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Pathobiology of Modic changes

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Abstract

Purpose—Low back pain (LBP) is the most disabling condition worldwide. Although LBP relates to different spinal pathologies, vertebral bone marrow lesions visualized as Modic changes on MRI have a high specificity for discogenic LBP. This review summarizes the pathobiology of Modic changes and suggests a disease model.

Methods—Non-systematic literature review.

Results—Chemical and mechanical stimulation of nociceptors adjacent to damaged endplates are likely a source of pain. Modic changes are adjacent to a degenerated intervertebral disc and have three generally interconvertible types suggesting that the different Modic change types represent different stages of the same pathological process, which is characterized by inflammation, high bone turnover, and fibrosis. A disease model is suggested where disc/ endplate damage and the persistence of an inflammatory stimulus (i.e., occult discitis or autoimmune response against disc material) create predisposing conditions. The risk to develop Modic changes likely depends on the inflammatory potential of the disc and the capacity of the bone marrow to respond to it. Bone marrow lesions in osteoarthritic knee joints share many characteristics with Modic changes adjacent to degenerated discs and suggest that damage-associated molecular patterns and marrow fat metabolism are important pathogenetic factors. There is no consensus on the ideal therapy. Non-surgical treatment approaches including intradiscal steroid injections, anti-TNF-α antibody, antibiotics, and bisphosphonates have some demonstrated efficacy in mostly non-replicated clinical studies in reducing Modic changes in the short term, but with unknown long-term benefits. New diagnostic tools and animal models are required to improve painful Modic change identification and classification, and to clarify the pathogenesis.

Conclusion—Modic changes are likely to be more than just a coincidental imaging finding in LBP patients and rather represent an underlying pathology that should be a target for therapy.

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Compliance with ethical standards

Conflict of interest None of the authors has any potential conflict of interest

Keywords

Low back pain; Modic changes; Bone marrow lesion; Endplate damage; Pathobiology

Introduction

Low back pain (LBP) is the world's most disabling condition with detrimental consequences due to increased use of health-care services and work disability [1]. Although LBP relates to different spinal pathologies, vertebral bone marrow lesions (BML) visualized as Modic changes (MC) on magnetic resonance imaging (MRI) have a high specificity for discogenic LBP [2]. Numerous clinical studies have investigated the prevalence, natural history, risk factors, and pain association of MC. However, comparably few studies have investigated the pathobiology of MC. Recent data indicate infectious and autoimmune etiologies, both of which presuppose structural damage of the disc. Additional insight comes from the study of BML in the femur/tibia of an osteoarthritic knee joint, which shares many characteristics with MC. This article reviews the current understanding of the pathobiology of MC and suggests a hypothetical disease mechanism. Uncovering this mechanism will be central for solidifying the role of MC in LBP.

Clinical presentation of Modic changes

BML are pathological changes of the BM composition. A subgroup of vertebral BML evident with MRI have been termed MC [3]. Modic changes are MRI signal intensity changes in the vertebral bone marrow (BM) that reflect lesions which are not related to marrow malignancy, pyogenesis, or seropositive rheumatic disorders [3, 4]. Three types of MC have been described based on their appearance in T1-weighted (T1w) and T2-weighted (T2w) images (Fig. 1). Modic changes type 1 (MC1) are hypointense on T1w and hyperintense on T2w. Modic changes type 2 (MC2) are hyperintense on T1w and hyper- or isointense on T2w. Modic changes type 3 (MC3) are hypointense on T1w and T2w [3]. However, the identification and classification can depend on the MRI field strength [105].

Prevalence, natural history, and risk factors for MC have been extensively studied and are reviewed elsewhere [5–10]. Overall, MC prevalence is high in LBP patients (43 % median prevalence in a meta-study) compared to only 6 % median prevalence of the asymptomatic population [5]. Of the different MC types, MC1 has been more associated with LBP than the others [2, 11]. Modic changes are more prevalent and more severe at the lower lumbar levels (L4–S1) [3, 12], are more prevalent in the anterior third of the vertebra [13, 14], are generally symmetric cephalad and caudad to a particular disc [15], and are commonly associated with disc degeneration (DD) [16], DD severity [17], and disc herniations [18].

Elucidation of MC etiology is hindered by the dynamic clinical presentation and multifactorial pathophysiology. MC1 and MC2 are interconvertible over time and can eventually convert to MC3 [9, 10, 17]. About 20 % of the lesions are mixed-type MC1/2 or MC2/3 [9, 36]. Risk factors for MC can be classified into disc/endplate damage (DD, disc herniation, endplate defects), systemic factors (smoking, ageing, male gender, genetics), and hyperloading (obesity, spinal deformities, high occupational load) [7, 14–24] (Fig. 2). The

unidentified and multifactorial nature of MC is especially true for MC1; conversely, MC2 mainly associates with hyperloading and systemic factors [7, 20, 22, 25].

