancing osteoblast differentiation (8,40). However, it must be noted that concurrent osteoclast activity may inhibit the healing response in MC1 (33). Although LEPR+ CXCL12+ BMSCs have the potential to differentiate into adipocytes, osteoblasts and chondrocytes, their lipogenic differentiation may be impaired in the pro-inflammatory environment of MC (24,41). This impairment could trigger excessive fibrosis, as previous studies have shown that BMSCs in MC1 exhibit a pro-fibrotic phenotype (8). Decker *et al* (40) proposed a thought-provoking hypothesis that CXCL12+ LEPR+ cells may transdifferentiate into myofibroblasts, contributing to the occurrence of myelofibrosis.

In the later stage of MC development, there is a clear shift in the bone marrow composition towards increased adipogenesis. Elderly men, especially those with diabetes and lower lumbar involvement, often exhibit higher adipose tissue content in their spinal marrow (13,26). Long-term chronic inflammation, coupled with the action of oxidized low-density lipoprotein, can promote an increase in adipocyte hypertrophy and activate peroxisome proliferator-activated receptor gamma (PPAR-γ), which may indirectly inhibit bone marrow hematopoiesis (27,28,32,42,43). This phenomenon could explain the observed decrease in neutrophil counts during the MC2 stage. Although the effect of adipocytes on bone marrow hematopoietic function may be multifaceted, their positive role in supporting the survival of hematopoietic stem cells cannot be denied (44,45). However, during the MC3 stage, due to irreversible osteogenesis and a decrease in adipocyte numbers, the overall regenerative potential significantly diminishes (39,46).

In summary, the transition from MC1 to MC2/MC3 may represent a continuous process from an acute inflammatory response to more chronic reparative mechanisms, characterized by varying inflammatory signatures and dynamic tissue remodeling. Future studies aim at elucidating the molecular signals driving this transformation could uncover novel therapeutic avenues, particularly in modulating the inflammatory pathways and cellular processes associated with these changes.

3. Involvement of the inflammatory system and the complement system

Neutrophils. Neutrophils, also known as polymorphonuclear leukocytes, are the initial responders to acute inflammation and are rapidly recruited to the site of tissue injury due to their critical role in the innate immune response (47). These cells originate from myeloid precursors in the bone marrow, whose

