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Immunobiology of Periprosthetic Inflammation and Pain Following Ultra-High-Molecular-Weight-Polyethylene Wear Debris in the Lumbar Spine

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Abstract

Introduction: Wear debris-induced osteolysis is a common cause of arthroplasty failure in several joints including the knee, hip and intervertebral disc. Debris from the prosthesis can trigger an inflammatory response that leads to aseptic loosening and prosthesis failure. In the spine, periprosthetic pain also occurs following accumulation of wear debris through neovascularization of the disc. The role of the immune system in the pathobiology of periprosthetic osteolysis of joint replacements is debatable.

Areas Covered: We discussed the stimulation of pro-inflammatory and pro-protective and pro-regenerative pathways due to debris from the prosthetics. The balance between the two pathways may determine the outcome results. Also, the role of cytokines and immune cells in periprosthetic inflammation in the etiology of osteolysis is critically reviewed.

Expert Commentary: Therapies targeting the inflammatory process associated with ultra-high-molecular-weight polyethylene wear debris could reduce implant failure. Additionally, therapies targeting neovascularization of discs following arthroplasty could mitigate periprosthetic pain.

Keywords

Discogenic pain; Immunopathogenesis; Inflammation; Macrophages; Periprosthesis; Osteolysis; Total Disc Replacement

1. Introduction

Intervertebral disc degeneration (IDD) is a significant cause of lower back pain and associated disability.[1] Increased age, mechanical loading, and genetics predispose

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Declaration of Interests

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individuals to IDD progression. Several processes are believed to contribute to the development of IDD.[2] Loss of nutritional supply and subsequent decrease in proteoglycan formation in the nucleus pulposus (NP) reduce disc hydration capacity, resulting in diminished disc turgor and strength. Injury to the annulus fibrosis (AF) promotes inflammatory change, destabilizes the NP, and impairs load tolerance. These changes increase the risk for further structural damage, while the healing process promotes nociceptive pain sensitivity to stimuli, complicating resolution of symptoms.[3]

Numerous molecular markers are associated with IDD. Matrix metalloproteinases (MMPs), especially MMP-3 promote AF degradation in response to injury early in the pathogenesis of IDD[4]. Tumor necrosis factor-α (TNF-α) has been shown to regulate the expression of several inflammatory cytokines, including IL-1β, IL-6, IL-8, IL-17 IL-18.[5] Additionally, reactive oxygen species increase stress and contribute to IDD.[6,7] These pathways represent potential targets for future therapeutic advancement.[8,9]

Currently, treatment options of IDD are limited. Surgery is an option for patients who do not get relief of symptoms with conservative treatment.[10] Spinal fusion procedures demonstrate clinical improvements compared to non-surgical measures.[11,12] In recent years, total disc arthroplasty using ultra-high-molecular-weight-polyethylene (UHMWPE) has gained popularity as a surgical alternative to spinal fusion for treating IDD. This shift is driven, in part, by the preference to maintain normal range of motion.[10] Though more long-term studies are necessary, current literature suggest superior or non-inferior performance of disc arthroplasty compared to spinal fusion techniques.[13–16] Many studies have examined periprosthetic inflammation and pain in knee and hip arthroplasties but few discuss the immunobiology associated with periprosthetic inflammation and pain in lumbar total disc replacements. The purpose of this review is to critically examine the immunological responses due to UHMWPE wear debris in lumbar total disc replacements, and associated periprosthetic inflammation and pain.

2. Ultra-High-Molecular-Weight-Polyethylene

The use of polymers in artificial joints began with the idea that natural joints function well because of their low coefficient of friction. Low friction results from increased lubrication from joint compression.[17] When cartilage is compressed, water is expelled from the tissue allowing for the contacting surfaces to separate. This phenomenon is called boundary lubrication, and is the foundation from which artificial joints were developed.[18] Boundary lubrication is composed of water, proteins, and other biochemical factors that reduce friction.[18] Damage to cartilage can result in the loss of its lubricious capability and lead to joint destruction. UHMWPE is used clinically because of its significant resistance to abrasion and wear, especially when compared to other polyethylene polymers such as high density polyethylene.[17] UHMWPE was first introduced to orthopedics in 1962 by Sir John Charnley through hip replacements, and remains the gold standard as orthopedic bearing material in joint replacements.[17] Other materials such as carbon-fiber reinforced applications were introduced, but did not demonstrate improved clinical results relative to the original UHMWPE prostheses.[18]

3. Osteolysis

Wear continues to be the greatest problem affecting implant success. The most frequent cause of implant failure in the medium to long term is aseptic loosening predated by periprosthetic osteolysis.[19–21] Prosthetic wear is defined as the loss of prosthetic material from the articulating interface of the joint due to abrasion, corrosion, and fatigue.[22,23] Wear on the implant results in particulate matter depositing in the periprosthetic space. This debris triggers an inflammatory response leading to periprosthetic osteolysis.[19]

Periprosthetic osteolysis is the process by which biological or mechanical forces initiate an immune response leading to implant loosening and failure.[23] This loosening is significant, and is the major cause of implant failure in total hip arthroplasty with estimated incidence rates ranging from 10–70%.[20,23] Wear rates exceeding 0.15 mm/year have been shown to significantly enhance the risk of aseptic loosening.[24] The volume of debris, as opposed to the size of the debris particles, is the major factor driving activation of those inflammatory cells.[20] Particles 0.1–1.0 μm in size are thought to be the most biologically active, but UHMWPE particles that measured 0.24 μm in length gave the greatest rates of bone resorption and inflammatory response. UHMWPE particles have been associated with the increase of several inflammatory cytokines: tumor necrosis factor alpha (TNF-α), interleukin (IL)-6, IL-1β, and prostaglandin E_2.[23] The overall response to UHMWPE particles has been characterized as a foreign body reaction marked by chronic granulomatous inflammation.[23] The mechanism by which debris leads to aseptic loosening is through the induction of inflammatory processes which promote bone resorption over bone formation.[19] This process is dominated by cells in the monocytic and osteoclastic lineage.[23] However, potential role of other immune cells, including lymphocytes, cannot be ruled out.