Growing evidences suggest that LBP patients with MC have a clinically different presentation than LBP patients without MC [16]: LBP patients with MC report a greater frequency and duration of LBP episodes and seek care more often [5]. This suggests different pain generators and potentially different responses to treatments [26–28]. For example, recent studies show that the presence of MC1 with chronic LBP is associated with a poor outcome to conservative treatment [6, 29]. MC1 patients also had worse outcomes after discectomy [30], which underscores the role of the vertebra as a possible pain generator. While the reason for vertebrogenic pain in MC is unknown [5], increased numbers of PGP-9.5 nerve fibers and TNF-α positive cells in MC1 and MC2 endplates may be important [31, 32] MC symptoms may also relate to psychosocial and genetic factors [33]. However, due to the absence of a treatment consensus for LBP patients with MC, insufficient clinical evidence currently exists supporting the effect of MC on the clinical outcome in patients with discogenic LBP [6].

Despite an abundance of imaging data from MC studies, few reports detail the histology and pathoanatomy of MC. Fibrosis, inflammation, and high bone turnover were described in three MC1 and MC2 specimens [3]. In MC1, fibrous tissue replaces normal BM between thickened trabeculae, endplates appear disrupted, and bone–disc junction is filled with vascularized granulation tissue, a sign of inflammation. In MC2, fatty marrow replaces the normal BM. Similar to MC1, in MC2 the endplate is disrupted with the presence of fibrovascular granulation tissue at the disc/ endplate junction. This is in agreement with our recent findings in cadaveric tissue with MC (Fig. 3). The importance of endplate damage in the etiology of MC is underscored by studies of surgical waste tissue from MC1 and MC2 patients that show cartilaginous endplate fragments with extruded disc material [34]. Dynamic interdependencies between bone and marrow compartments in MC are demonstrated by histomorphometric analysis of biopsies that reveal a high bone turnover in MC1, reduced bone formation in MC2, and a stable sclerotic state in MC3 [35]. Sclerosis was also reported in mixed-type MC1/2 and MC2/3 [36]. In summary, the few histological studies show inflammation, high bone turnover, and fibrosis in MC (Fig. 4).

Etiopathogenesis of Modic changes

Despite the clinical evidence that MC are painful, the etiology and pathobiology of MC are unknown. Although MC strongly associate with DD, it remains unclear why some patients with DD develop MC and others do not. It is likely that the propensity to develop MC relates to the composition and function of the BM and its communication with the disc through the endplates. The fact that all MC are interconvertible and that mixed-type MC1/2 and MC2/3 exist suggests that different MC types represent different stages of the same pathological process [2]. However, one pathogenesis does not inevitably exclude multiple etiological factors. Different conditions may predispose to new MC1 or MC2 or to convert existing MC to another type. These conditions are discussed below.

Etiological factors

In contrast to age-related “red” to “yellow” marrow conversion, which starts in the diaphyseal region and extends toward proximal and distal metaphysis [37], MC typically starts adjacent to a degenerated discs at the endplates [3, 4, 16, 19]. The bigger the MC, the more likely is the disc degenerated [17]. These observations provide compelling evidence of a connection between DD and MC and suggest that MC is unrelated to age-related marrow conversion. Despite the high specificity of MC for DD, the low sensitivity indicates that DD alone is not sufficient to trigger MC in most cases [16].

The presence of endplate defects may explain the difference between specificity and sensitivity. Endplate defects co-locate with MC and are predictive for future MC [3, 38]. Yet, because endplate damage promotes DD [38–41], evidences linking endplate damage to MC independently of DD are unavailable. Similar to endplate damage, disc herniation predisposes to DD and MC [18, 19]. Given the specificity of MC for disc damages (endplate damage and disc herniation), disc damage should be considered as a predisposing factor to MC rather than an incidental finding (Fig. 5).

Endplate damage causes a cascade of degenerative changes in both the vertebra and the disc. Endplate damage increases intraosseous pressure [42] and causes stress concentrations within the disc, both of which could deteriorate cell metabolism and promote degenerative changes [39, 43–45]. Endplate damage also affects metabolite transport between the BM and the disc [46, 47]. Endplate damage as a result of acute or chronic overloading leads to a hydraulic disc/vertebra coupling, increased convective flow [46–48], and efflux of inflammatory mediators and extracellular matrix (ECM) catabolites from the disc into the BM. For example, acute vertebral burst fracture and focal endplate collapse can cause MC1-like BML in the adjacent BM [49, 50]. Yet, most BML related to acute endplate injury stabilize over time, and the pain is short lived [50]. Hence, in traumatic cases it appears that the BML stimulus can resolve. However, when endplate damage is more severe, LBP is more likely to be chronic [51], indicating a persistent stimulus and a prolonged inflammatory process [41, 51]. This is consistent with the general healing paradigm, where a failure to remove the inflammatory stimulus causes a chronic inflammation with fibrosis and granulation tissue. Coexistence of persistent inflammatory stimuli with ineffective healing leads to damage accumulation and a “frustrated healing response” characterized by chronic inflammation, fibrosis, and high bone turnover (Fig. 4). Two etiologies are suggested for MC1, which explain the nature of the persistent stimuli: (1) occult discitis; and (2) autoimmune reaction of BM to disc cells/ECM [52, 53]. Both etiologies presuppose structural disc damage, either herniation or endplate damage.

