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REVIEW

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# The role of the complement system in disc degeneration and Modic changes

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## Abstract

Disc degeneration and vertebral endplate bone marrow lesions called Modic changes are prevalent spinal pathologies found in chronic low back pain patients. Their pathomechanisms are complex and not fully understood. Recent studies have revealed that complement system proteins and interactors are dysregulated in disc degeneration and Modic changes. The complement system is part of the innate immune system and plays a critical role in tissue homeostasis. However, its dysregulation has also been associated with various pathological conditions such as rheumatoid arthritis and osteoarthritis. Here, we review the evidence for the involvement of the complement system in intervertebral disc degeneration and Modic changes. We found that only a handful of studies reported on complement factors in Modic changes and disc degeneration. Therefore, the level of evidence for the involvement of the complement system is currently low. Nevertheless, the complement system is tightly intertwined with processes known to occur during disc degeneration and Modic changes, such as increased cell death, autoantibody production, bacterial defense processes, neutrophil activation, and osteoclast formation, indicating a contribution of the complement system to these spinal pathologies. Based on these mechanisms, we propose a model how the complement system could contribute to the vicious cycle of tissue damage and chronic inflammation in disc degeneration and Modic changes. With this review, we aim to highlight a currently understudied but potentially important inflammatory pathomechanism of disc degeneration and Modic changes that may be a novel therapeutic target.

**Abbreviations:** AF, annulus fibrosus; BGN, biglycan; BM, bone marrow; C, complement component; *C. acnes*, *Cutibacterium acnes*; CD, cluster of differentiation; CEP, cartilage endplate; CFB, complement factor B; CFD, complement factor D; CLBP, chronic low back pain; CLU, clusterin; COMP, cartilage oligomeric protein; CRP, C-reactive protein; CSTD, cathepsin D; CSTL, cathepsin L; DAMP, damage-associated molecular pattern; DCN, decorin; DD, disc degeneration; FMOD, fibromodulin; HMGB1, high-mobility group box 1; IL-1β, interleukin 1β; KLK3, kalikrein 3; MASPs, MBL-associated serine proteases; MBLs, mannose-binding lectins; MC, Modic changes; NETs, neutrophil extracellular traps; NP, nucleus pulposus; SAP, serum amyloid P-component; TCC, terminal complement complex; TGF-β1, transforming growth factor β1; TLR, toll-like receptor; TNF-α, tumor necrosis factor α; VEGF, vascular endothelial growth factor; VIM, vimentin.

KEYWORDS
complement system, disc degeneration, low back pain, Modic changes

## 1 | INTRODUCTION

Peripheral nociception of chronic low back pain (CLBP) can be caused by a variety of structural pathologies.[1] Degenerated lumbar intervertebral discs are commonly found in CLBP patients and are a source of pain.[2–4] Pathomechanisms of disc degeneration (DD) are complex and all three tissue structures of the disc are affected: the central nucleus pulposus (NP), the surrounding annulus fibrosus (AF), and the cranial and caudal cartilage endplates (CEPs).[5,6] The process of DD involves inflammatory, catabolic, neurotrophic, and pro-angiogenic processes that are interrelated and with varying time-dependent and inter-patient contributions to DD and pain sensitization.[7] Ultimately, DD leads to disc dehydration, disc resorption, and disc height reduction. It has become clear that DD is not an isolated process of the disc but that it strongly associates with the occurrence and progression of pathologic changes of surrounding structures, for example, damages of the bony endplates,[8] Modic changes (MC) in the adjacent bone marrow (BM),[9,10] facet joint degeneration, paraspinal muscle atrophy, myosteatosis,[11,12] and with systemic immunometabolic changes.[13] The porous vertebral endplates, consisting of the CEPs and the bony endplates, are a main communication route of the disc with surrounding structures and tightly regulate the in- and efflux of substances to and from the disc.[14–16] Hence, endplate damages are detrimental for disc health.[9,15,17] Anatomically, the nearest communication partner of the disc is the vertebrae and in particular the BM. Within the vertebrae, the highly cellularized BM, with a myriad of different immune and stromal cell types, provides ample possibilities to respond to factors released by the disc.[17,18] The BM is vascularized and hence also represents the gate for communication of the disc with the systemic circulation.[19] Consequently, serum biomarkers have been found to associate with DD and MC,[20,21] and vice versa, extra-discal factor can affect DD.[13,17]

