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REVIEW

Involvement of NF-κB/NLRP3 axis in the progression of aseptic loosening of total joint arthroplasties: a review of molecular mechanisms

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Abstract

Particulate wear debris can trigger pro-inflammatory bone resorption and result in aseptic loosening. This complication remains major postoperative discomforts and complications for patients who underwent total joint arthroplasty. Recent studies have indicated that wear debris-induced aseptic loosening is associated with the overproduction of pro-inflammatory cytokines. The activation of osteoclasts as a result of inflammatory responses is associated with osteolysis. Moreover, stimulation of inflammatory signaling pathways such as the NF-κB/NLRP3 axis results in the production of pro-inflammatory cytokines. In this review, we first summarized the potential inflammatory mechanisms of wear particle-induced peri-implant osteolysis. Then, the therapeutic approaches, e.g., biological inhibitors, herbal products, and stem cells or their derivatives, with the ability to suppress the inflammatory responses, mainly NF-κB/NLRP3 signaling pathways, were discussed. Based on the results, activation of macrophages following inflammatory stimuli, overproduction of pro-inflammatory cytokines, and subsequent differentiation of osteoclasts in the presence of wear particles lead to bone resorption. The activation of NF-κB/NLRP3 signaling pathways within the macrophages stimulates the production of pro-inflammatory cytokines, e.g., IL-1β, IL-6, and TNF-α. According to in vitro and in vivo studies, novel therapeutics significantly promoted osteogenesis, suppressed osteoclastogenesis, and diminished particle-mediated bone resorption. Conclusively, these findings offer that suppressing pro-inflammatory cytokines by regulating both NF-κB and NLRP3 inflammasome represents a novel approach to attenuate wear-particle-related osteolytic diseases.

Keywords Wear particle · Aseptic loosening · Total joint arthroplasty · Inflammation · NF-κB · NLRP3

Introduction

Total joint arthroplasty (TJA) is a surgical procedure to remove a part or whole damaged joint (knee, hip, shoulder, fingers, etc.) and replace it with appropriate materials. Over past decades, it has been considered one of the most effective orthopedic surgical interventions and the gold-standard treatment in patients with end-stage osteoarthritis to relieve pain, correct deformities, and improve mobility (Bumpass and Nunley 2012; Mandl et al. 2018; Mehdipour et al. 2020). It has been estimated that about 570,000 total knee arthroplasty (TKA) and 1.28 million total hip arthroplasty (THA) will be performed annually by 2030 alone in the USA (Steven Kurtz et al. 2007; Sloan et al. 2018). This procedure remarkably relieves pain, improves function, and promotes the quality of life in patients (Skou et al. 2015; Sanei et al. 2016; Mehdipour et al. 2020). Nowadays, the usual patient age for THA and TKA has been estimated to be less than 65 years (Kurtz et al. 2009). The success of TJA varies associated with the type and severity of deformities. Patient satisfaction was reported in 90.3% of patients at 1 year after TKA surgery (Harris et al. 2013), and the 10-year survival rate of 90 to 95% was demonstrated (Abdel et al. 2011). Recently, the number of younger patients receiving TJA has dramatically risen (Losina et al. 2012; Ravi et al. 2012). Unfortunately, the component wear and loosening rate is higher in these younger patients as a more active population