Biologic plausibility for an infectious etiology stems from the disc’s anaerobic environment, the high potential for disc tissue damage, and the low capacity for repair. Peripheral disc damage could allow access by low virulent skin microorganisms such as anaerobic *Propionibacterium acnes* (*P. acnes*) [54]. These bacteria can invade the circulatory system due to innocuous events such as tooth brushing [55]. Immune surveillance and the aerobic environment in the blood and BM hinder a systemic infection and diagnosis [56]. However, the absence of immune surveillance and low oxygen tension in the disc provides an ideal environment for bacterial growth. The slowly developing occult discitis gives rise to

increasing amount of bacterial metabolites (propionic acid, lipase) and cytokines as a response of disc cells to the infection [54]. Disc cells secrete IL-6, IL-8, and PGE-2 after stimulation by bacterial endotoxins [57]. The persistent efflux of cytokines and bacterial metabolites from the disc could cause inflammation of the adjacent BM [56]. Elevated high-sensitivity C-reactive protein serum values in MC1 patients corroborate the presence of inflammation [58]. Furthermore, patients with infected herniated discs developed significantly more MC1 at the herniation level than non-infected herniations (80 vs. 44 %) [59]. However, a best-evidence synthesis from 11 studies investigating the relationship between bacteria and LBP or MC concluded that only moderate evidence exists to support a relationship between the presence of bacteria and both LBP with disc herniation and Modic Type 1 change with disc herniation [101].

The etiology of MC may also include autoimmunity. After embryologic formation of the disc, the nucleus pulposus (NP) no longer makes any contact with the systemic circulation, and consequently it is sequestered from leukocytes. NP cells maintain the immune privilege by expressing Fas ligand, which induces apoptosis in infiltrating lymphocytes [60]. Endplate damage co-locates NP with BM leukocytes. Increased levels of Fas receptor have been found in MC endplates, indicating an adaptive response to higher levels of Fas ligand, possibly from co-located NP [61]. Peripheral disc damage can expose the NP to the immune system, where it is recognized as “foreign” and triggers an autoimmune response [62–65]. Indeed, autografting the NP into immune-active tissue in animal models causes an abundant expression of cytokines [62, 64] and infiltration of macrophages, activated B- and T-cells [62, 66]. This is in agreement with findings in herniated and degenerated discs [63, 67]. In addition, NP cells elicit a primary immune response in macrophages and natural killer cells [68, 69]. Disc ECM is also linked to immunity, as disc proteoglycans can enhance lymphocyte transformation in vitro [65] and mice immunized with cartilage proteoglycans show strong mononuclear cell infiltration into the disc and almost completely resorbed discs [70]. It is not surprising therefore that this form of autoimmunity is presumed to prolong clinical symptoms in LBP patients [65].

Pathobiological factors

Disc/endplate damage, occult discitis, and autoimmunity are plausible explanations for MC etiology, but they do not account for why some patients with disc/endplate damage develop MC while some do not. This discrepancy may ultimately relate to the inflammatory potential of the disc and the capacity of the BM to respond to the inflammatory stimulus.

Discs adjacent to MC produce higher amounts of cytokines (IL-6, IL-8, TNF-α) and osteoclastic factors (RANKL, M-CSF, NFATc1, RUNX1, OSCAR) than discs of the same degeneration degree without adjacent MC (Fig. 6) [71, 72]. These cytokines interfere with the cellular composition of the adjacent BM (Fig. 7) and alter trabecular bone mass. For example, MC biopsies reveal high bone turnover in MC1, possibly due to an inflammatory process and reduced bone formation in MC2 [35]. On the other hand, trabecular thickening in histological sections of MC1 [3] (Fig. 3) and sclerosis in MC3 and mixed-type MC1/2 and MC2/3 were reported [3, 36]. Therefore, bone formation/resorption is a transient or individual phenomenon depending on the osteocyte/osteoclast ratio.

Toll-like receptor (TLR) stimulation of disc and marrow cells likely plays an important role in MC. Degenerated discs express more TLR1/2/4/6 than non-degenerated discs, possibly due to higher TNF-α/IL-1β levels [73, 74], and TNF-α/IL-1β enhances TLR2-mediated IL-6 and IL-8 secretion by disc cells, the same cytokines that are increased in discs adjacent to MC. TLR activation enhances transcription of NF-κB-responsive genes, a central signaling pathway in DD and OA [75]. TLR signaling is also linked to T cell activation and autoimmunity [76]. TLR are receptors for bacterial cell wall proteins and damage-associated molecular pattern (DAMPs). DAMPs are a heterogeneous group of molecules and are considered as “danger molecules”, because they are released from necrotic cells or generated after mechanical or enzymatic tissue damage (Fig. 6). ECM fragments (fibronectin, short hyaluronic acid fragments) are DAMPs that play a crucial role in OA [75].