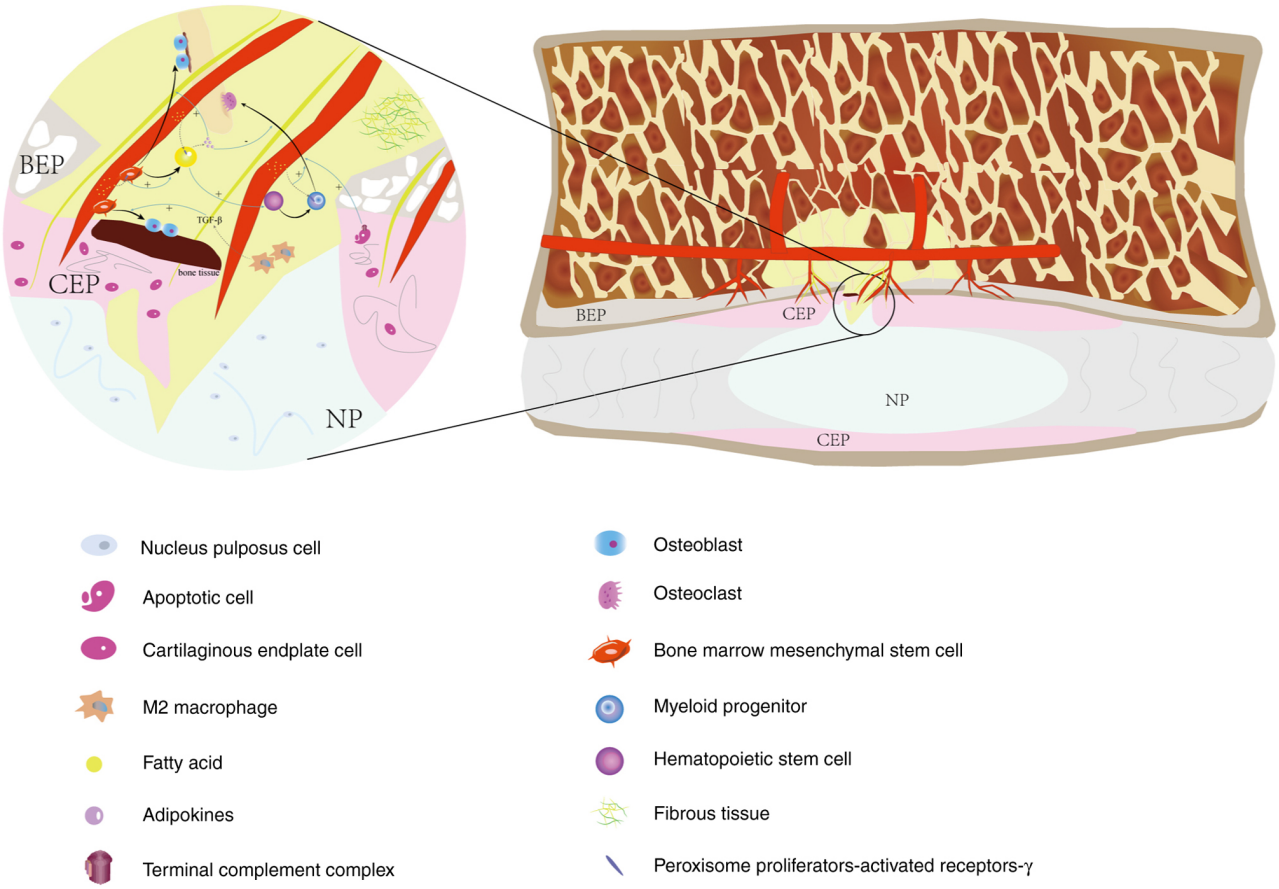


Figure 4. The pathological changes characteristic of MC2. There is noticeable degeneration of the endplate injury margins and a continued reduction in disc height. Compared with MC1, the inflammation within the bone marrow appears to diminish, resulting in an increase in localized fatty regions. It is hypothesized that BMSCs may differentiate into adipocytes in MC2; however, the precise mechanisms and implications of this differentiation remain unclear. The observed shift from inflammatory tissue to fatty and fibrotic tissue is highlighted, although the exact role of the complement system in this transition is still under investigation. MC1, Modic type 2 changes; BMSCs, bone marrow stromal cells; BEP, Bone endplate; CEP, Cartilage endplate; NP, Nucleus pulposus.

production is regulated by granulocyte colony-stimulating factor (48). A recent study highlighted that the presence of *Cutibacterium acnes* in MC1 significantly influences the bone marrow microenvironment (49). In the presence of high concentrations of *Cutibacterium acnes*, macrophages in the bone marrow are exposed to pathogen-associated molecular patterns following severe endplate damage, promoting the release of macrophage colony-stimulating factor (M-CSF) and recruiting monocytes and macrophages (50). Meanwhile, TLR activation plays a crucial role in the recruitment of neutrophils to the site of injury (50).

Neutrophils are crucial in early immune responses, as they phagocytose bacteria, clear dead cells and eliminate microbial debris (51). In the context of MC, there is evidence suggesting that neutrophils promote inflammation by forming neutrophil extracellular traps, which may further activate the complement system and exacerbate inflammatory responses (52,53). Neutrophils also release matrix metalloproteinase-9 (MMP-9), involved in the degradation of the ECM in NP cells, which may exacerbate tissue damage and promote additional complement activation (31). MMP-9 also plays a crucial role in vascular regeneration, as it activates vascular endothelial growth factor (VEGF) and promotes vascular growth at the site of injury (54). Notably, in MC1 patients with high levels of *Cutibacterium acnes* GCNs, neutrophil degranulation was identified as a key enrichment process, supporting a sustained antimicrobial response characterized by the upregulation of cytokines such as IL-8 and ENA-78, which attract and activate neutrophils (49).

By contrast, in individuals with lower concentrations of *Cutibacterium acnes*, different immune responses may predominate. The increased expression of IL-13 and the activation of T and B cells suggest that an autoimmune mechanism may also be involved in MC1 (24). Following severe endplate damage, neutrophils accumulate and mature and may eventually be cleared by macrophages, which helps to eliminate inflammation (49,55). These findings suggest that the concentration of *Cutibacterium acnes* may significantly affect the behavior of neutrophils, ultimately impacting the inflammation and healing processes in MC.