4. Macrophages

While bone remodeling was once believed to involve only osteoblasts and osteoclasts, it is now accepted that cross-talk with inflammatory cells, such as macrophages, is essential.[25] UHMWPE particles phagocytosed by resident macrophages cannot be processed due to the resistance of the material to an acidic environment. Debris accumulates, and increases a cell-mediated immune response leading to osteolysis.[22] The inflammatory reaction leading to osteolysis occurs if the debris is biologically stimulating immune cells to release factors affecting the structural cells. In the host-defense mechanism, there is a trigger of both pro-inflammatory and pro-protective and pro-regenerative pathways due to debris from the prosthetics. This is primarily determined by the amount of debris if exceeding a certain threshold, degree and duration of wear or damage, and the co-morbidities and epigenetic factors.[22]

The pro-protective and pro-regenerative pathways are resultant from crosstalk between cells of the innate immunity and mesenchymal cells.[25] The initial step in bone healing is an inflammatory response governed by neutrophils and the recruitment of macrophages through IL-6 and chemokine ligand 2 (CCL2) signaling that serve to reinstate homeostasis. Neutrophils, macrophages, and osteoclasts attack the offending injurious stimulus and begin

the transformation of macrophages into a pro-healing phenotype. Macrophages activated with interferon-gamma (IFN-γ) behave as the inflammatory M1 phenotype and secrete the inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), and interleukin-1 beta (IL-1β), and chemokines like CCL2 resulting in increased tissue damage and additional leukocyte infiltration. Macrophages exposed to interleukin- 4 (IL-4) or byproducts of tissue destruction and debris express the anti-inflammatory M2 phenotype.[21] The polarization of macrophages from the proinflammatory M1 subtype to the anti-inflammatory M2 subtype allows for the secretion of various cytokines and chemokines that promote angiogenesis such as vascular endothelial growth factor (VEGF) and the activation of osteoblast activity.[25] Additionally, mesenchymal cells modulate the catabolic activity of the inflammatory cells to resolve the inflammatory response and result in normal tissue.[25] Failure to modulate or resolve the inflammatory response results in continued tissue destruction and may be characterized by continued secretion of inflammatory cytokines.[25] Some studies have reported an increased M1/M2 ratio in periprosthetic tissue comparted to osteoarthritic tissue, and the modulation of macrophage polarization was considered an effective means to mitigate wear-debris-induced osteolysis.[21] An *in vivo* study by Wang *et al*[21] showed that increased levels of the M2 phenotype resulted in amelioration of bone loss in murine calvarial models. These findings support the posit that pro-inflammatory M1macrophages contribute to osteolysis, while the M2 phenotype has a more protective role in osteoimmunology. Limiting M1 cytokine production and activation of osteoclasts is a crucial point to reduce periprosthetic osteolysis.[26]

Acute inflammation stimulated by wear debris is characterized by the infiltration of neutrophils and other inflammatory cells from the perivascular space.[24] The progression of acute inflammation to chronic inflammation begins with the recruitment of macrophages, the main responder to wear-debris. Chronic inflammation is the state in which inflammation, fibrosis, and repair are occurring simultaneously and is characterized by the presence of macrophages, lymphocytes, fibroblasts, mesenchymal cells, and the proliferation of blood vessels and tissue remodeling.[24] *In vitro* studies by Chen *et al*[27] demonstrated macrophage activation by cobalt wear-debris resulting in a Th17 cell inflammatory response. Th17 inflammation has been previously implicated in rheumatoid and psoriatic arthritis, and the Th17 response was directly associated with the risk of osteolysis development as reported by Chen *et al*[27]. More studies must be performed to investigate the role of a Th17 response in UHMWPE debris opposed to those associated with metal arthroplasty.

The activated macrophages residing in bone, termed osteomacs, mediate bone remodeling. Osteomacs release various cytokines, chemokines, and growth factors to recruit inflammatory cells, and promote vascularization.[25] The release of inflammatory cytokines, including TNF-α, IL-1β, and IL-6 that promote bone resorption by increasing osteoclast activity.[25] Constant wear or damage, such as particle debris, would lead to prolonged immune activation and promote catabolic effects on the joint and surrounding tissue, which may result in pain.[23,28] In comparison, acute bone injury leads to an osteomac activation resulting in anabolism and healing.[25] Macrophage-derived TNF-α and IL-1 can promote osteoclastogenesis by indirectly stimulating receptor activator of nuclear factor kappa B ligand (RANKL) expression and suppressing osteoprotegerin (OPG) in osteoblasts and fibroblasts.[23–25]

Previous arthroplasty studies revealed that UHMWPE particles activate fibroblasts and macrophages through toll-like receptors (TLRs) to secrete TNF-α and IL-1β which synergistically act to recruit more macrophages.[23,28] Additionally, damage associated molecular patterns (DAMPs) released from damaged tissue may also activate TLRs and participate in the myeloid differentiation primary response 88 (MyD88) leading to osteolysis through macrophage recruitment and activation.[23] Additional investigations exploring specific DAMPs and their role in wear-debris induced inflammation are warranted to determine the role of specific DAMPs and the underlying cellular mechanisms. While macrophages are the primary source of inflammatory signals during the initial phase of bone healing, osteoblasts and chondrocytes are responsible for the release of inflammatory cytokines within 3–7 days of injury.[25] A successful orthopedic implant results from the acute immune response forming a stable implant-tissue complex.[24] The acute response is characterized by local peri-implant hematoma formation, and activation of the coagulation and complement cascades.[24] Activation of these pathways release chemokines to recruit macrophages, which continue the inflammatory reaction and ideally form granulation tissue around the implant. After being encapsulated by granulation tissue, the implant is integrated into the bone to form a functional construct.[24] Activated fibroblasts from the granulomatous formation can perpetuate chronic granulomatous inflammation by inappropriately expressing survival cytokines. These survival signals can prolong the life of other activated cells which continue to secrete pro-inflammatory cytokines and continue inflammatory responses.[19]

5. Inflammation

Osteoclasts are the primary effector cells in osteolysis, and the magnitude of bone degradation depends upon the number of activated osteoclasts and their individual capacity to resorb bone.[29] The immune response to UHMWPE particles is characterized by cells of monocyte or osteoclastic lineage.[26] The number of activated osteoclasts is dictated by RANKL activity, which is modulated by inflammatory cytokines.[30] The ability of the osteoclast to resorb bone is a product of cytoskeletal reorganization.[29] The inflammatory response perpetuated by wear-debris recruits osteoclasts that release direct mediators of further osteolytic activity.