The response of the BM to cytokines and DAMPs leaking from the disc through endplate defects into the BM depends on the composition of the BM itself. It is known that vertebral marrow adipose tissue (MAT) content is higher in males, at lower lumbar levels, and in older individuals [77]. These same three factors associate with the prevalence of MC [14]. MAT has high amounts of saturated fatty acids, minimally modified and oxidized low-density lipoproteins, which activate TLR2/4 [75, 77]. Therefore, ECM fragments draining from a degenerated disc into a fatty BM increase the total concentration of TLR ligands and NF-κB-controlled cytokines. This process may be triggered off MC in patients treated with chemonucleolysis, a non-surgical technique for treating a bulging disc by injecting an enzyme to digest the disc ECM. The enzymatic process leads inevitably to the generation of abundant ECM catabolites and DAMPs, which may be the cause for the development of MC in these patients. Chronic stimulation of TLRs was demonstrated to cause neo-adipogenesis [78] and induce adipocyte hypertrophy [79], thereby facilitating fatty marrow conversion as in MC2.

The interrelationship between fat metabolism and marrow composition and its relationship to MC is unknown, but some insights may be gained from the studies of BML in osteoarthritis (OA). Modic changes adjacent to a degenerated disc share many characteristics with BML in the femur/tibia of an osteoarthritic knee joint (Table 1). High serum lipids, obesity, age, and male gender increase the risk of developing BML in the knee [80]. OA patients also show an increased prevalence for DD [81], pointing to shared pathological variables at a systemic level. Therefore, knowledge from OA/BML research at peripheral skeletal sites may also help clarify the etiopathogenesis of MC.

The adverse biological effects of fat on OA and DD are manifold. Long chain fatty acids increase MAT by binding to PPARγ [82] (Fig. 7), which in turn reduces bone density and increases fracture risk [83]. Higher serum lipid concentration also enhances lipid peroxidation, a process resulting in increased advanced-glycation end products (AGE) [84]. AGEs are formed through non-enzymatic reactions between glucose and proteins. AGEs cross-link ECM molecules and decrease the hydrophilic charge of proteoglycans [85], changes that directly and indirectly increase tissue stiffness. Besides the physical consequences of AGE accumulation, there are biological consequences as well. AGEs and one of their receptors (RAGE) elevate the level of reactive oxygen species, induce inflammatory changes that promote ECM catabolism, and also promote DD in diabetes

mellitus [86, 87]. In OA, the adverse effects of AGE are amplified by the overexpression of RAGE [88]. RAGE cross talks with TLR [89], which is important since RAGE is also a receptor for DAMPs [73, 89].

In addition to the osteoclastic factors released by discs adjacent to MC, high MAT further stimulates osteoclastogenesis by the activation of PPARγ with fatty acids [90]. The adipogenic and anti-hematopoietic effect of PPARγ also leads to the depletion of BM cellularity [82, 91]. However, since adipocytes maintain the most primitive hematopoietic stem cell, recovery of a normal BM cellularity is possible [17, 91]. Indeed, resolution of MC2 occurs [17]. However, if in addition to the hematopoietic depletion also the adipocytic compartment is ablated and irreversible osteogenesis occurs [91], a situation resembling MC3 [17].

Hyperloading-related risk factors indicate that mechanical aspects also intervene with MC pathobiology (Fig. 2). The interrelationship of mechanical and biological factors is implicated by Wolff's law, which posits that loading alters bone metabolism [92]. The intricate co-regulation of osteogenesis, adipogenesis, and hematopoiesis [82, 93] further suggests that chronic hyperloading also affects adipogenesis and hematopoiesis. Therefore, obesity may be a risk factor not only because of increased spinal forces, but also because of its influence on osteogenesis, adipogenesis, and hematopoiesis. For example, greater abdominal fat correlates with higher MAT [77], which associates with bone weakness (fragility fracture, Schmorl's nodes, wedging) [83, 94] possibly due to lower trabecular bone mineral density [77].

Taken together, evidence suggests that structural damage triggers a pro-inflammatory reaction in the disc, which in turn could allow microbial infiltration and/or autoimmune reactions that intensify and prolong nociceptor stimulation by chemical or mechanical stimuli. The increased inflammatory potential of the disc activates pro-inflammatory signaling cascades in the BM and favors adipogenesis and osteoclast activation. The propensity to develop MC1 or MC2 may depend on the intensity and persistency of the inflammatory stimuli as well as on the composition and metabolic state of the BM.