Macrophages. Macrophages originate from the mononuclear phagocyte system and serve a critical role in maintaining tissue homeostasis in conjunction with parenchymal cells (56). These cells can be roughly divided into two phenotypes: M1 and M2 macrophages, each with distinct immune functions. M1 macrophages are characterized by their pro-inflammatory effects, secreting cytokines such as IL-1, IL-6 and tumor necrosis factor-α, actively participating in immune surveillance and antigen presentation. By contrast, M2 macrophages

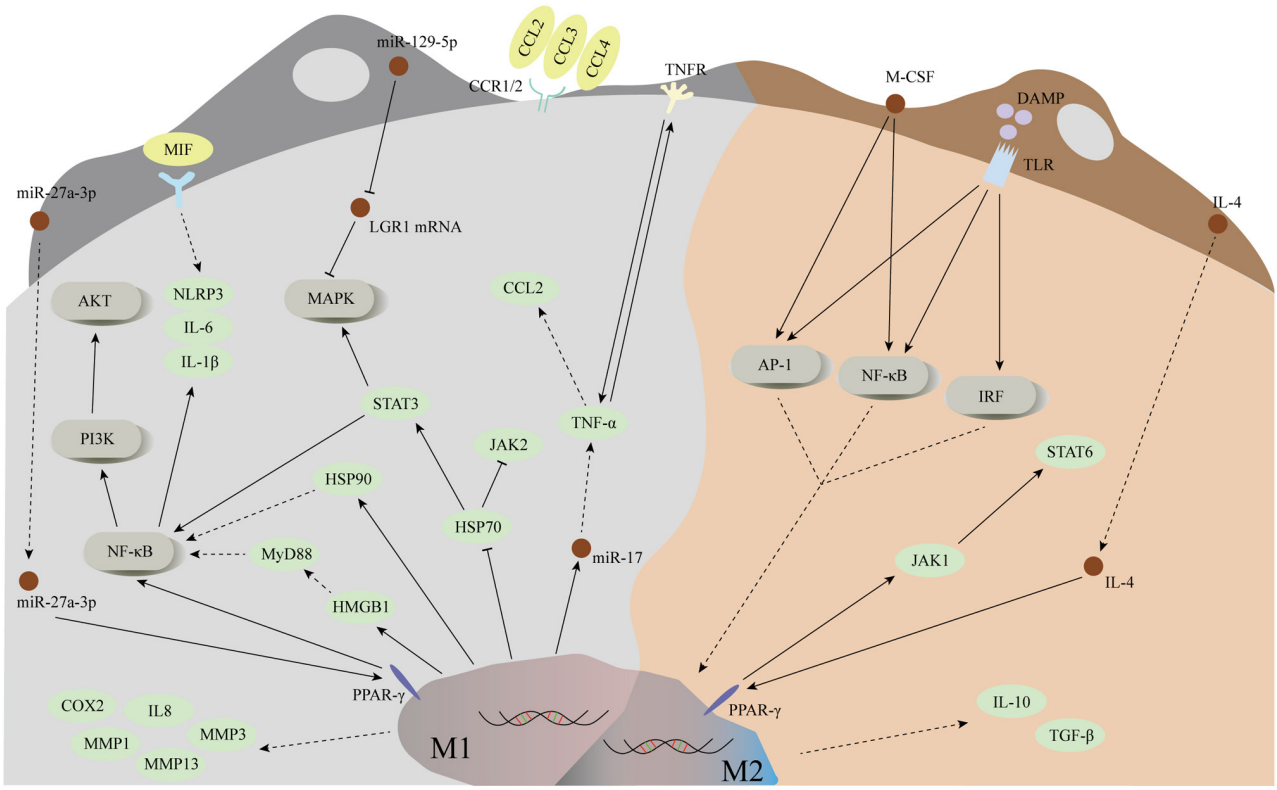


Figure 5. The intricate interplay of various proteins and signaling pathways involved in MC. The green ovals represent proteins secreted by macrophages, highlighting their role in the inflammatory response associated with MC. The yellow ovals denote proteins produced by BMSCs or NP cells, underscoring their contributions to the cellular microenvironment in MC. Brown circles represent RNA molecules that may be involved in gene expression regulation and cellular signaling. Gray rectangular boxes depict key signaling pathways implicated in pathophysiology of MC, including but not limited to the RANK/RANKL/OPG pathway and Wnt/β-catenin signaling. Although the roles of these proteins and pathways are supported by existing research, the precise interactions and mechanisms still require further investigation. MC, Modic change; BMSCs, bone marrow stromal cells; NP, nucleus pulposus; RANKL, Receptor activator for nuclear factor-κB ligand; OPG, osteoprotegerin.