Additionally, recent evidence has implicated inflammasome activity as a contributing factor to periprosthetic osteolysis. Crystalline particles have been implicated in the pathogenesis of inflammasome mediated diseases, and wear debris from a joint implant is consistent with this picture.[29] The mechanisms underlying the effects of particle-activated inflammasomes include an increased production of reactive oxygen species in phagocytes, and rupture of phagosomes releasing cathepsins into the cytoplasm of the cell resulting in cell death.[29] Studies have demonstrated that polyethylene-based wear-debris induces fewer inflammatory reactions compared to metal wear debris in murine models in the *in vivo* studies.[31]

Inflammatory reactions associated with wear particles are propagated by several signaling pathways, the most important involves the transcription factor NF-κB.[24] Described as the master regulator of the immune response, NF-κB stimulates osteoclastogenesis following activation by RANKL. Expression of RANKL increases following increased levels of TNF-

α and IL-1β.[23] NF-κB may be activated through several mechanisms, but results in gene transcription encoding pro-inflammatory cytokines that propagate inflammatory reactions.[24] In addition to increasing activation of NF-κB, TNF-α has been shown to activate osteoclasts, but in a mechanism independent of RANKL.[23] Increased activation of RANKL has been observed in the periprosthetic tissue of patients with implant loosening.[24] RANKL can in turn increase TNF-α production, which increases NF-κB activation forming a positive feedback loop.[23]

TNF-α may induce paradoxical effects depending on its concentration. It can either promote or suppress osteogenesis.[25] Transient signaling triggers the release of messenger molecules to recruit mesenchymal stem cells necessary for bone regeneration, and promotes matrix mineralization along with IL-1β.[25] High constant levels of TNF-α are damaging to tissues and can induce arthritis-like symptoms in patients.[25] IL-1 works synergistically with TNF-α, as studies demonstrated decreased TNF-α-induced RANKL gene expression in IL-1R deficient cells.[23] Similarly, IL-1 is capable of directly stimulating osteoclastogenesis in the presence of low levels of RANKL.[23] NF-κB, TNF-α, and IL-1 can work synergistically to promote osteoclast differentiation but still mediate proinflammatory effects independent of one another.[23,32] The role of the various cytokines and transcription factor involved in periprosthetic inflammation is important, as many show potential for targeted therapy. The key cytokines and a most potent transcription factor are critically discussed in the following sections.

5.1. TNF-α

Expression of TNF-α is one of the primary inflammatory effects of UHMWPE prosthetic vertebral disc replacement implant wear debris.[28] Despite its known role as a key regulator of particle-mediated implant loosening, targeting of TNF-α has yet to produce viable treatment options. TNF-α inhibitors and small interfering RNA (siRNA) vectors have been studied, but the findings from experimental animals do not correlate with those in clinical cases. Etanercept, a competitive TNF-α inhibitor, abrogated titanium particle induced osteolysis and minimized macrophage mediated cytokine release in a murine model.[33] Despite these encouraging results, the same efficacy has not been translated to clinical practice. Etanercept treatment for prevention of polyethylene wear particle osteolysis in a one-year clinical study failed to outperform placebo. This study only had 20 participants and did not have sufficient statistical power.[34] For definitive conclusions regarding the efficacy of Etanercept, larger clinical with sufficient power are necessary.

Unlike Etanercept, which inhibits TNF-α binding to its receptor, siRNA can be used to selectively inhibit gene expression, and studies by Yu *et al*[35] used an adenoviral vector to deliver siRNA targeting TNF-α expression in mice. Titanium particle induced osteolysis was prevented and osteoclast numbers reduced following siRNA treatment.[35,36] Similarly, other groups have used a lentiviral vector to deliver siRNA in mouse models with resultant decrease in osteolysis in response to titanium or ceramic particles.[37,38] Sun *et al*[39] confirmed that siRNA could effectively inhibit TNF-α expression of human macrophages exposed to titanium particles *in vitro*.[39] Local administration of siRNA has been studied in other diseases, and offers an intriguing treatment option. Local delivery could alleviate side effects

associated with systemic therapies.[40] However, significant barriers including cost and efficacy have prevented translation from the lab into clinical practice.[24] Also, it is important to critically examine and overcome potentially off-target effects, toxicity, and unsafe delivery methods while using siRNA as a potential therapeutic agent.

5.2. IL-1

In addition to TNF-α, IL-1 plays a prominent role in periprosthetic inflammation.[24] TNF-α may regulate IL-1-mediated activation of RANKL and subsequent osteoclastogenesis.[41] In their study, Wei *et al*[41] reported reduced osteoclastogenesis in IL-1 receptor (IL-1R) knockout mice. This suggests that the osteoclastogenic function of TNF-α is regulated, at least in part, by IL-1, but that TNF-α retains independent mechanisms of osteoclast promotion.[41] Correspondingly, Yang *et al*[42] found that increased expression of IL-1R antagonist (IL-1Ra) in a murine model with UHMWPE particles was associated with decreased numbers of osteoclasts, and expression of TNF-α and IL-1.[42] Delivery of the anti-inflammatory cytokine IL-10 had similar effects on osteoclast number and expression of TNF-α and IL-1.[42] Thus, targeting IL-1 may yield therapeutic options to prevent osteolysis. However, no effective translations to clinical use exist, and the IL-1 monotherapy is highly unlikely due to the independent role of TNF-α.

5.3. IL-4

IL-4 opposes the inflammation and osteoclast promoting effects of IL-1 and TNF-α and has shown promise as a clinically useful cytokine for osteolysis prevention.[43,44] IL-4 also prevents osteoclastogenesis by inhibiting NF-κB and MAPK activation in addition to RANKL signaling through an independent mechanism.[45] Adding recombinant IL-4 and OPG minimized polyethylene particle osteolysis in mouse models.[46,47] While IL-4 impairs osteoclastogenesis, its effects on mesenchymal stem cell (MSC) differentiation into osteoblasts are controversial. Impairment of MSC conversion to osteoblasts disrupts the peri-implant balance between osteoclasts and osteoblasts, favoring bone resorption.[48] A study by Lin *et al*[43] reported decreased osteogenesis in a continuous MSCs-secreting IL-4 model, however, Sato *et al*[49] reported that continuous implant release of IL-4 significantly abrogated UHMWPE-induced trabecular loss and improved cortical thickness. It is likely that IL-4 mediates these effects by shifting macrophages from a pro-inflammatory M1 state to a pro-regeneration M2 state.[49] Local recombinant IL-4 administration from drug eluting hydrogel implants could target inflammation and osteoclastogenesis to reduce osteolysis. This potential treatment modality should be further developed.