Experimental models

The gaps in knowledge about MC pathophysiology, such as the molecular and cellular changes in MC and their relation to disc health and metabolism, combined with the practical and ethical limitations of clinical studies, motivate the development of experimental models. Only few animal models succeeded in generating marrow changes, always in conjunction with inducing DD in the adjacent disc [99–101]. Chronic axial compression of mouse tail segments induced DD and BML consistent with increased marrow vascularity and cellularity [99]. Enzymatic and surgical disc decompression caused trabecular microfracture and subsequent healing with endochondral ossification and mesenchymal replacement of BM [101]. Triple stab injury of rat tail discs induced trabecular thickening and fibrovascular replacement of the adjacent BM [100]. All three studies indicate that disc injury may play an important role in promoting MC. However, disc injury inevitably alters load distribution of the vertebrae and increases cytokine expression. Clarifying the relative importance of these

factors in MC etiology will represent an important step toward developing effective therapeutic interventions.

Conclusion and future direction

Current knowledge about MC is derived almost exclusively from cross-sectional or longitudinal clinical studies. Data indicate infectious and autoimmune etiologies, both of which presuppose structural damage of the disc/endplate anatomy. These different etiologies may also work in conjunction and eventually proceed along common pathological pathways. Further, different types of MC may represent different stages of the same pathological process. The pathway is not necessarily a sequential progression through the different types of MC, but conversion from MC1 or MC2 to any other MC is possible. Ultimately, the propensity to develop MC seems to depend on three factors: structural disruption of the disc/endplate, inflammatory potential of the disc, and the capacity of the BM to respond to higher inflammatory stimuli. In vitro and animal experiments are required addressing the role of these factors in the pathogenesis of MC. Furthermore, basic research will have to increase the body of evidence for the autoimmune and the infectious etiology.

The treatment of MC is limited by several factors. First, MC are often under-appreciated as a source of pain. Second, it is unknown why MC hurt. Third, no treatment consensus is established because, fourth, the etiology and the underlying pathogenesis is unknown. Clinical trials for novel non-surgical treatments of MC focused on suppressing inflammation/infection with anti-TNF-α antibody, antibiotics, or intradiscal steroid injections [27, 28, 95, 96]. Attempts have also been made to attenuate bone resorption and osteoclast recruitment with bisphosphonates [97], because it is known that OA patients taking the bisphosphonate alendronate have less frequent BML [98]. While these studies showed some beneficial effects at the 1-year follow-up, larger studies with long-term follow-up are needed.

Diagnostic tools are needed to define MC phenotypes and their variants and identify painful MC. Traditional T1w and T2w MRI may not be sensitive enough to pick up early signs of MC or the clinically most relevant phenotypes. In this regard, imaging of endplate degeneration [102] may become an essential decision-making tool in LBP patients. Furthermore, diagnostic strategies based on serum/urine biomarkers or BM biopsies may help distinguish infectious from autoimmune etiologies. Biomarkers and new imaging sequences may also be employed to distinguish symptomatic from non-symptomatic MC (Fig. 5). Finally, animal models that recapitulate the key features of MC are needed to test therapy mechanisms and screen for new treatments. Summarizing, we recommend testing the following hypotheses to develop an effective treatment for MC.

- The formation of Modic changes requires at least a disc/endplate damage plus a persistent stimulus.
- Disc/endplate damage causes detrimental biological and biomechanical changes in the disc and the bone marrow.
- Occult discitis and innate-type immune response to disc material are persistent stimuli.

- The composition of the bone marrow affects the severity of the response to the persistent stimulus and ultimately decides on the formation of MC.
- Treatments that do not target the etiological factors (endplate damage, persistent stimulus, bone marrow composition) are not effective in the long term.
- Modic changes and bone marrow lesions in osteoarthritic joints share similar basic pathogenetic mechanisms.

Ultimately, MC are likely more than just a coincidental imaging finding in LBP patients, but rather represent an underlying pathology that should be a target for therapy.

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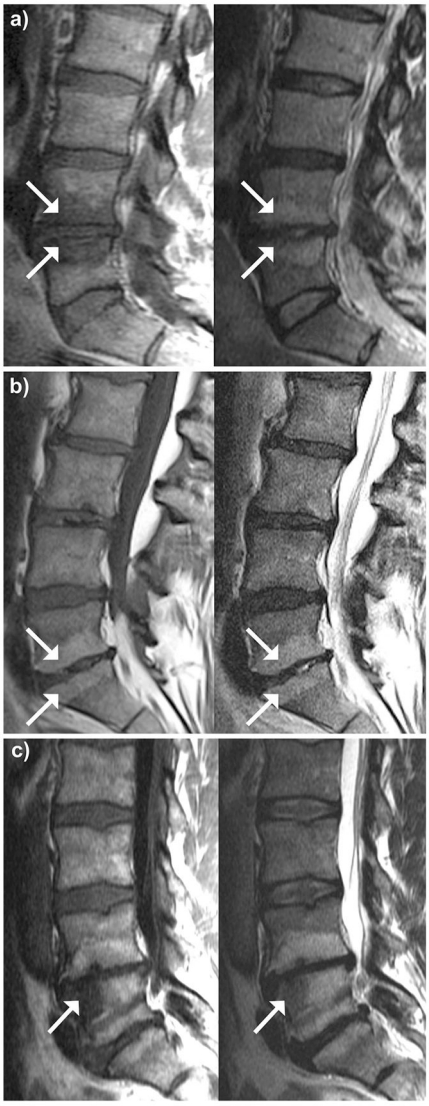

Fig. 1.