exhibit anti-inflammatory and immunosuppressive effects, releasing cytokines such as IL-10 and transforming growth factor-β (TGF-β), facilitating tissue repair and inflammation resolution (57). In the context of disc pathology, particularly for NP cells that typically exist in an immune-privileged environment, macrophage infiltration following EP injury may disrupt this immune isolation. Once the immune barrier is compromised, macrophages are hypothesized to cause ECM degradation, potentially exacerbating inflammatory pain (58).

Although direct experimental evidence confirming the role of macrophages in NP pathology is currently lacking, several studies have proposed their involvement based on general immunological mechanisms (8,39). Studies have demonstrated that when immune protection is compromised, macrophages may recognize NP cells and these damages may worsen following EP damage (24,59). Following EP injury, NP cells are exposed and it is hypothesized that macrophages are recruited to the injury site in response to chemotactic signals. Degenerated discs may further exacerbate inflammation by releasing additional pro-inflammatory factors, potentially promoting capillary infiltration and further recruitment of macrophages (58). As the condition progresses, M1 macrophages, which dominate the initial inflammatory responses, are likely to be gradually replaced by M2 macrophages.

The interaction between M1 and M2 macrophages is hypothesized to have a profound effect on BMSCs and their osteogenic differentiation process (60,61). Specifically, M1 macrophages are thought to promote early osteogenic differentiation, although they may not be as effective in supporting complete mineralization of the bone matrix (62,63). In practical observations, it was found that osteoblasts secreted M-CSF and RANKL, which played key roles in promoting osteoclast differentiation (64) (Fig. 5). Additionally, M-CSF can promote the transformation of M1 macrophages to M2 macrophages by upregulating the expression of c-Jun N-terminal kinase and nuclear factor kappa-B (NF-κB) (65,66).

Conversely, M2 macrophages are hypothesized to contribute to bone matrix mineralization and BMSC osteogenic differentiation, thus aiding in tissue repair (63). The increase in the ratio of osteoclasts to osteoblasts is thought to exacerbate the porous structure in the EP, promote sensory nerve innervation and potentially increase pain (64,67,68). Overall, the coordinated regulation of M1 and M2 macrophages is hypothesized to significantly affect neural sensitivity and facilitate the repair of the EP at the site of injury. Future research should focus on validating these mechanisms and their clinical relevance (16).

M1 macrophages. M1 macrophages secrete TNF-α, a potent pro-inflammatory cytokine, which plays a critical role in regulating inflammation, lipid metabolism and apoptosis (69,70). *In vitro* study has revealed that TNF-α may act as an inducer of DD, mimicking its pathological mechanism (71).

When immune barrier function of NP is impaired, extensive infiltration of macrophages follows (24). TNF-α secreted by M1 macrophages is hypothesized to activate NP cells, promoting their expression of various chemokines such as chemoattractant cytokine ligand (CCL2) and CCL3 (72). Studies have shown that CCL2 is primarily responsible for macrophage recruitment, while the CCL3-chemokine receptor 1 (CCR1) signaling axis plays a crucial role in macrophage infiltration (72,73). *In vitro* experiments have shown that inhibiting CCR1 can effectively reduce the expression of chronic inflammation in intervertebral discs and limit macrophage migration (74). Additionally, TNF-α enhances the expression of CCL4 by activating the p38-MAPK and NF-κB signaling pathways in NP cells, thereby further promoting macrophage infiltration (75). It is known that TNF-α and IL-1β can upregulate MMPs in M1 macrophages, which contribute to ECM degradation (76). Moreover, these cytokines are also hypothesized to stimulate the production of nerve growth factors, which may lead to nerve infiltration and trigger LBP (77). It is worth noting that TNF-α has also been found to induce the aging of NP cells, which may be related to the decrease in intervertebral height and play a certain role in the pathological development of MC.