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(Lübbeke et al. 2011; Camus and Long 2018). Aseptic loosening is the most common cause of the late failure of TKA, with assessed occurrence approximately 15–20% of cases in a 20-year time period of time (Sharkey et al. 2014). Nonetheless, more than 10–20% of patients need revision TJA due to loosening associated with well-documented biological and mechanical factors (Sloan et al. 2018; Milošev et al. 2006; Langton et al. 2010). The generation of micro/nano-scale wear debris due to mechanical forces and biological interactions leads to the local inflammation and activation of macrophages, multinucleated foreign-body giant cells (FBGCs), T cells, and B cells (Vasconcelos et al. 2016). FBGCs are formed by the fusion of macrophages (giant cells) generated in response to the presence of a large particle, which notably contributes to peri-implant osteolysis (bone resorption), leading to aseptic loosening (Sheikh et al. 2015; Camus and Long 2018). Aseptic loosening of prosthetic components following osteoclastic resorption is the most common cause of revision surgeries (Revell 2008). The slow inflammatory responses are primarily associated with macrophages/monocyte phagocytosis of metal particles (Goodman 2007). Despite establishing various types of aseptic loosening models, the precise molecular mechanism underlying wear debris-associated activation of macrophages remains unknown. Pro-inflammatory cytokines, e.g., interleukin (IL)-1β, are the most potent factors produced by metal particle-stimulated macrophages (Mohammed et al. 2020; Landgraeber et al. 2014). Among all kinds of inflammasomes, the NOD-like receptor (NLR) family pyrin domain containing 3 (NLRP3) is a large intracellular molecular that mediates the cleavage of pro-IL-1β and pro-IL-18 into active IL-1β and IL-18 by activated caspase-1 (Casp1) (Mohammed et al. 2020). Metal debris acts as a danger signal and stimulates the NLRP3 inflammasome in the macrophages (Jämsen et al. 2020). Likewise, wear particle-induced periprosthetic inflammation activates nuclear factor κB (NF-κB). This transcription factor that mediates a large array of genes, e.g., NLRP3, involves in the regulation of pro-inflammatory cytokines (Bauernfeind et al. 2009). These molecular events participate in the pathophysiology of the aseptic prosthesis loosening.

Therefore, targeting NF-κB/NLRP3 axis has attracted attention as a potential approach for alleviating the activation of macrophages, resulting in reduced risk of aseptic loosening. The presented review aimed to demonstrate the association of NF-κB/NLRP3 signaling pathways with aseptic loosening after primary TJA. Furthermore, the potential strategies with the ability to regulate inflammatory responses for treating aseptic loosening were summarized (Table 1).

Pathological features of aseptic loosening

Metal particles with different shapes and sizes are formed at areas of impingement, modular interfaces, prosthetic joint articulations, and non-articulating interfaces (Goldring et al. 1993). The wear particles are rarely larger than 5 μm in diameter. The results indicated that the cellular responses to metal debris might depend on the size, shape, charge, structure, composition, and number of particles (González et al. 1996; Sabokbar et al. 2003). The etiology of hypersensitivity and immune responses to metal implant debris in TJAs remains uncertain. It has been identified that reactions to metal implant particles are an important cause of implant failure (Reito et al. 2016). Implant debris induces a broad range of pathologic reactions in the peri-prosthetic soft tissue, including metallosis, peri-osteal soft tissue tumor, allergic reactions, and toxicity responses (Daniel et al. 2012; Natu et al. 2012). Orthopedic implants are commonly composed of metals, e.g., nickel (Ni), chromium (Cr), and cobalt (Co) (Kręcisz et al. 2012). The most frequent metal sensitizer of clinical relevance is Ni followed by Co and Cr. These metals are most often associated with hypersensitivity reactions (Merritt et al. 1996; Duarte et al. 2018). Corrosion mechanisms in metal implants in contact with biological systems lead to the generation of degradation products such as soluble metal ions and particulate (Wawrzynski et al. 2017). The wear debris-induced pathogenic features are associated with inflammatory responses and osteolytic processes (Longhofer et al. 2017). The particulate debris induces chronic inflammatory responses mediated by various cell types, including lymphocytes, fibroblasts, macrophages, FBGCs, neutrophils, and — most prominently — osteoclasts (Abu-Amer et al. 2007). The higher level of inflammatory factors is associated with activation of osteoclast, exacerbation of osteoclastogenesis, and finally promotion of osteolysis in the metal-bone interface regions (Hirashima et al. 2001; Jiang et al. 2013). The aseptic lymphocyte-dominated vasculitis-related lesions after metal-on-metal (MOM) arthroplasties are characterized by the fibrin deposition, presence of macrophages containing phagocytize debris, peri-vascular infiltration of lymphocytes, and necrosis in the peri-implant tissues (Willert et al. 2005a; Khawaja et al. 2017; Langton et al. 2018b). These lesions result from elevated levels of metal ions in the joint fluid of MOM bearings (Langton et al. 2018a).