5.4. NF-κB

NF-κB is a key regulatory molecule in periprosthetic inflammation caused by UHMWPE debris particles.[24] TNF-α, IL-1β and TLRs induce NF-κB expression in chronic inflammatory states. NF-κB promotes inflammation independently, and in concert with TNF-α, and IL-1β. However, NF-κB primarily contributes to aseptic implant loosening by osteoclastogenesis and osteolysis.[24] TNF-α, and IL-1β promote RANKL secretion, activating the classical and alternative NF-κB pathways. NF-κB binds DNA, altering transcription and driving osteoclastogenesis.[24]

Sartori *et al*[50] reported that UHMWPE particles upregulated several pro-inflammatory genes in mouse RAW 264.7 macrophage cell culture. UHMWPE particles induced TNF-α, PGE_2, and NF-κB expression, though IL-6 and IL-1β were not significantly increased.[50] Lipopolysaccharide (LPS) was also added to RAW 264.7 cells. LPS was previously demonstrated to induce inflammation and NF-κB activation in the presence of titanium particles,[51] as well as to impair UHMWPE implant integration with host bone in an *in vivo* rat femur model.[52] LPS increased expression of TNF-α, PGE_2, NF-κB, IL-6 and IL-1β compared to the non LPS groups in RAW 264.7 cells.[50] Sartori *et al*[50] also found that UHMWPE particles promoted osteoclastogenesis even in the absence of RANKL or other factors *in vitro*.[50]

NF-κB modulation using an oligodeoxynucleotide (ODN) decoy holds promise for osteolysis prevention therapy. Lin and Goodman[53] treated murine RAW 264.7, mouse bone marrow derived macrophages, and human macrophage THP1 cells with NF-κB decoy ODN *in vitro*.[53] Decoy ODN contains a NF-κB binding element which competitively inhibits NF-κB from binding promoter regions of inflammatory genes.[53] Similar NF-κB ODN constructs have been used to study other diseases.[54–57] NF-κB ODN reduced macrophage migration and expression of several inflammatory molecules induced by UHMWPE or LPS, including TNF-α, IL-1β, MCP1, MIP1α, IL-8, IL-6, and CXCL1.[53] NF-κB ODN also mitigates the UHMWPE wear debris response *in vivo*. NF-κB ODN sharply increases OPG expression,[58] attenuates TNF-α expression,[53] prevents migration of macrophages and osteoclasts, promotes expression of the IL-1Ra, and correspondingly decreases RANKL secretion. ODN has been shown to improve qualitative calvarial bone mineral density in murine models.[53] ODN abrogates bone density and trabecular volume loss surrounding mouse femur implants continuously releasing UHMWPE particles. ODN also reduces the number of osteoclasts[59] and systemic macrophage migration to the femur implant interface.[60]

MSCs can differentiate into osteoblasts and can mitigate UHMWPE-mediated bone density loss. MSCs may play a vital role in preventing periprosthetic osteolysis.[48,61] NF-κB has been shown to prevent differentiation of MSCs into osteoblasts via degradation of β-catenin.[62] The NF-κB decoy ODN improves the viability of mouse and human MSCs treated with UHMWPE particles and increases OPG expression through a TGF-β-dependent signaling pathway.[63] Inhibition of NF-κB signaling could prevent UHMWPE implant degradation and wear and tear by several mechanisms, including decreasing inflammatory response, promoting osteogenesis, and mitigating osteoclastogenesis.[63] Local ODN administration techniques should be developed for the prevention of UHMWPE-induced periprosthetic inflammation and arthroplasty failure.

6. Chemokines and their Receptors in Cellular Recruitment

In addition to osteoclasts, macrophages play a significant role in osteolysis. Recruitment of systemic monocytes to the implant site is a key step in the progression of the wear debris-induced inflammatory response.[28] Interventions that could reduce numbers of macrophages and osteoclasts could mitigate osteolysis. Monocyte chemoattractant protein-1 (MCP-1), also known as CCL2, drives systemic and local recruitment of monocytes and macrophages

to implant wear debris.[64] CCL2 mediates macrophage recruitment by binding to its receptor CCR2. Gibon *et al*[65] found reduced macrophage invasion and osteolysis in CCR2−/− knockout mice treated with UHMWPE particles.[65] Other studies developed femoral implants with a layer-by-layer coating for local release of the seven-amino acid truncated (7ND) CCL2 mutant protein in mice.[66] CCL2 inhibition with 7ND reduced macrophage invasion at the implant site in response to polyethylene particles.[66] Jiang *et al*[67] confirmed that local 7ND treatment decreases polyethylene induced macrophage and osteoclast numbers in addition to increasing bone density in mouse calvaria models.[67] These findings were replicated in mouse femoral implants by Nabeshima *et al*.[64] Local release of 7ND is an intriguing strategy to prevent CCL2-mediated recruitment of inflammatory cells, and thus could prove to be an effective treatment modality to prevent implant loosening.

CX3CR1 is a chemokine receptor common to mice and human that is expressed on osteoclasts, monocytes, macrophages and cytotoxic T cells. Modulation of the binding of CX3CL1 ligand to CX3CR1 and its signaling pathway has been suggested as a possible treatment for rheumatoid arthritis.[68] CX3CR1$^{-/-}$ (knockout) mice demonstrated decreased levels of macrophage infiltration as well as lower expression of inflammatory markers TNF-α, and IL-1β.[69] Binding of CX3CR1 to the chemokine ligand CX3CL1 contributed to monocyte recruitment in response to UHMWPE debris.[69] Different chemokines for inflammatory cell recruitment are likely to compensate in the absence of CX3CR1, limiting potential efficacy of treatment. However, treatment with targeted blockade of CX3CR1 signaling may mitigate implant loosening and extend implant lifespans.[69]

Alternatively, Gibon *et al*[61] determined that MSC recruitment is driven in part by CCR1 signaling in response to UHMWPE wear debris. The group had previously demonstrated that CCR1 is involved in recruiting macrophages and MSCs in response to polymethylmethacrylate (PMMA) particles.[70] CCR1 is a chemokine receptor that promotes recruitment of macrophages and MSCs. CCR1 receptor antagonism disrupts the ability of MSCs to respond to UHMWPE debris. This impairs the ability of MSCs to balance the osteolytic process, leading to greater bone resorption.[61] Chemokine pathways are vital for recruitment of inflammatory and regenerative cell populations. Therapies aimed at modulating these pathways may improve management of peri-implant inflammation (Figure 1). Development of drug releasing implants for local administration of chemokine modulators could avoid systemic side effects and increase efficacy.[64,66] Macrophage and MSC recruitment to wear particle debris is complex, and various chemokines are involved. Combination treatment targeting multiple chemokine pathways may achieve optimal osteolysis prevention.