MC are a clinically relevant pathology that exemplifies the consequences of endplate damage and of disrupted regulation on the disc-BM crosstalk.[22–27] Discs adjacent to MC release higher amounts of pro-inflammatory cytokines, which participate in a pro-inflammatory crosstalk with the MC BM, possibly by draining through damaged endplates into the BM.[24,28–31] Associations of endplate damage with inflammatory cell infiltrates and fibrotic changes in the MC BM underscore the detrimental consequences of endplate damage.[32,33] While endplate damage and DD are a prerequisite for the development of MC, not all endplate damages and all degenerated discs trigger MC.[8,9,33–35] The precipitating factor for MC is suggested to be either a low-virulent bacterial infection of the disc with *Cutibacterium acnes (C. acnes)* or an autoimmune response of the BM against the disc.[23,36,37] In the bacterial MC etiology, intradiscal *C. acnes* produce virulence factors,[38,39] stimulated disc cells to release pro-inflammatory and neurotrophic cytokines, leading to DD, endplate resorption, and MC-like BM changes.[40–42] The pro-inflammatory cocktail of virulence factors and cytokines presumably drains through damaged endplates into the adjacent BM and supports the occurrence of MC. In the autoimmune etiology, endplate damage exposes the normally immune-privileged disc to immune cells of the BM and triggers an inflammatory non-self-reaction with proliferation of lymphocytes and production of auto-antibodies.[18,43–47] The different etiologies activate different immune mechanisms in the affected MC BM.[37] This highlights that the disc is not an isolated tissue but strongly communicates with the BM and with systemic components, in particular when the endplates are damaged, and the BM shows reactive changes such as MC. In summary, it has become clear that DD is not just a local biomechanical deterioration of the disc, but that the disc is in a vivid crosstalk with the BM and with systemic components.

The role of systemic components in DD and MC is still poorly understood. Some evidence exist around adipokines and lipid metabolism, yet a causal relationship has not been proven.[13,48] Recent studies identified the complement system as another systemic component that plays a role in DD and MC. In this narrative review, we summarize the current evidence for the involvement of the complement system in DD and MC, and propose potential mechanisms how the complement system might contribute to DD and MC. The aim of this review is to elucidate a potential role of this important inflammatory mechanism in DD and MC.

## 2 | THE COMPLEMENT SYSTEM

The complement system is part of the innate immune system.[49] With its more than 40 identified proteins, the complement system is part of our body's first line of defense. It plays an important role in tissue homeostasis, as well as in inflammatory processes.[50] The complement system can be activated through three main pathways: The classical pathway, the lectin pathway, and the alternative pathway[51] (Figure 1).

Immunoglobulins, immune complexes, matrix fragments, and pentraxins can trigger the classical complement system pathway by activation of the C1-complex.[49,52] In contrast, the lectin pathway does not involve C1-complex activation, but becomes activated by pattern recognition molecules like mannose-binding lectins (MBLs) that recognize carbohydrates on pathogens.[53] The alternative pathway is continuously activated as a result of spontaneous complement component (C)3 hydrolysis.[51] All three pathways converge at the formation of a C3 convertase, which cleaves C3 into the anaphylatoxin C3a and C3b. C3b forms together with the C3 convertase the C5 convertase, which cleaves C5 into the anaphylatoxin C5a and C5b. While the