IL-1β is considered a key inflammatory mediator involved in numerous inflammatory processes. *In vitro* co-culture studies with bone marrow and bone marrow monocytes in MC models report significant upregulation of IL-1β, which promoted additional pro-inflammatory cytokines, thereby amplifying the inflammatory response (78) IL-1β is associated with increased disc inflammation by upregulating inflammatory mediators such as IL-6, IL-8 and prostaglandin E2 (PGE2), which may also lead to mitochondrial dysfunction and accumulation of reactive oxygen species (79,80). IL-1β also triggers apoptosis of NP cells through the NF-κB and MAPK pathways, further exacerbating DD (81,82). Inhibiting the expression of high mobility group box-1 protein and blocking the activation of the MyD88/NF-κB pathway, as well as the NLRP3 inflammasomes in NP cells, reduces the secretion of inflammatory factors, prevents M1 macrophage polarization and alleviates NP cell damage (83). A study conducted by Zhang *et al* (84) demonstrated that the heat shock protein 90 inhibitor, 17-AAG, attenuated the pro-inflammatory activity of M1 macrophages by targeting the NF-κB and MAPK pathways. Additionally, 17-AAG inhibited M1-induced NP cell inflammation and catabolism in NP cells by enhancing the expression of the HSP70, JAK2 and STAT3 pathways. Furthermore, 17-AAG diminished the fibrotic phenotypes induced by macrophages in NP cells by suppressing the expression of migration-inducing proteins and reducing pathological angiogenesis (85).

IL-1α is released by monocyte macrophages and is activated following apoptosis of necrotic cells, making it another key inflammatory mediator (86). Research has shown that co-culturing bone marrow mononuclear cells with NP cells results in increased secretion of IL-10, which is modulated by IL-1α (78). Necrotic apoptosis regulates the maturation and release of IL-1α through the activation of calpain (86). It is hypothesized that IL-1α may accelerate DD by inhibiting ECM synthesis and promoting ECM degradation. Additionally, IL-1α may induce LBP by stimulating NP cells to release PGE2 and other inflammatory mediators, which may activate nerve roots infiltrating the cartilaginous endplate (87).

Furthermore, the upstream regulatory mechanisms of inflammatory cytokines have been extensively investigated. For instance, transfection of M1 macrophages with miR-17 significantly increases the release of TNF-α, indicating a correlation between miR-17 and increased TNF-α secretion (88). Moreover, it has been reported that extracellular vesicles from BMSCs can deliver miR-129-5p to NP cells, thereby downregulating the p38-MAPK signaling pathway. miR-129-5p can also bind to the 3'-untranslated region of leucine-rich glycoprotein-1 (LRG1), inhibiting its expression, which may inhibit M1 macrophage polarization and foster M2 macrophage polarization along with the release of anti-inflammatory factors (89) (Fig. 5). Furthermore, exosomes from myeloid cells containing miR-27a-3p have been shown to target the PPARγ/NFκB/PI3K/AKT signaling pathway, thereby promoting the polarization of M1 macrophages (90).

M2 macrophages. M2 macrophage polarization is regulated by cytokines and microbial byproducts in tissues (91). With prolonged immune exposure to microfractures of the endplate, the expression of IL-1β is hypothesized to decrease, while the concentration of IL-4 may gradually increase. This increase is thought to promote the polarization of M1 to M2 macrophages at the site of injury (91,92). During the process of clearing apoptotic neutrophils, monocyte-derived macrophages have been reported to secrete IL-10, utilizing the STAT signaling pathway (93). In a model of inflammatory bowel disease, IL-10 was shown to inhibit mTORC1 activation through the STAT3 pathway, thereby potentially modulating macrophage metabolic activity and promoting an anti-inflammatory phenotype (94). Additionally, activation of the PPAR-γ receptor has been proposed to promote M2 polarization through its interaction with the JAK1-STAT6 pathway (95,96). Despite the partial understanding of the precise anti-inflammatory mechanisms of IL-10, M2 macrophages are hypothesized to be crucial in tissue repair by releasing TGF-β, particularly in granulation tissue rich in M2 macrophages (97). The downregulation of miR-133a is associated with the loss of type II collagen targeting MMP9 during DD, supporting the pathological role of MMP9 (98). Additionally, MMP9 is hypothesized to activate latent TGF-β by inducing fibroblast contraction, providing insights into the potential role of TGF-β in disc degeneration-related fibrosis (99). TGF-β is a key regulatory factor in fibrosis, promoting the differentiation of BMSCs into myofibroblasts, a hallmark of MC (100). Although data on TGF-β activation factors are still limited, MMP9-mediated TGF-β stimulation, as demonstrated in lung fibroblasts, suggests its possible involvement in MC fibrosis, indicating that MMP9 can trigger fibrosis activation (8,99). TGF-β acts through the Smad signaling pathway, promoting the differentiation of BMSCs into osteoblasts and regulating the fibrotic microenvironment (101). However, in the context of MC, this mechanism of promoting fibrosis is still speculative and requires further investigation (102,103).