Mid-sagittal T1-weighted (*left*) and T2-weighted images (*right*) of lumbar spines showing the three types of Modic changes (*arrows*). **a** Modic change type 1 at inferior L4 and superior L5. **b** Modic change type 2 at inferior L5 and superior S1. **c** Mixed Modic change type 2/3 at superior-anterior L5 with *arrowhead* pointing at Modic change type 3. Modic changes type 2 are also present at inferior L4, inferior L5, and superior S1. Pure Modic changes type 3 are rare. No such MRI scans were available to us

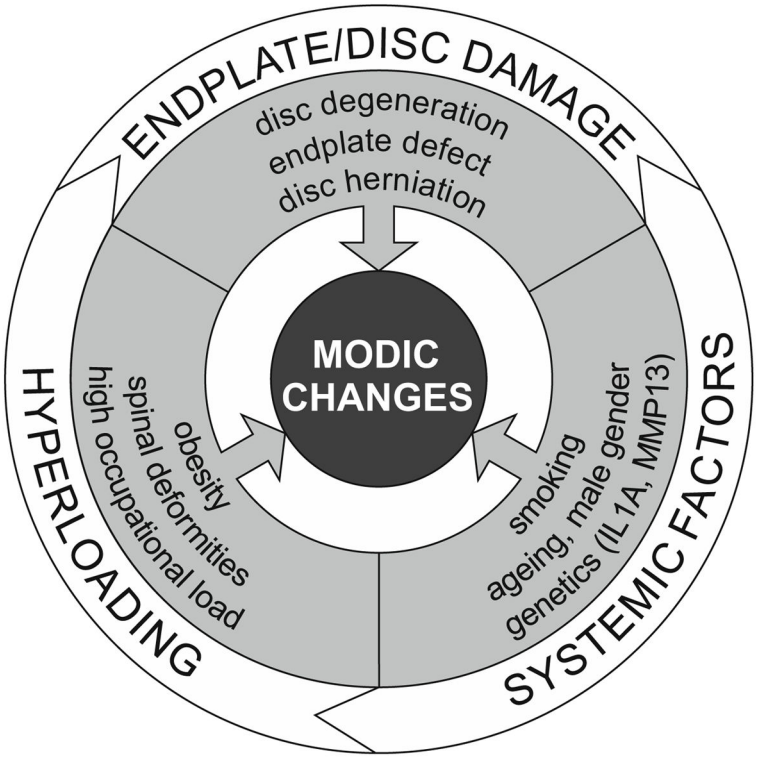

Fig. 2.

Risk factors for Modic changes. Systemic factors may also affect hyperloading and disc/endplate damage pathologies. Hyper-loading may also affect disc/endplate damage

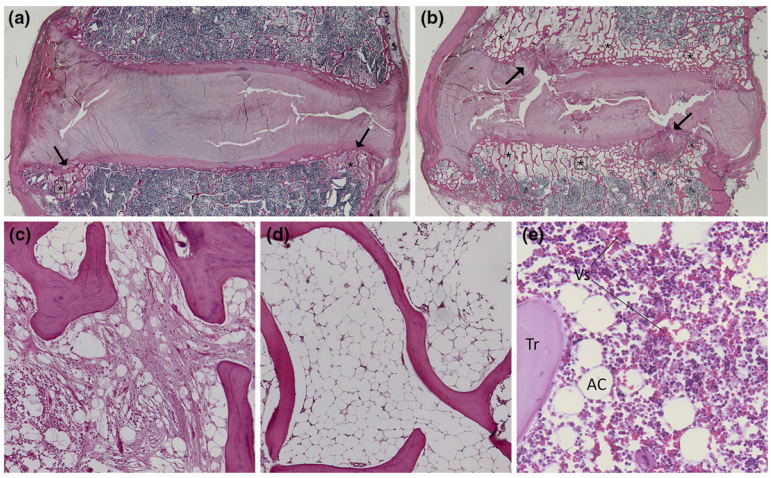

Fig. 3.

Mid-sagittal histological sections of spinal segments with bone marrow lesions characterized as Modic changes on MRI. Sections are stained with hematoxylin and eosin. Original magnifi-cations are ×0.5 (**a**, **b**), and ×10 (**c**–**e**). **c** and **d** are magnifications from the areas indicated on **a** and **b**, respectively. **a**, **c** Modic change type 1 characterized by fibrovascular tissue (*asterisks*) and trabecular thickening. The changes parallel endplate irregularities (*arrow*). **b**, **d** Modic change type 2. Fatty marrow replacement (*asterisks*) occurs along the entire endplates cephalad and caudad to the disc. Fibrotic tissue can be found at locations of endplate damage (*arrows*). **e** Healthy vertebral bone marrow with (Tr) trabecular bone, (AC) adipocytes, and (VS) vascular sinus