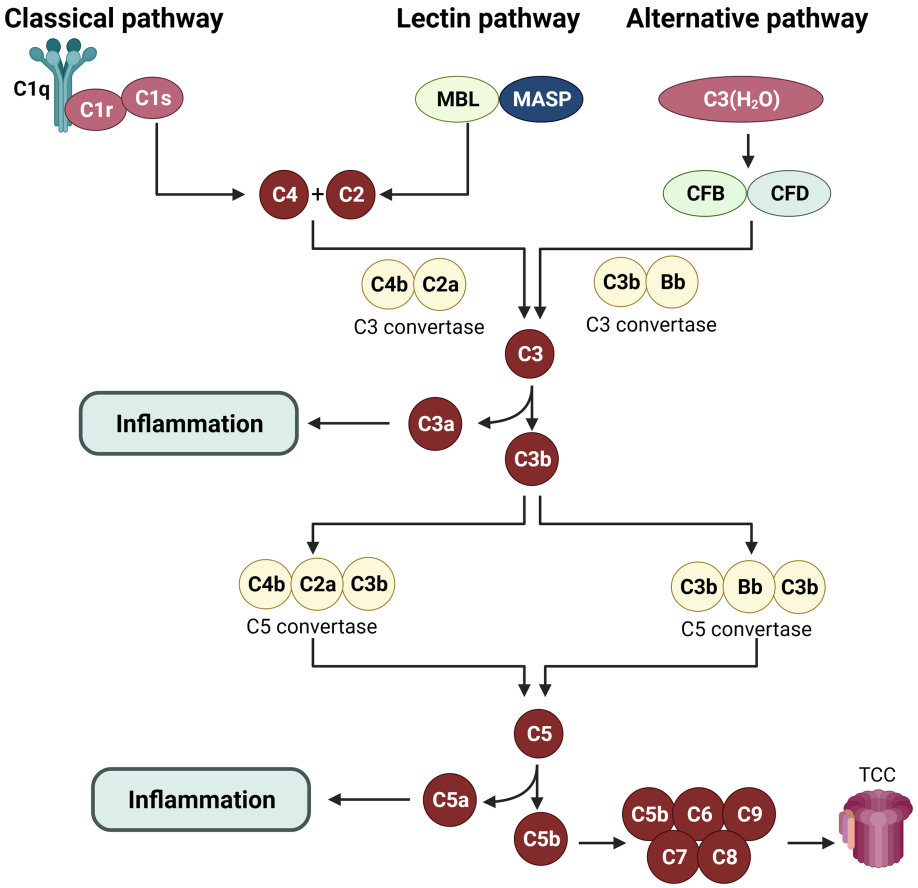


**FIGURE 1** The complement system. The complement system can be activated via the classical (left)-, the lectin (middle)-, and alternative (right) pathway. The classical pathway is induced for example by binding of antigen–antibody immune complexes (not shown) to C1q, leading to the assembly and activation of the C1 complex (C1Q, C1S, C1r). The C1 complex cleaves C4 and C2 into C4a, C4b, C2a, and C2b fragments which leads to the formation of the C3 convertase (C4b2a). The lectin pathway is activated by the binding of mannose-binding lectin (MBL) (or other lectin proteins) to specific carbohydrates on pathogens. MBL-associated serine proteases (MASPs) are activated, leading to the cleavage of C4 and C2 resulting in the C3 convertase like the classical pathway. The alternative pathway is constitutively active at low levels. C3 undergoes a slow spontaneous hydrolysis ($C3(H_2O)$) which binds to complement factor B (CFB), followed by complement factor D (CFD)-mediated cleavage of CFB to create the C3 convertase (C3bBb). At the convergence point, all three pathways lead to the formation of C3 convertases. These convertases cleave C3 into C3a and C3b fragments. C3b forms together with the C3 convertases the C5 convertases, which cleaves C5 into C5a and C5b. C5b forms with C6–C9 the terminal complement complex (TCC), which promotes cell lysis or induces a pro-inflammatory response. C3a and C5a both act as anaphylatoxins that promote inflammation.

anaphylatoxins C5a and C3a act as pro-inflammatory mediators, C5b is an important subunit for the formation of terminal complement complex (TCC) which is formed by the subsequent assembly of the complement components C6, C7, C8, and several C9 molecules.[54]

TCC binds to cell membranes and forms a transmembrane pore. As a result, target cell lysis can occur.[55–57] TCC induced cell lysis mainly appears in aged erythrocytes and certain Gram-negative bacteria.[58] Besides this, TCC binding to the cell surface at sub-lytic levels can promote inflammation by activating pro-inflammatory cell signaling pathways.[59,60]

Proteins like the C-reactive protein (CRP)[61] or the TCC-inhibitory glycoprotein cluster of differentiation (CD59)[62] do not belong to the complement system proteins themselves, but interact (activate or inhibit) with complement proteins. Hence, we here refer to them as complement interactors.

## 3 | EVIDENCE FOR COMPLEMENT SYSTEM INVOLVEMENT IN DD AND MC

Only few studies investigated the involvement of the complement system in DD and MC (Table 1, Figure 2). Dysregulated complement components in degenerated discs and in MC BM are indicative for an involvement of the complement system in these spinal pathologies.

Degenerated discs, particularly stronger degenerated discs or sequestered discs, have more TCC.[63,64] CD59 expression increases with amount of TCC, a potential protection mechanism from the lytic effects of the TCC. The mechanisms leading to more TCC deposition in degenerated discs are not known but could originate from the endplates themselves, since it was shown that soluble factors secreted from degenerated endplates mediate direct C5 cleavage, which is

**TABLE 1** Overview of studies that reported complement proteins and interactors in DD and MC.[63,64]

| References | Tissue | Methods | Main findings |
|---|---|---|---|
| Ariga et al.[65] | Human surgical disc tissue | • Immunohistochemistry | • CTSD and CTSL immunolocalized in disc cells |
| Grönblad et al.[63] | Human surgical disc tissue | • Immunohistochemistry | • Increased TCC formation in degenerated disc tissue |
| Rajasekaran et al.[66] | Human surgical disc tissue | • Label-free proteomics | • Increased in MC discs: C1s, C1q, C1r, C8b, SAP<br>• Decreased in MC compared to non-MC discs: C3, C9, CFH, BGN, VIM |
| Teixeira et al.[64] | Human surgical disc tissue | • Immunohistochemistry | • Positive correlation of TCC deposition and its inhibitor CD59 with degree of DD |
| Teixeira et al.[67] | Human surgical disc tissue/disc cells | • Disc tissue/cell culture<br>• Immunohisto/−cytochemistry | • IL-1β stimulation decreases TCC+ disc cells<br>• CTSD and zymosan increases TCC deposition<br>• Complement interactors CD46, CD55, CD59 increased during culture |
| Dudli et al.[68] | Human surgical BM plasma | • Enzyme-linked Immunosorbent Assay (ELISA) | • Increased CRP levels in MC BM correlates with blood CRP levels |
| Heggli et al.[33] | Human cadaveric bone marrow | • Label-free proteomics | • Increased in MC BM versus intra-patient control: C1qb, C1qc, C5, C8a, C8b, C8g, C9, CFB, CFH, FMOD, BGN, DCN |
| Kuhn et al.[69] | Human surgical disc cells | • Disc cell culture<br>• Immunocytochemistry<br>• Anaphylatoxin generation | • Zymosan promotes anaphylatoxin generation and TCC deposition<br>• CTSD cleaves C5 |
| Mengis[70] | Human surgical disc tissue | • TAILS<br>• LC–MS/MS | • Increased in MC versus non-MC: KLK3, CLU<br>• Decreased in MC versus non-MC: CLU (MC-subtype specific differences) |

Abbreviations: BGN, biglycan; C, complement component; CD, cluster of differentiation; CFB, complement factor B; CFH, complement factor H; CLU, clusterin; CRP, C-reactive protein; CTSD, cathepsin D; CTSL, cathepsin L; DCN, decorin; FMOD, fibromodulin; IL-1β, interleukin 1β; KLK3, kalikrein 3; LC–MS/MS, liquid chromatography tandem mass spectrometry; TAILS, N-terminal amine isotopic labeling of substrates (TAILS); TCC, terminal complement complex; VIM, vimentin.