BMSC. Myelofibrosis is a potential adverse effect within the pathophysiological spectrum of MC1 (37). Decker *et al* (40) confirmed that CXCL12+ LEPR+ BMSCs are the predominant source of myofibroblasts in primary myelofibrosis.

Additionally, in comparison with MC2, CD90+ BMSCs are observed more frequently in the fibrotic microenvironment of MC1 (25). In MC1, the three critical signaling pathways of Notch, Wnt/β-catenin and Hedgehog are prominently enriched in perivascular BMSCs, thereby playing a pivotal role in driving the pro-fibrotic phenotype (8). The Hedgehog and Wnt/β-catenin signaling pathways facilitate osteoblast differentiation while inhibiting adipocyte differentiation (104,105). However, the Notch pathway exhibits a dual role: It is essential for osteogenesis but can also inhibit osteogenesis under specific conditions. For example, studies indicate that the introduction of Notch ligands or overexpression of the Notch target gene hairy and enhancer of split 1 in MSCs can suppress the expression of PPARγ and C/EBPα, thereby inhibiting lipogenesis and promoting osteogenesis; conversely, Notch can also inhibit osteogenesis by suppressing the Wnt/β-catenin pathway (106). Consequently, the inhibition of lipid differentiation observed in MC1 may result from the interaction of these signaling pathways. Nonetheless, the precise mechanism driving the differentiation of LEPR-high BMSCs into myofibroblasts remains elusive and may be initiated by the 'thwarted healing response' hypothesis proposed by Dudli *et al* (37).

While direct research on adipocyte-predisposed differentiation of BMSCs in MC2 pathology is lacking, Dudli *et al* (37) used osteoarthritis as a model to speculate on the possible mechanisms involved in MC2. They hypothesized that TLRs played a pivotal role in both osteoarthritis and MC pathophysiology (37). In osteoarthritis, TLRs act as receptors for DAMPs generated by ECM degradation. The ECM degradation associated with MC-induced DD may chronically activate TLRs, prompting BMSCs to differentiate into adipocytes (107). As mentioned previously, these adipocytes could release fatty acids, which might accelerate the progression of MC through the PPARγ pathway.

Complement system. New evidence suggests that the complement system may play a critical role in the pathology of MC, although specific studies are still scarce. Heggli *et al* found that during the progression of MC, the levels of complement proteins C5, C8 alpha chain and factor B were elevated in the bone marrow (107), indicating activation of both classical and alternative complement pathways (7,39).

It is hypothesized that mechanisms such as cell death, matrix degradation and bacterial infection may trigger complement activation in MC (107). Similar to osteoarthritis, necrotic cells in MC may release DAMPs, which may activate the classical complement pathway, based on reasonable inference of similar conditions (34,39,108). As shown in the study by Dudli *et al* (20), the presence of necrotic cells in MC is supported by elevated levels of lactate dehydrogenase. Additionally, degradation of the disc matrix may release DAMPs, which may interact with the bone marrow through ruptured endplates and further activate the complement system (24). As proposed by Albert *et al* (109), the presence of *Cutibacterium acnes* in intervertebral discs exacerbated these ruptures and increased the likelihood of complement activation.