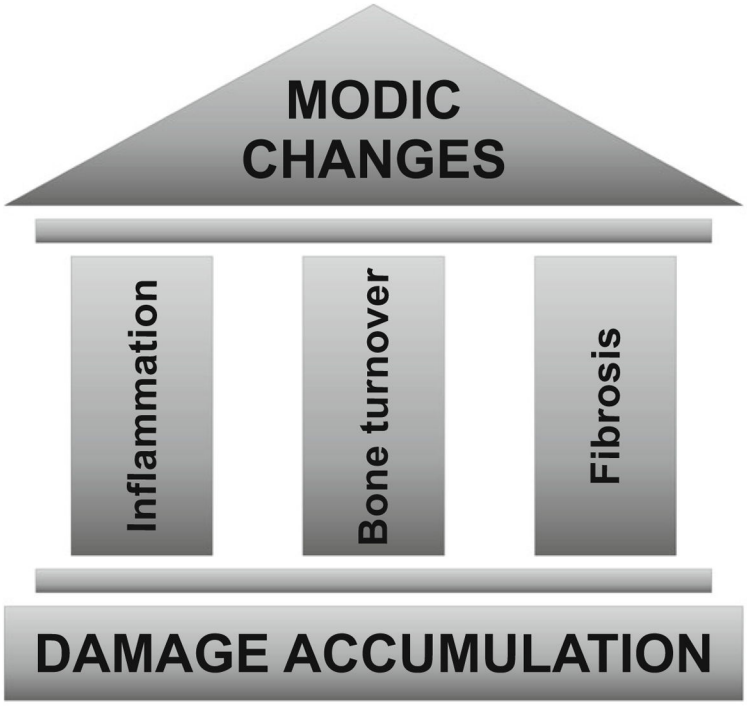

Fig. 4.
The three pathobiological pillars of Modic changes

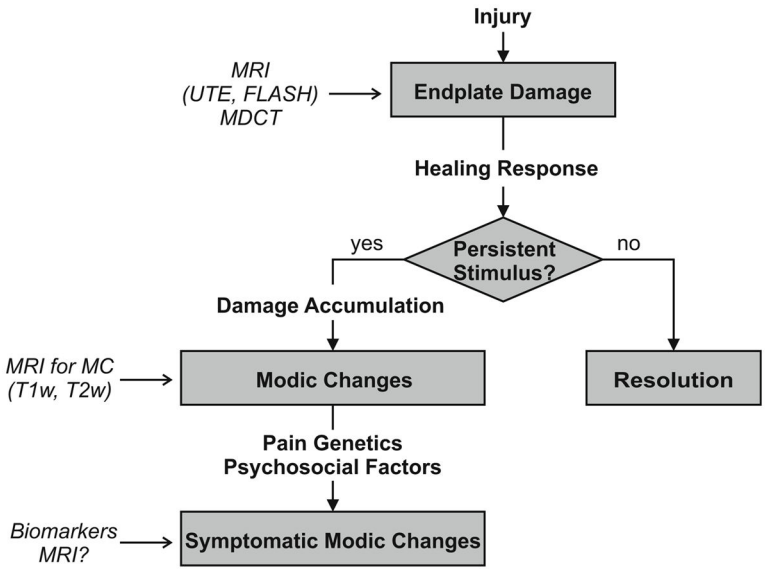

Fig. 5.

Hypothetical model for the pathogenesis of Modic changes. An endplate damage is a predisposing condition for Modic changes. Endplate damage can be diagnosed with UTE and FLASH MRI sequences as well as with multidetector computed tomography (MDCT). Endplate damage triggers a healing response. The Modic etiology requires a persistent stimulus, which impedes resolution of the damage. The concomitant existence of a healing response and a persistent stimulus leads to accumulation of damage and to a ‘frustrated healing response’ characterized by chronic inflammation, high bone turnover, and fibrosis, the three pathobiological pillars of Modic changes, which can be visualized with T1-and T2-weighted MRI sequences. The severity and persistency of the stimulus as well as individual factors (pain genetics, psychosocial factors) may decide if the Modic changes become painful. Novel diagnostic tools (biomarkers, MRI) are required to distinguish painful from non-painful Modic changes

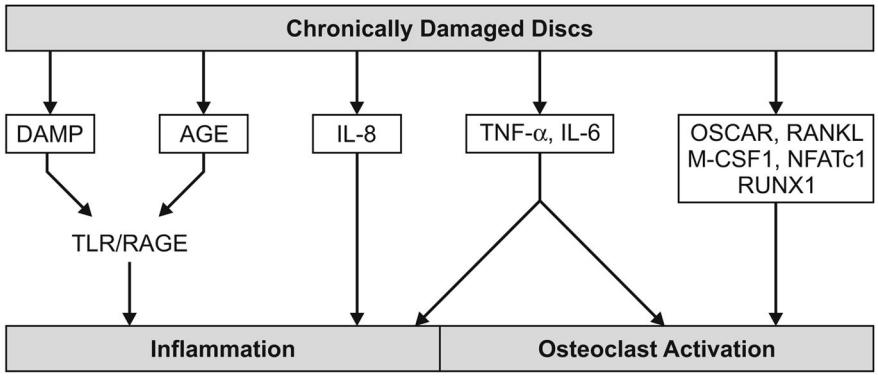

Fig. 6.