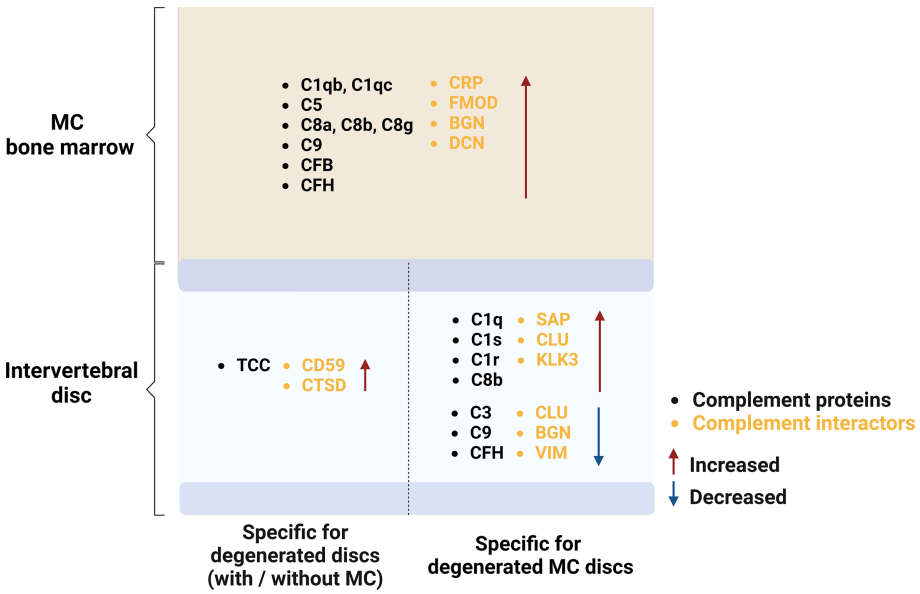


**FIGURE 2** Simplified overview of dysregulated complement proteins (black) and complement interactors (yellow) in degenerated discs (with and without Modic changes (MCs)) (top, left), degenerated MC discs (top, right), and MC BM (bottom). C, complement component; CRP, C-reactive protein; TCC, terminal complement complex; KLK3, kallikrein 3; CLU, clusterin; SAP, serum amyloid P-component; BGN, biglycan; VIM, vimentin.

central for TCC formation.[67] Besides this, increased TCC deposition could also be mediated by cathepsin D (CTSD), a matrix degrading lysosomal protease found to be increased in degenerated disc tissue,[65] as CTSD promotes TCC deposition in disc tissue culture.[69]

Increased TCC and CD59 deposition appears consistent in all degenerated discs, regardless of adjacent MC.[64] However, some complement factors, particularly members of the classical pathway such as C1-complex proteins (C1s, C1q, and C1r) are increased in

MC discs. Furthermore, lower C3 levels were detected, suggesting increased cleavage into C3a and C3b fragments. Elevated TCC protein C8b and reduced C9 in MC discs may indicate activity in TCC assembly/disassembly processes. MC discs also show decreased complement factor H (CFH), an inhibitor of the alternative complement pathway. Additionally, higher levels of complement interactors serum amyloid P-component (SAP) and Kalikrein 3 (KLK3), as well as increased/decreased levels of clusterin (CLU) (MC-subtype specific differences), were reported.[70] SAP is a member of the pentraxin family that activates the classical pathway.[71] KLK3 is an enzyme that activates the complement system via C3 cleavage.[72] CLU is a glycoprotein known to inhibit TCC formation.[73,74] In MC discs, the complement interactors biglycan (BGN) and vimentin (VIM) were decreased.[66] BGN is a proteoglycan able to bind to C1q and interact with the classical complement pathway. VIM is an intermediate filament protein shown to inhibit TCC formation.[49] In summary, degenerated discs with and without adjacent MC have multiple dysregulated complement components, which gives evidence for complement involvement in DD.