In osteoarthritis, the terminal complement complex (TCC) is crucial in mediating cell death and inducing phenotypic changes in chondrocytes following cartilage injury (110). Riegger *et al* (110) hypothesized that TCC could also influence the cell death and healing dynamics of MC, potentially creating a feedback loop that intensifies the condition. Furthermore, complement fragments C3a and C5a, integral components of TCC, exhibit notable pro-inflammatory effects, enhancing the inflammatory response of osteoblasts and promoting osteoclast formation, which may in turn affect the MCs (36,37).

The complement system is associated with chronic inflammation involving MC. Specifically, C3a and C5a fragments can stimulate the production of IL-1β, a critical pro-inflammatory cytokine and VEGF, which is pivotal in supporting neovascularization (35,36). While the formation of VEGF driven by the complement system has been established in osteoarthritis, it is reasonable to hypothesize that a similar mechanism operates in MC (35). Furthermore, as highlighted by Llorian-Salvador *et al* (34), complement activation is correlated with elevated levels of TGF-β, a key factor in fibrotic transformation.

The complement-mediated process may also be involved in neurogenesis, which may explain the observed inward growth of nerve fibers into ruptured endplates in MCs, a concept explored by Fatoba *et al* (111). In conclusion, although the role of the complement system in MC remains largely speculative and current research is devoid of direct evidence, it is widely hypothesized that complement activation could trigger inflammation, angiogenesis, fibrosis and neurogenesis, which may collectively drive the pathological progression of MC. Further investigation is warranted to clarify these mechanisms and their clinical implications.

4. Clinical implications

The current classification systems for MC, namely MC1, MC2 and MC3, are generally deemed inadequate to fully encompass the complexity of the pathological processes involved. This classification scheme relies on key features such as endplate morphology, bone marrow edema and the proportion of edematous-fatty tissue. However, this simplification limits its ability to effectively guide clinical decision-making (1). The MC classification is grounded in key characteristics such as endplate morphology, extent of bone marrow edema and the ratio of edematous-fatty tissue (Table I). Nevertheless, categorizing MC into three types fails to capture the full complexity of the condition, nor does it adequately assist in guiding clinical decision-making for conditions such as discogenic LBP.

Studies have demonstrated an association between MC and discogenic LBP, which directly influences patients' quality of life (2,112). There remain challenges in distinguishing MC from other spinal ailments, such as infections and tumors, on MRI scans, particularly in instances of mixed MC, a common clinical scenario. The persistent moderate inter-observer variability further complicates this diagnostic challenge, highlighting the ongoing uncertainty in MC diagnosis (113). Moreover, the moderate differences among observers underscore a significant degree of uncertainty in MC diagnosis (3).

The advancement of deep learning (DL) technology has significantly enhanced medical imaging, enabling the

Table I. MC Classification.

First author/s, year	Sample size	Results	(Refs.)
Xu *et al*, 2016	276	MC can be further subdivided into 10 distinct types: type I, type II, type III, type I-II, type II-I, type I-III, type III-I, type II-III, type III-II and type I-II-III. Endplate edema is responsible for most mixed types, especially types I-II and II-I. It is important to note that endplate sclerosis observed on CT images may not exclusively indicate Modic type III but is actually present across all types of MC.	(113)
Feng *et al*, 2018	133	Three types of endplate defects, focal, angular and erosive, were categorized. These three types of endplate defects observed on conventional MR images likely represent different underlying pathologies and may significantly contribute to the pathogenesis of MC.	(126)
Udby *et al*, 2022	-	According to the area of MC in the sagittal section, the categories are defined as follows: Type A corresponds to an MC area smaller than 25% of the vertebral height, Type B encompasses an MC area between 25 and 50% of the vertebral height and Type C refers to an MC area exceeding 50% of the vertebral height.	(127)
Rajasekaran *et al*, 2024	1,530	The DEBC was established by incorporating STIR images and examining the entire interdependent complex, categorizing conditions into: Type A: acute inflammation; Type B: chronic persistence; Type C: latent; Type D: inactive. Type B exhibits the highest incidence. Notably, the highest ratio of cases requiring surgery was observed when both disc herniation and DEBC type changes were present concurrently.	(116)

MC, Modic change; CT, computed tomography; DEBC, disc-endplate-bone-marrow classification; STIR, short τ inversion recovery.

automatic extraction and classification of features from large datasets. These advances have improved the diagnostic consistency of radiologists in identifying MCs on MRI (114,115). This innovation is expected to increase the diagnostic accuracy of spinal disorders.