7. Inflammatory Response in Discogenic Pain

Intervertebral disc pain is believed to be the product of a messenger cascade that ultimately results in blood vessels and sensory fibers invading the disc.[71–73] Understanding the mechanism of pain associated with degenerative disc disease (DDD) can help provide insight into the mechanism of pain associated with total disc replacement. Several mechanisms resulting in discogenic pain have been investigated. Recent studies suggest that Th17 cells largely contribute to discogenic pain associated with disc herniation and chronic

back pain.[74,75] Cheng *et al*[74] demonstrated in an *in vivo* study that Th17 levels and interleukin-17 (IL-17) levels in the peripheral blood were strongly associated with ruptured lumbar discs and increased levels of pain compared to herniated lumbar discs. Increased IL-17 production could lead to increased PGE_2 secretion resulting in increased pain.[74] Studies by Luchting *et al*[75] further support the importance of Th17 involvement in the pathogenesis of lumbar pain. Investigations into the role of Th17 cells and their mediators may provide useful insight into the pathogenesis of discogenic pain, and wear-debris induced osteolysis. Currently, the most supported mechanism outlining the pathogenesis of discogenic pain involves angiogenesis and neurogenesis.

The release of certain cytokines such as IL-1β stimulates the release of growth factors including nerve growth factor (NGF) and vascular endothelial growth factor (VEGF) which promote neurogenesis and angiogenesis, respectively.[28,71,72,76] Nerve fiber in-growth into previously aneural tissue characterizes the onset of pain.[28,71,72,77,78] DDD has been characterized as three phases that culminate in discogenic pain.[71] The first phase is an initiating event that triggers cytokine release in the nucleus pulposus and annulus fibrosis. The second phase is characterized by inflammation, in-growth of neurons, and angiogenesis. The final phase is sensitization of the nerve endings in the dorsal root ganglia (DRG) resulting in pain.[79] Inflammatory cytokines play a central role in discogenic pain by facilitating changes in nociceptive channel activity and apoptosis of cells in the DRG.[79] Histologic analysis of UHMWPE wear debris on human subjects has been shown to lead to inflammation within the annulus fibrosis.[28,78] Wear-debris-induced inflammation has been shown to be driven by macrophages and osteoclasts, and the ensuing inflammatory milieu results in periprosthetic pain due to the unique neural anatomy of the spine compared to the knee or hip joint.

7.1. Neovascularization and Innervation in the Disc

Binch *et al*[72] hypothesized that nucleus pulposus cells may be responsible for promoting innervation and vascularization of the disc by secreting various neurotropic and angiogenic factors. Secretion of neurotropic factors and upregulation of their respective receptors have been shown to be modulated by cytokines.[66] Neurotropic factors include NGF, brain derived neurotropic factor (BDNF), and neurotrophin 3 (NT3). Receptors include tropomysin receptor kinase (trk) A, B and C. Blood vessels extensively infiltrate into degenerative nucleus pulposus tissue following signals from VEGF and pleiotrophin. Increased levels of pain-related peptides, include substance P and calcitonin gene related peptide (CGRP), have been observed in patients demonstrating periprosthetic pain.[66] Normally, only the outer third of the annulus fibrosis is innervated. Actively growing unmyelinated pain fibers using substance P as its neurotransmitter characterize the pain observed in discogenic pain.[71] NGF promotes growth and survival of unmyelinated fibers, and was the first neurotropic cytokine to be described in discogenic pain along with its high affinity receptor trk-A.[71]

Expression of NGFβ along with trk-A was found in disc cells in patients who had painful intervertebral discs (IVDs) with in-growing nerves. Additionally, NGFβ was found to be expressed by invasive microvasculature within the IVD with accompanying unmyelinated fibers. This finding suggests the role of NGFβ production in driving the nerve growth and

was substantiated by the findings of Freemont *et al*[71] who showed that unmyelinated nerve fibers grow into the IVD in response to local NGF signaling. The nerves accompanying those vessels actively express trk-A, and are believed to be the major contributor to pain in the IVD.[71] Trk-A stimulated neurons activate signaling cascades leading to neuron growth, survival, and differentiation.[71] Genetic analysis of trk-A revealed the critical effect of different polymorphisms resulting in receptor abnormalities for congenital insensitivity to pain. Further bodies of evidence have implicated trk-A in pain regulation.[71] The hypothesis that discogenic pain results from and is modulated by increased trk-A activation through NGF signaling is gaining further support.

Release of NGF is required to potentiate signal cascades through trk-A, and studies by Krock *et al*[76] demonstrated NGF expression in IVDs is regulated by toll-like receptor 2 (TLR-2) activation. IL-1β and TNFα have been known to increase levels of NGF and BDNF in isolated disc cells, and TLR activation has been shown to increase levels of IL-1β in disc cells.[76] Krock *et al*[76] found that IL-1β stimulation of TLR2 increased NGF expression at all-time points, while TNF-α stimulation promoted early NGF expression when compared to untreated cells. Exposure to inflammatory cytokines induces NGF production and is the first step leading to neural growth and pain. Additionally, IL-1β significantly increases VEGF. VEGF expression potentiates the ingrowth of endothelial cells which have been shown to express NGF and further promote innervation within the IVD.[72] Following TLR2 activation, NF-κB potentiates the signal cascade resulting in NGF expression.[76] Alarmins, or damage-associated molecular proteins from extracellular debris, may also activate TLR2 in addition to inflammatory cytokines. Alarmin-induced activation of NF-κB promotes NGF expression. Additionally, NF-κB activation also leads to the expression of IL-1β, which could further stimulate TLR2 in an autocrine fashion and create a positive feedback loop.[76] An *in vitro* study by *Binch et al*[72] suggests IL-1β is the key regulatory cytokine involved in the innervation and vascularization of IVDs, while the major signaling component responsible for expression of NGF is NF-κB. Inhibition of NF-κB activation could serve as a therapeutic target by decreasing expression of NGF and subsequent discogenic pain.[76] Chronic pain associated with total disc replacement follows a similar mechanism to that seen in DDD. Potential therapeutic targets include inhibition of NF-κB and TLR-2.