A proteomic study of human cadaveric spines assessed the protein expression in endplate-near MC and control BM and correlated it with adjacent endplate degeneration.[33] Proteomic analysis of the BM revealed increased levels of complement proteins C1qb, C1qc, C5, C8a, C8b, C8g, C9, CFB, and CFH in MC BM. This indicates involvement of the classical and alternative complement pathway and formation of TCC complex.[75] Furthermore, the proteoglycans and complement interactors fibromodulin (FMOD), BGN, and decorin (DCN), which are all capable of binding to C1q and activating/inhibiting the classical complement system pathway, were found to be upregulated in MC BM. A further study assessed MC BM aspirates from patients undergoing spinal fusion surgery. They found that increased CRP levels in MC BM correlated with blood CRP levels.[76] This supports previous reports of increased serum CRP in MC patients and pinpointed the MC lesion as the relevant area for elevated CRP levels.[77] CRP is an acute-phase protein, like SAP, also belonging to the pentraxin family of innate pattern recognition molecules. It is also involved in complement system activation of the classical pathway through binding to C1q.[71]

Endplate damages are always present in MC and facilitate a biological and physiochemical crosstalk between the disc and BM MC.[24,28] Hence, a complement factor exchange and potentially also a disc-endplate-BM complement crosstalk is plausible. Positive correlation of C1q and C8b proteins in MC BM with the severity of degeneration of the adjacent endplate support the notion of a complement system crosstalk.[33] Proteomic analysis can only indicate enriched or depleted concentration of proteins and does not allow to draw conclusions about complement system activation or inhibition. Yet, dysregulated complement components in DD and MC give evidence that that the complement system might be involved in these spinal pathologies.

## 4 | POTENTIAL MECHANISMS OF THE COMPLEMENT SYSTEM IN DD AND MC

Tissue damage and chronic inflammation are hallmarks of DD and MC.[23] The vicious cycle of tissue damaging and chronic inflammation can occur independently of the complement system and is not the scope of this review. However, tissue damage and chronic inflammation are both strongly linked to non-homeostatic activities of the complement system.[78] Hence, involvement of the complement system in DD and MC is likely. In this chapter, we discuss the potential mechanisms by which the complement system contributes to the vicious cycle of tissue damaging and chronic inflammation in (MC) degenerated discs and BM and the possible consequences (Figure 3).

### 4.1 | Tissue damage activates the complement system

MC occur adjacent to degenerated discs at locations where endplates are damaged and endplate damage is a risk factor for MC development.[8,9,23,34,35,68,79–81] Endplate damage has several consequences that can lead to complement activation in MC: (1) it results in necrotic cell death at the bone-disc junction and (2) it promotes commingling of normally immune privileged disc materials with BM, which (i) exposes degenerated disc fragments to BM leukocytes, (ii) allows bacterial infiltration, and (iii) enables the formation of immune complexes (Figure 3, Nr. 1).

#### 4.1.1 | Cell death

Endplate damage leads to necrotic cell death and necrosis in MC BM is evident by increased LDH.[68,76,82] CRP, which is increased in MC BM, might bind to exposed phosphocholine on damaged cell membranes of necrotic cells and potentially activates the complement system via C1q.[71] Necrotic cells also release intracellular components that can act as damage-associated molecular patterns (DAMPs) like high-mobility group box 1 (HMGB1), which could also initiate classical complement system activation in MC[83,84] Necrosis as a potential complement system activator in MC is supported by findings from osteoarthritis, a degenerative joint disease characterized by excessive breakdown of articular cartilage and increased chondrocyte death, where chondrocyte necrosis leads to complement activation.[85] While under physiological conditions tissue damage-mediated complement system activation helps to clear dying cells and remove immune complexes /pathogens, persistent and accumulating cell damage can exceed homeostatic activation and amplify rather than suppress pro-inflammatory processes.[86] Taken together, increased concentrations of LDH, CRP, and C1q in MC BM suggest that cell necrosis is a potential complement system activation mechanism in MC (Figure 3, Nr. 1.1).