Factors released by a chronically damaged disc can cause inflammation and osteoclast activation in the adjacent bone marrow. Endplate damage leads to a hydraulic disc/vertebra coupling and increased efflux of these factors into the adjacent bone marrow where they can cause Modic changes

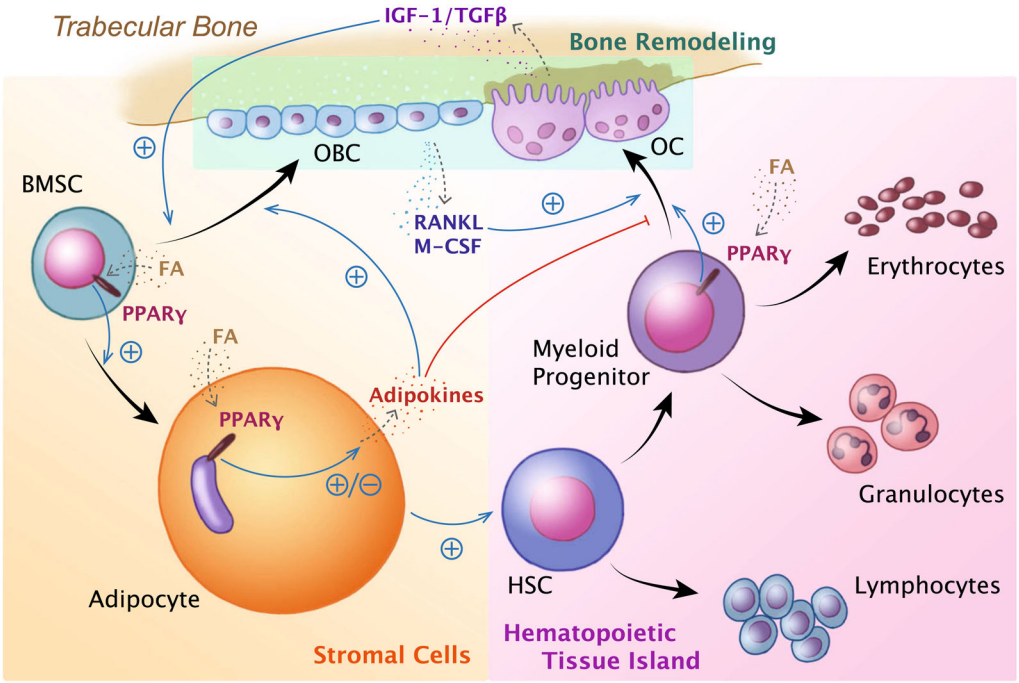

Fig. 7.

Interdependency of stromal and hematopoietic bone marrow cell differentiation and their effects on bone remodeling. Bone marrow-derived mesenchymal stem cells (BMSC) differentiate mainly into adipocytes or osteoblast cells (OBC) in a reciprocal manner. Hematopoietic stem cells (HSC) differentiate into osteoclasts (OC) besides other blood cells. Osteoblasts and osteoclasts deposit and erode the bone matrix, respectively. Fatty acids (FA) bind to PPARγ. PPARγ regulates the lineage commitment of both BMSC toward adipocytes and away from osteoblasts, and of myeloid progenitors toward OC. In adipocytes, PPARγ stimulation regulates adipokine secretion. Adipokines positively regulate osteoblastogenesis and negatively regulate osteoclastogenesis. Osteoclastogenesis is positively regulated by M-CSF and RANKL, which can be secreted by OBCs. OC secrete IGF-1 and TGFβ, which drive OBC differentiation

Table 1

Similar characteristics of MC and BML in knee OA [80, 103, 104]

Characteristic	Similarity
MRI modalities	MC1 and OA-BML are identified as T1w↓, T2w↑
Prevalence	Prevalence is higher in clinical (OA-BML and MC: 6 and 14 %) than non-clinical (OA-BML and MC: >50 and 43 %) population
Pain	MC and OA-BML are mostly painful in conjunction with joint degeneration, but the reason for pain is unknown.
Joint degradation	Lesion is dynamic and associates with the progression of joint degeneration
Risk factors	Shared risk factors for MC and OA-BML are age, male, obesity, and joint misalignment. These are also risk factors for disc degeneration and knee cartilage degeneration
Suggested etiologies	Overload, damage of joint cartilage, and inflammation
Natural history	Dynamic, conversion/resolution generally within 1–3 years in < 37 % (MC) and <66 % (OA-BML)

‘Joint’ refers to disc and knee, ‘joint degeneration’ to DD and OA

MRI magnetic resonance imaging, *MC* modic changes, *BML* bone marrow lesion, *OA* osteoarthritis, *T1w* T1-weighted images