Fibroblasts play a key role in the development of neuropathic pain in total disc replacements by promoting angiogenesis within periprosthetic tissue.[80] Fibroblasts play an active role in osteolysis following stimulation by prosthetic wear debris and cytokines produced by macrophages. Stimulation of the fibroblast leads to suppression of osteoblasts and activation of osteoclasts.[80] Fibroblasts from periprosthetic tissues respond more aggressively to particular wear debris and create a more osteolytic response. In contrast, fibroblasts from normal synovial tissues do not respond as aggressively when introduced to wear debris in a laboratory setting.[80] The reason behind the increased response in periprosthetic fibroblasts is currently unknown.[80]

A study conducted by Veruva *et al*[28] determined the amount of wear particles from UHMWPE debris strongly correlated with the levels of TNFα, IL-1β, VEGF, NGF, substance P, macrophages and blood vessels in patients with periprosthetic pain in human subjects using immunohistochemistry. UHMWPE wear debris is linked to an increased

inflammatory response within the lumbar spine leading to osteolysis and pain, the major reason for joint revision.[28] Wear debris induces pain through the same process observed in DDD by recruiting vasculature and unmyelinated fibers to the lumbar spine. Wear debris may play a larger role in facilitating pain, as IL-1β, VEGF, and substance P were expressed to a higher extent in the total disc replacement tissues compared to tissues from patients with DDD.[28] Furthermore, the mode of wear debris affects inflammatory response and biological activity. Baxter *et al*[77] showed that debris generated by impingement, unintended articulation between nonbearing surfaces, generated a significant and unexpected biological response.[77] Many wear modalities result in an inflammatory response and osteolysis, but wear induced by impingement results in larger and more numerous debris particles. Therefore, implant impingement may be associated with negative consequences such as pain.[77] Inflammatory cells such as macrophages contribute to the onset of pain, but persistent pain is driven by invading blood vessels. Veruva *et al*[25] found increased levels of IL-1β, VEGF, NGF, and substance P correlated with increased numbers of blood vessels.[28] When blood vessels were removed, a >25% decrease in NGF, and substance P within the IVD was observed[25]. It was inferred that NGF is largely produced by endothelial cells and vascular smooth muscle cells.

Thus, targeting VEGF may serve as a potential therapy for periprosthetic pain, but more research is warranted to support its efficacy. Linking wear-induced inflammation, innervation, and pain with vascularization provides important insight that could contribute to our understanding of the pathogenesis of lumbar discogenic pain.[28] Studies indicate wear-debris in the lumbar spine initiates a cascade that begins with fibroblast activation, macrophage infiltration, increased vascularization, and ultimately ends with innervation and nociception (Figure 2).[28] Wear debris-induced inflammation and osteolysis has been documented in hip and knee joint arthroplasty but has not been associated with pain. The association of osteolysis and pain in lumbar total disc replacement appears to be a mechanism unique to the spine.[28] Current treatments to mitigate lumbar pain include anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs (NSAIDs), steroidal injections and physical therapy.[81] Other therapies, such as bisphosphonates have been proposed and shown promise in pilot studies, but require clinical trials for further investigation.[82] Goodman *et al*[83] proposed novel biologic strategies targeting macrophage trafficking to the implant site, increased polarization of macrophages from M1 to the M2 phenotype, and local inhibition of NF-κB transcription factor by decoy ODN have shown significant promise in preclinical studies and should prompt further investigation as therapeutic agents.

7.2. Prosthetic Loading in Total Disc Replacement

The most common indications for total disc replacement are to maintain spine mobility and mitigate pain.[84] In addition to immunologic stimulus for pain, different biomechanical loading patterns following a lumbar total disc replacement may also contribute to persistent pain.[81] Pain patterns, described by Siepe,[84] begin with lumbar facet or sacroiliac pain, and are the most common reason for unsatisfactory results following disc replacement surgery.[84] Patients with early onset pain (less than 6 months following procedure) have a significantly higher risk of developing persistent problems. Suboptimal outcomes and higher incidences

of posterior joint pain were observed for arthroplasties at the L5-S1 level, and combined arthroplasty of the L4-L5 and L5-S1 levels.[84] The manner in which the prosthesis bears forces could have potential effects on pain. Fixed bearing devises showed increased vascularization in tissues with wear and necrosis than in tissues without wear. Comparatively, mobile bearing lumbar total disc replacements demonstrated low-to-moderate vascularization and necrosis.[78] Loading analysis following total disc replacements demonstrated increased facet loading and decreased motion compared to adjacent spinal segments due to disruption of stabilizing ligaments during surgery.[81] Pain refractory to conventional treatment such as injection and physical therapy, may be treated with spinal cord stimulation to achieve better outcomes.[81]

8. Conclusions

The general sequence describing periprosthetic inflammation in joint arthroplasty following knee or hip replacement is the formation of polyethylene debris due to wear. This debris induces an inflammatory response that primarily involves cells in the monocyte and osteoclast lineage, but prolonged inflammation can also involve fibroblasts and potentially other cells, including lymphocytes. Activated macrophages and osteoclasts release cytokines such as TNF-α, and IL-1. These signals suppress osteoblastic cytokines such as OPG, and activate NF-κB, the transcription factor which has the greatest control over the inflammatory response. A positive feedback loop between those cell lines, NF-κB, and cytokines result in a dysregulation of homeostasis promoting bone resorption and continuous inflammation of adjacent tissues. Bone loss and weakening of adjacent tissues ultimately leads to implant loosening and failure. Periprosthetic pain following lumbar total disc replacement could result from immunologic and biomechanical mechanisms. Immunobiologic pain following total disc replacement follows a similar mechanism to chronic pain experienced in DDD. Wear-induced debris particles as opposed to fragments from the extracellular matrix initiate an inflammatory cascade which facilitates angiogenesis. Microvessels invading the IVD or periprosthetic tissue release a variety of factors, the most important being NGF to drive the growth of unmyelinated fibers alongside the new vessels. Unmyelinated fibers can then relay the sensation of pain. The process associating osteolysis and pain is unique to the lumbar spine and has not been observed in arthroplasties of other joints including the knee and hip. Therapy to mitigate chronic lumbar pain following a total disc replacement includes injection and physical therapy, arthroplasty revision surgery, and spinal cord stimulation.

Expert Commentary and Five-Year View

Periprosthetic inflammation and subsequent aseptic implant loosening appear to be mediated by similar mechanisms in total disc replacements and arthroplasties of other joints, including the knee and hip. Aseptic loosening is a major cause of implant failure and revision surgery in various joints. Immunological treatment preventing inflammation and implant loosening would improve quality of life, decrease associated costs, and reduce the need for arthroplasty revision procedures. Targeting the molecular mediators of inflammation such as TNF- α with Etanercept has yet to yield efficacious prevention of clinical osteolysis. However, recent pre-clinical research suggests there are several potential immunobiological targets which warrant further investigation. The use of siRNA to reduce inflammatory

signaling, anti-inflammatory cytokines such as IL-4, and the creation of ODN constructs to inhibit NF-κB activity are potential treatment modalities. Further development is needed before these techniques can be tested in the clinical setting. Modulation of cell recruitment is another area that needs further study. Limiting invasion of inflammatory cells including macrophages and osteoclasts and enhancing MSC differentiation to osteoblasts could restore the periprosthetic balance between bone deposition and breakdown. The complex periprosthetic inflammatory signaling and the associated cellular interactions appear to mediate osteolysis and implant loosening by several reinforcing, and independent mechanisms. It is probable that the most clinically efficacious strategies will include a combination of immunological targets.