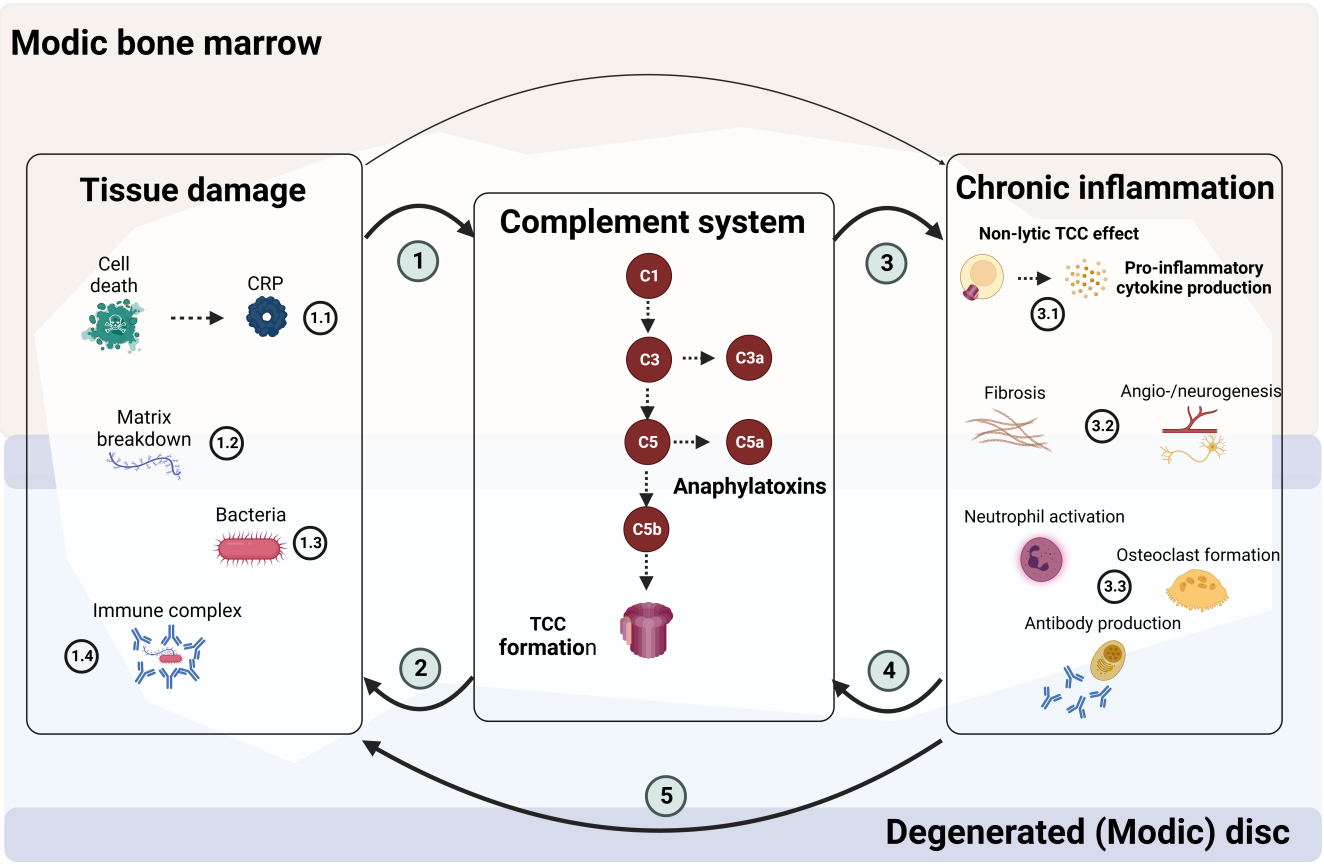


**FIGURE 3** Potential mechanisms how the complement system could be involved in the MC pathomechanisms. Tissue damage leads to cell death (1.1), matrix breakdown (1.2), and enables the entry of bacteria (1.3). Matrix fragments and bacteria (bacterial components) might induce an adaptive immune response leading to the formation of immune complexes (1.4). All these consequences resulting from tissue damage can activate the complement system (1). Complement activation can lead to terminal complement complex (TCC) formation and embedding into nucleated cells, which further promotes cell necrosis, thereby directly contributing to tissue damage after directly contributing to tissue damage (2). TCC deposition into nucleated cells can also lead to increased pro-inflammatory cytokine production (3.1), contributing to chronic inflammatory processes (3). Complement activation can directly promote tissue fibrosis, angio-and neurogenesis (3.2). Furthermore, complement activation can lead to osteoclast and neutrophil activation, and triggers an adaptive immune response characterized by plasma cell produced immunoglobulin production (3.3). Neutrophil extracellular traps released by activated neutrophils and immunoglobulins produced by plasma cells can in turn promote further complement activation (4). Activated neutrophils and osteoclasts promote further tissue damage that indirectly activates the complement system again (5). Increased secretion of immunoglobulins against for example matrix fragments lead to the formation of immune complexes and hence, also to an indirect activation of the complement system.

### 4.1.2 | Matrix breakdown

Damaged cartilage in osteoarthritis releases matrix degradation components including fibronectin, FMOD, collagen type II and matrix fragments generated by overactivated proteases (DAMPs) that activate the complement.[62,87] During DD, extracellular matrix is also degraded and fragmented by overexpressed matrix proteases suggesting a potential complement activation mechanism in DD and MC. The fact that the degradome of MC discs appears to be more complex compared to that of degenerated discs without adjacent MC suggests a potential role for degraded matrix and matrix fragments (DAMPs) in complement system activation in MC.[70] Matrix-mediated complement activation may occur within the degenerated disc or, due to the hydraulic and biological coupling of the MC disc with the BM resulting from endplate damage,[24,28] matrix components are likely to leak into the adjacent BM, potentially triggering complement activation. MC BM contains higher levels of the proteoglycans FMOD, BGN, and DCN.[33] FMOD directly binds to C1q and activates the classical complement system pathway.[52,88,89] On the other hand, BGN and DCN also bind to C1q but do not activate the classical pathway,[89] but rather inhibit it.[90] In summary, stronger fragmentation of the MC disc matrix and increased matrix proteins in MC marrow give indications for a disc matrix dependent complement activation mechanism in MC (Figure 3, Nr. 1.2).

### 4.1.3 | Infiltration of bacteria

Bacteria/bacterial components can activate the complement system. Endplate damage disrupts the fine mesh of collagens and

proteoglycans of the CEP, which normally prevents the in- and efflux of larger molecules and cells into the disc.[14,16,28,91,92] Disc herniations in most cases also disrupt the CEP because most herniations occur as avulsion type between the CEPs and bony endplate.[91,92] Consequently, endplate damage and herniations are seen as gate for bacterial entry to the disc (i.e., *C. acnes*),[93,94] which might lead to complement activation via the classical and alternative pathway in the disc[95] *C. acnes* are found in disc tissue, specifically in MC discs, but not in the BM.[37,96] Hence, it remains to be elucidated if (i) the complement system can be locally activated in disc, (ii) which complement factors are present in disc tissue, either through local production by disc cells or through influx from the BM, and (iii) if and how bacterial-mediated complement activation in the disc also affects the MC marrow (Figure 3, Nr. 1.3).