While DL models substantially enhance MC detection, they often neglect pathological processes occurring in adjacent discs and tissues. To address this gap, Rajasekaran *et al* (116) integrated disc herniation and short tau inversion recovery (STIR) sequence data into MC classification, thereby improving the predictive capability for surgical intervention and postoperative complications. This study did not comprehensively address the broader pathological changes associated with MC. To enhance the understanding and management of LBP, a more holistic approach is required, encompassing not only MC and DD but also high-intensity zones, endplate defects and vertebral bone marrow steatosis. Collecting detailed clinical data, exploiting MRI sequences such as T1, T2 and STIR, as well as employing advanced AI and scoring systems, such as the Japanese Orthopaedic Association score, can contribute to the development of predictive models. These models will enhance the precision of MC staging and prognostic assessments, optimize clinical decision-making and improve patient outcomes.

Furthermore, MC are frequently identified as a factor associated with LBP and have been established as an independent risk factor for severe and disabling episodes of LBP (117,118). One study reported that the prevalence of any form of MC was 43% in patients with nonspecific LBP and/or sciatica, compared with just 6% in the general population (119). The current treatment options primarily include conservative management, discectomy, lumbar fusion and intraosseous basivertebral nerve radiofrequency neurotomy.

However, different treatment modalities for various types of MC may lead to distinct outcomes. For instance, following discectomy, the difference in improvement of LBP or Oswestry disability index (ODI), or visual analogue scale (VAS) between patients with or without preoperative MC did not exceed the minimal clinically important difference (117). By contrast, a 2022 meta-analysis concluded that the presence of preoperative MC did not significantly influence clinical outcomes following lumbar discectomy (120). However, this meta-analysis did not compare improvements across different Modic types at specific follow-up time points. A 2023 meta-analysis further addressed this issue, revealing that patients with MC1 reported more LBP than those with other Modic types. Most of these patients also reported greater leg pain than back pain. Additionally, in patients with lumbar disc herniation and preoperative MC1, functional improvements at the 2-year follow-up were statistically lower compared with patients without MC1 or with MC2 (121). As to intraosseous basivertebral nerve radiofrequency neurotomy, a relatively recent treatment, a 2022 meta-analysis reported success rates of 65 and 64% for pain relief at 6 and 12 months, respectively. The improvement rates in ODI scores of ≥15 points at 6 and 12 months were 75 and 75%, respectively. This indicates moderate-quality evidence supporting the efficacy of intraosseous basivertebral nerve radiofrequency neurotomy in alleviating pain and disability in most patients with vertebrogenic LBP (122).

As previously discussed, bone marrow inflammation, the immune response around the endplate and the higher density of sensory nerve fibers in MC1 compared with other Modic types all contribute to a relatively poorer long-term prognosis when the surgical intervention does not involve the vertebral body and endplate (4,24,123). Given the substantial overlap in pain referral patterns from other spinal structures, including the intervertebral disc, sacroiliac joints and facet joints, this may also explain why the pain relief outcomes with intraosseous basivertebral nerve radiofrequency neurotomy are not as favorable as expected (124,125).

5. Conclusion

The multifaceted pathology of MC involves intricate interactions between immune responses, chronic inflammation and structural damage to the vertebral endplates. Key factors such as endplate microfractures and *Cutibacterium acnes* infection are still being elucidated, with the complement system being pivotal in sustaining inflammation and fibrosis. Therapeutic targets such as the RANK/RANKL/OPG axis and the Wnt/β-catenin pathway hold promise for restoring endplate integrity and halting the progression of MC.

The integration of AI into imaging techniques has notably enhanced the diagnostic precision of MC, particularly in identifying mixed types and assessing their effects on adjacent tissues. Future research should focus on elucidating the molecular mechanisms driving the advancement of MC, aiming to formulate more effective and tailored therapies for discogenic LBP.

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Authors' contributions

All authors participated in the study design and manuscript writing. WJZ and SRZ were responsible for literature collection, analysis and interpretation, contributing significantly to the writing of the present review. JMZ and ZHX drafted the main manuscript text and prepared the figures. ZY, WX and PL critically reviewed the article for important intellectual content. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study received approval from the Ethics Committee of Tongji Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology (approval no. TJ-IRB202402127).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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