Current challenges to the progression of joint replacement osteolysis prevention include the possible insufficiency of mouse research models in faithfully replicating human conditions. Potential immunological differences may exist between species. Additionally, no model has thus far analyzed the effects of arthroplasty implants over a period of time analogous to the lifespan of standard human arthroplasties. Finally, mouse wear debris models may not replicate the conditions of *in vivo* human joint implants, specifically the conditions native to human total disc replacement implants.

In the next five years, techniques abrogating the inflammatory response and preventing recruitment of macrophages and osteoclasts should continue to progress. Some of these modalities have been more extensively developed than others at this point. However, the transition from bench research to human clinical experimentation should be well underway within next 5-years.

Osteolysis has been observed in nearly all arthroplasty locations, but periprosthetic pain remains unique to the spine. The most common reason for total disc replacements is pain, and pain following revision is often a cause for failure. The production of wear debris and the chronic inflammatory response are common to nearly all arthroplasties. Affecting changes in the amount and quality of debris and mitigation of the chronic inflammatory response may reduce pain. Recent studies investigating materials other than UHMWPE such as Polyetheretherketone (PEEK) have not demonstrated a significant reduction in wear debris. Exploring the properties of other materials is encouraged and may result in less wear and benefit arthroplasties in the knee and hip in addition to the spine. While inflammatory signals have been demonstrated to play a role in periprosthetic pain, neovascularization appears to be the cornerstone of the new onset pain. General strategies mitigating inflammatory cytokines have shown limited success. A novel strategy targeting vasculature may yield the greatest benefit. Neovascularization of the disc and subsequent innervation are the only steps distinguishing osteolysis in the lumbar spine from osteolysis in other joints.

The next five years should demonstrate increased investigation into the inhibition of neovascularization of spinal discs. The proposed etiology of discogenic pain in DDD and periprosthetic pain appears to follow the same mechanism. If successful, medical therapies targeting neovascularization may benefit those with painful DDD and prevent the need for total disc replacements in addition to mitigating periprosthetic pain. Current studies use immunohistochemistry to quantify the levels of messengers within the intervertebral disc.

Transitioning to in vivo models may be the next step in order to attempt therapeutic approaches.

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Reference annotations

*Of interest

**Of considerable interest

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Key Issues

- UHMWPE is the current gold standard material for use in total disc replacements, however wear on the prosthesis triggers inflammatory responses resulting in osteolysis, pain, and implant failure.
- Macrophages and fibroblasts play the largest role in the pathophysiology of inflammation, osteolysis, and pain in total disc replacement.
- Several mediators including IL-1β, TNFα, NF-κB, and CCL2 have been demonstrated to play a role in chronic periprosthetic inflammation and osteolysis. Current therapies targeting those have not yet been shown to be successful.
- Recent evidence suggest neovascularization into the disc and secretion of neurotropic messengers by those vascular endothelial cells are responsible for periprosthetic pain following lumbar total disc replacement.

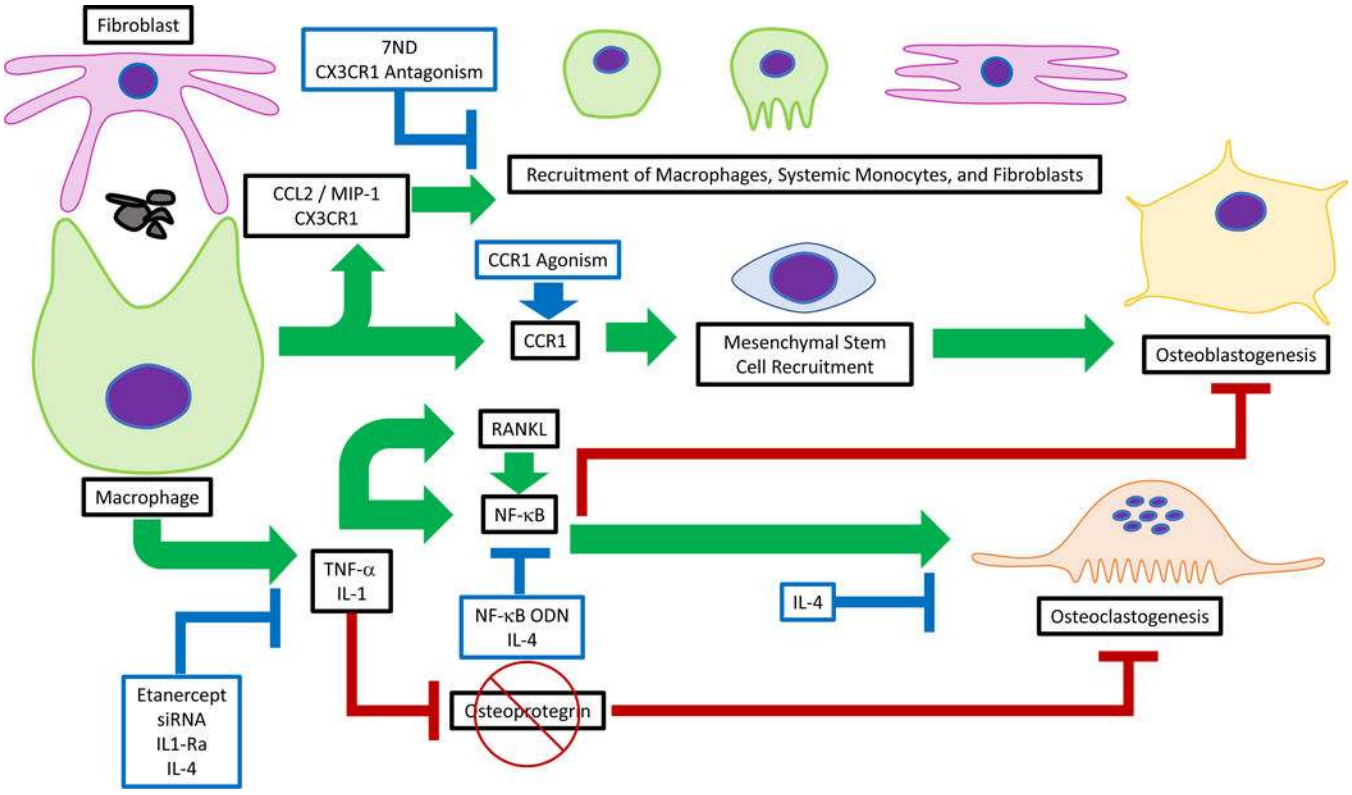

Figure 1:

This schematic diagram depicts various interactions between cells and mediators leading to bone remodeling following exposure to UHMWPHE wear debris. The green arrows demonstrate an activating response; the red lines represent inhibiting response; and the blue boxes and arrows demonstrate possible sites for therapeutic agents. A blue arrow demonstrates activation of a substrate while a bar demonstrates inhibition. Macrophage and fibroblast activation by UHMWPE wear debris initiates inflammatory signaling mediated by tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1). TNF-α and IL-1 activate receptor activator of nuclear factor kappa-B ligand (RANKL) and nuclear factor kappa-B (NF-κB) while preventing osteoprotegrin activity. This interaction promotes osteoclastogenesis and inhibits osteoblast formation. Treatment with Etanercept or small interfering RNA (siRNA) targeted inhibition of TNF-α, IL-1 receptor antagonism, IL-4, and NF-κB inhibition with oligodeoxynucleotide (ODN) reduce inflammatory signaling and osteoclastogenesis. Macrophage release of chemokine ligand 2/monocyte chemoattractant protein-1 (CCL2/MCP-1) and Chemokine (C-X3-C Motif) Receptor 1 (CX3CR1) recruit local macrophages, systemic monocytes, and fibroblasts. CX3CR1 antagonism and 7ND, a CCL2/MCP-1 mutant protein, reduce recruitment of inflammatory cells. Macrophage expression of CCR1 drives recruitment of mesenchymal stem cells which may differentiate into osteoblasts.

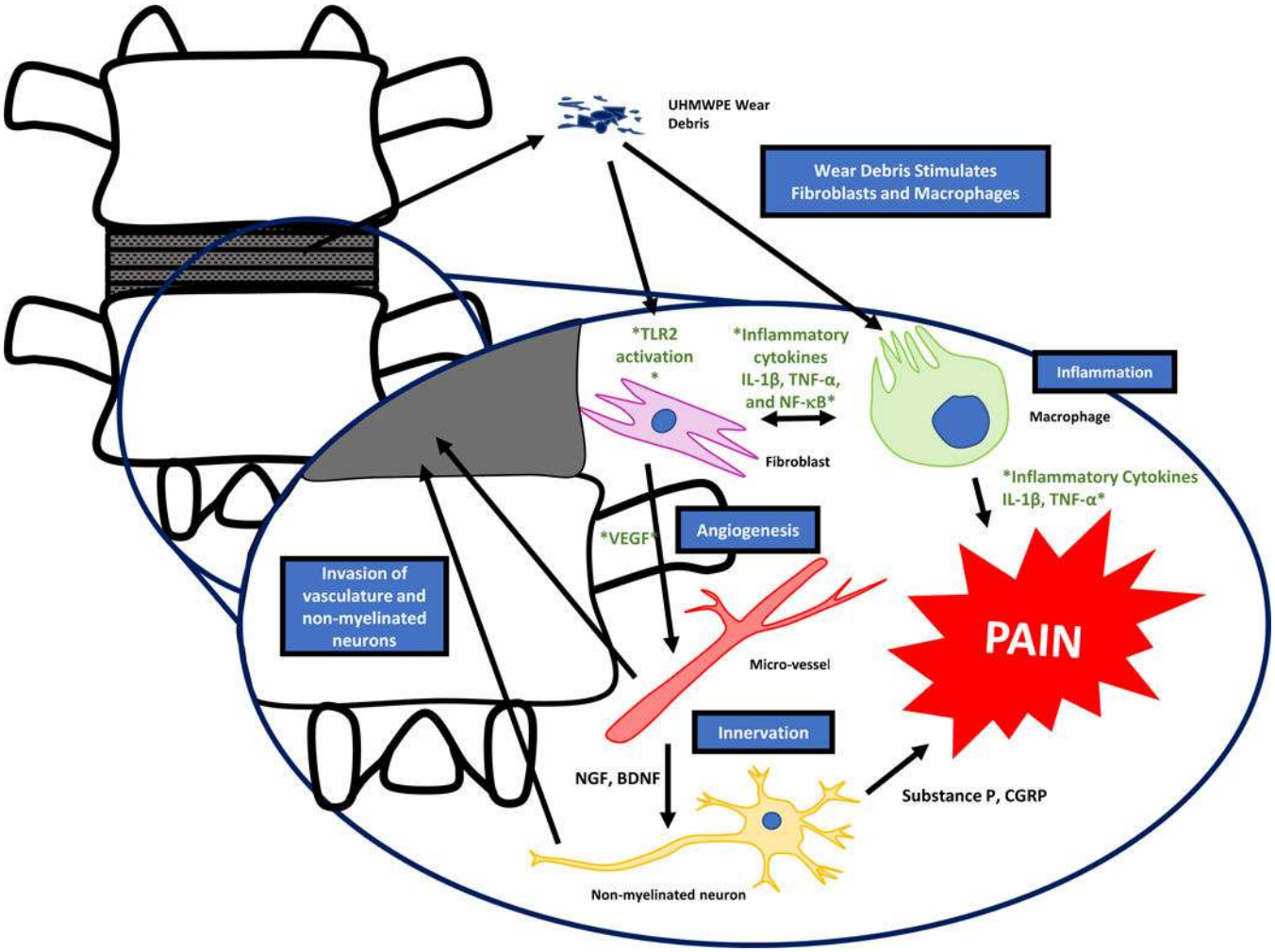

Figure 2:

The schematic diagram depicts the signaling cascade believed to result in periprosthetic pain following a lumbar total disc replacement. Wear debris activates macrophages and fibroblasts through toll-like receptor 2 (TLR2) and leads to the secretion of several cytokines including interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and activation of the transcription factor nuclear factor-kappa B (NF-κB). Those factors propagate an inflammatory response which could result in pain. Activated fibroblasts and nucleus pulposus (NP) cells may also secrete vascular endothelial growth factor (VEGF) resulting in neovascularization of the disc. The endothelial cells of the new vessels secrete neurotropic factors nerve growth factor (NGF) and brain derived neurotropic factor (BDNF) resulting in neural invasion of the disc alongside the new vessels. The new nerves are unmyelinated and can convey nociceptive signals via substance P and calcitonin gene related peptide (CGRP). Transmission of those signals to the dorsal root ganglion (DRG) can result in pain. The steps highlighted in green represent potential therapeutic targets. Inhibition of inflammatory cytokines IL-1β, TNF-α, and transcription factor NF-κB have been proposed to have therapeutic effect. Additionally, inhibition of TLR2 though receptor antagonists, and VEGF antagonists may also have a role in pain reduction.