## 4.2 | Production of complement factors by disc and endplate cells

Articular chondrocytes derived from osteoarthritic cartilage synthesize complement components, and stimulation of chondrocytes with the bacterial cell wall component LPS or proinflammatory cytokines results in the production of complement factors.[97–101] The source of complement factors in DD and MC is unknown and needs to be investigated in future studies. Complement factors are mainly synthesized in the liver, but are also produced locally in inflamed tissue.[102] This data suggests that increased matrix components, DAMPs and bacteria in MC and DD could stimulate disc cells to produce complement factors via TLRs, similar to what has been shown in chondrocytes.[99] However, previous work showed that, in vitro, human disc cells are not able to produce soluble TCC components in presence of IL-1β or CTSD.[67] Additionally, while the presence of TLRs has been shown in disc cells, it remains to be investigated whether CEP cells also express TLRs and whether this results in local complement factor production.[103–107]

### 4.2.1 | Immune complexes

In RA, the formation of immune complexes consisting of autoantibodies against cartilage proteins like collagen II, cartilage oligomeric protein (COMP), FMOD fragments, or aggrecan was shown to lead to the activation of the complement system.[78,108–114] Similarly, cartilage-matrix-immunoglobulin immune complexes induce complement activation in osteoarthritis.[115] Endplate damage compromises the immune privilege of the disc, leading to the exposure of disc cells and matrix to BM leukocytes, which can trigger a non-self reaction in lymphocytes with immunoglobulin.[18,43,44] Infiltration of lymphocytes and plasma cells has been found in MC lesions,[32,82] infiltration of T-cells has been reported in experimental models of MC,[42,43] and auto-antibodies against type I, II, IV collagen, and aggrecan have been found in degenerated discs.[46] Immunoglobulins and immune complexes can activate the classical pathway of the complement system by binding to C1q and ultimately leading to TCC formation.[52,116] Bacterial-immunoglobulin immune complexes in MC BM could also have formed as a response to bacterial components that have drained through damaged endplates into the MC BM, which induced an adaptive immune response characterized by immunoglobulin production against bacterial compounds. Thus, complement activation through immune complexes in DD and MC is a plausible mechanism (Figure 3, Nr. 1.4).

CRP, DAMPs, bacteria, and immune complexes induce several pro-inflammatory mechanisms. Complement activation is one mechanism, yet other pro-inflammatory mechanisms of these compounds can contribute to chronic inflammation in DD and MC independent of complement activation. Hence, the complement system represents a further mechanism that may act in concert with other pro-inflammatory mechanisms to maintain homeostasis or to intensify an inflammatory response.

## 4.3 | Activated complement system promotes further tissue damage

Complement system activation leads to higher levels of pro-inflammatory anaphylatoxins C3a and C5a and increased TCC formation. This could lead to complement-mediated tissue damage in MC and DD. Degenerated osteoarthritis cartilage shows increased TCC deposition in chondrocytes, which correlates with increased necroptotic markers.[117] The critical role of the TCC in osteoarthritis was shown in mice deficient for the TCC component C6. These mice were protected against osteoarthritis,[62] yet they had lower bone mass and impaired fracture healing, mainly because of increased osteoclast activity.[118] Similar mechanisms are plausible in DD and MC: Since increased TCC deposition was shown in disc cells, it is possible that complement activation with TCC formation could promote further (necrotic) cell death that in turn again amplifies complement system activation and defines a vicious cycle (Figure 3, Nr. 2).

## 4.4 | The complement system contributes to chronic inflammatory processes

Chronic inflammation is characterized by concomitant inflammation and tissue repair processes. Inflammatory infiltrates, BM stromal cell-mediated fibrosis, and increased angio−/neurogenesis in MC BM are signs of chronic inflammation.[23,32,119,120] Chronic inflammation in degenerated (MC) discs is, among others, characterized by increased expression of pro-inflammatory mediators such as interleukin 1β (IL-1β), tumor necrosis factor α (TNF-α). Here, we show how the activated complement system might contribute to chronic inflammatory processes (Figure 3, Nr. 3).

#### 4.4.1 | Sub lytic TCC effects on nucleated cells

Even though TCC formation is well known to induce pathogen lysis, TCC can also be deposited into nucleated cells which resist TCC-mediated cytolysis by expression of inhibitors such as CD59.[121] In this case, TCC may induce intracellular signaling which initiates the production of pro-inflammatory cytokines such as IL-1β.[59,60,69] Hence, complement activation with TCC formation and deposition on disc cells and potentially also on MC BM immune cells might contribute to inflammation with increased production of pro-inflammatory cytokines (Figure 3, Nr. 3.1).

#### 4.4.2 | Complement system contribution to fibrosis, angio-, and neurogenesis

Complement system activation may further contribute to fibrosis and angiogenesis/neurogenesis in MC. Complement activation promotes fibrosis in various organs by for example, inducing epithelial-to-mesenchymal transition or increasing the production of transforming growth factor β1 (TGF-β1). Importantly, targeting complement factors was found to ameliorate fibrosis.[122,123]

Complement activation in MC might further promote neovascularization by increasing the production of the pro-angiogenic vascular endothelial growth factor (VEGF).[124] In osteoarthritis, normally avascular cartilage becomes vascularized,[125,126] which appears to be mediated by VEGF.[127] The production of VEGF is stimulated by C3a and C5a.[128] Therefore, neovascularization in MC may result from complement activation. In addition, the complement system also regulates neurogenesis.[129] This could stimulate nerve fiber ingrowth into the CEP and contribute to increased sensory nerve fiber density in MC endplates.[80,130] Together, there is biological plausibility that the activated complement system could be involved in fibrotic-, angio-, and neurogenic processes, however, to date there is no evidence that supports direct involvement of the complement system in these MC processes (Figure 3, Nr. 3.2).

#### 4.4.3 | Potential role of the complement system on inflammatory pathomechanisms

Anaphylatoxins C3a and C5a, produced during complement activation, bind to receptors on various immune cells. C5a is a potent chemoattractant and activator of neutrophils, while C3a attracts and activates eosinophils and neutrophils.[131] Binding of C3a or C5a to dendritic cells can lead to the loss of immune tolerance as a first step to induce autoimmunity,[132] and anaphylatoxin receptor activation on B-cells controls the production of autoantibodies.[132] C5a can also activate osteoclasts or stimulate osteoblasts to produce osteoclastogenic factors.[51,59,133,134] C3 and C5 have been found in higher concentrations in MC discs or BM, and neutrophils, plasma cells, dendritic cells, and osteoclasts are more frequent or activated in MC BM.[30,32,82,135,136] Hence, it is plausible that anaphylatoxins which play a role in immune cell and osteoclast recruitment might also be involved in MC (Figure 3, Nr. 3.3).

### 4.5 | Complement activation by activated immune cells

Neutrophil activation, marked by the excessive formation of neutrophil extracellular traps (NETs), is a distinctive feature in diseases like rheumatoid arthritis, where the complement system plays a pathomechanistic role.[137–139] There is evidence that MC BM neutrophils are activated, and that NET formation is increased.[130] Since NETs were shown to activate the complement system, this could further exacerbate complement system activation in MC.[140,141] In addition, inflammatory infiltrates in MC also consist of immunoglobulin producing plasma cells.[32] Immunoglobulins can activate the complement system, indicating that increased plasma cell infiltrates contribute to a vicious cycle of complement activation and inflammatory processes in MC (Figure 3, Nr. 4).

Activated neutrophils are very tissue destructive. Hence, neutrophil activation could also indirectly activate the complement system in MC by damaging tissue and cells, which in turn again fuels complement activation (Figure 3, Nr. 5). Similarly, osteoclasts are also destructive and probably also indirectly promote complement system activation in MC.

In summary, there is evidence for dysregulated complement factors and interactors in degenerated discs and MC BM. Here, we show how the complement system could be involved in MC and that it is a yet unexplored inflammatory pathomechanisms that potentially contributes to the vicious cycle of complement activation and tissue damage.

## 5 | CONCLUDING REMARKS AND FUTURE RESEARCH

Only few studies investigated the role of the complement system in DD and MC, yet these studies suggest an involvement in their pathogenesis. The reason for the dysregulated concentrations, the activation mechanisms, as well as the consequences of it remain unclear. For example, in MC, enhanced tissue damage, CRP concentration, and complement factors need to be causally linked with complement activation and radiologic MC progression. Functional studies are required to clarify if the complement system has a pathologic role in DD and MC. Since mice deficient in C6 are protected from development of osteoarthritis,[62] similar in vivo studies could be informative about the role of the complement system in DD and MC. The cascade structure of the complement system requires presence of multiple complement factors in the same tissue. Hence, it further needs to be clarified if all essential complement factors are present in the disc and the BM. The disc, the endplate, and the BM are a unit in the segmental degenerative processes, in particular in the presence of structural disc damage such as endplate damages and disc herniation. Hence, complement

components can be exchanged between the compartments and can contribute to the assembly of the factors required for the complement cascade. Furthermore, the consequences of the activation of the complement system needs to be clarified to understand its pathomechanistic role and to understand potential consequences and possibilities of therapeutic interference in DD and MC. Lastly, it is essential to clarify the potential for therapeutic intervention in the complement system to modify disease progression.

In conclusion, only few studies reported on complement factors in DD and MC. The complement system is tightly intertwined with processes known to occur during DD and in MC, like increased cell death, auto-antibody production, bacterial defense processes, neutrophil activation, and osteoclast formation. Yet, mechanistic studies are missing that clarify the role of the complement system in DD and MC, which ultimately would offer the possibility for novel therapeutic approaches.

## AUTHOR CONTRIBUTIONS

This study was conceived and written by Irina Heggli, Stefan Dudli, Graciosa Q. Teixeira, and Cornelia Neidlinger-Wilke. James C. Iatridis critically revised the manuscript. All authors approved the final version.

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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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