A growing body of evidence has confirmed that implant failure is linked to implant-related metal hypersensitivity (Hallab et al. 2004; Davies et al. 2005). It was found that interferon-gamma (IFN-γ) released from Th1 cell is prominently associated with metal-induced hypersensitivity

Table 1 Targeting inflammatory responses for alleviation of metal debris-induced aseptic loosening

Authors (year)	Model	Particles	Treatment/dosage	Main results
Ren et al. (2006)	In vitro RAW 264.7 Mouse BMDMs	PMMA + UHMWPE RANKL	Erythromycin (5 μg/ml)	-Inhibited expression of CPK, NF-κB, IL-1β, and TNFα -Decreased DNA-binding activity of NF-κB -Suppressed osteoclastogenesis and reduced number of $TRAP^+$ cells
Clohisy et al. (2006)	In vivo Male BALB/c mice In vitro Mouse BMDMs	PMMA	NBD peptide RANKL	-Inhibited NF-κB activity -Reduced number of osteoclasts -Arrested osteoclastogenesis
Ren et al. (2007)	In vivo Female BALB/c mice	UHMWPE	VEGF inhibitor (5 μg/kg/day, intra-pouch injection, 2 weeks)	-Inhibited inflammatory responses (reduced the membrane proliferation, inflammatory cells, and expression of TNF-α and IL-1β) -Reduced the number of $TRAP^+$ cells and -Regulated bone resorption (loss of bone collagen content and bone erosions)
Chen et al. (2012)	In vivo Female BALB/c mice	Ti	Tetracycline (50 mg/kg/IP)	-Inhibited inflammatory osteolysis -Downregulated MMP-9, TNF-α, RANK, and RANK -Reduced number of $TRAP^+$ cells (osteoclast-like cells)
Yang et al. (2012)	In vivo Female BALB/c mice In vitro RAW264.7 cell line	UHMWPE UHMWPE	*Angelica sinensis* (50 and 500 mg/kg) *Angelica sinensis* (50 and 200 mg/L)	-Inhibited TNF-α and IL-1β -Reduced the osteoclast numbers and osteolysis area -Reduced bone resorption -Inhibited TNF-α and IL-1β
Lin et al. (2014)	In vitro -Primary mouse and human macrophages -Mouse RAW 264.7 and human THP1 macrophage cell lines	UHMWPE	NF-κB decoy oligodeoxynucleotide	-Suppressed production of chemokine and pro-inflammatory mediators (e.g., MCP1, MIP1α, and TNF-α)
Sato et al. (2015)	In vivo Male C57BL/6 mice	Polyethylene	NF-κB decoy oligodeoxynucleotide	-Suppressed inflammation via regulation of TNF-α, RANKL, IL-1 receptor antagonist, and OPG
Jiang et al. (2016)	In vivo Male BALB/c mice	UHMWPE	CCL2 proteins, 7ND (1 μg in 50 μl of PBS, local injection)	-Suppressed bone loss (increased bone healing and bone mineral density) -Reduced osteoclasts ($TRAP^+$ cells)and inflammatory cells ($CD11b^+$ cells, macrophages)
Wang et al. (2016)	In vivo Female BALB/c mice In vitro BMDMs RAW264.7 cells	Ti RANKL	siRNA targeting CXCR2	-Inhibited osteolysis (improved BV/TV, BMD, and total porosity) -Inhibited CXCR2 expression -Suppressed osteoclast formation (reduced number of $TRAP^+$ cells) - Regulated the secretion of RANKL and OPG expression in osteoblasts

Table 1 (continued)

Authors (year)	Model	Particles	Treatment/dosage	Main results
Ping et al. (2017)	In vivo C57BL/6 J male mice In vitro BMDMs	Ti RNKL	Melatonin (5 and 50 mg/kg/IP for 4 weeks) Melatonin (0.0, 0.25, 0.5, and 1.0 mM for 4 h)	-Reduced osteolysis -Decreased levels of TNF-α, IL-1β, and IL-6 -TNF-α, IL-1β, IL-6, and p65 -Suppressed NF-κB cascade (regulation of p-IκBα, p65, and p-p65) -Attenuated the number of osteoclasts ($TRAP^+$ cells) -Reduced osteoclastogenesis -Inhibited osteoclastic F-actin ring formation -Decreased osteoclastic resorption
Wu et al. (2021)	In vivo Male C57BL/6 J mice In vitro BMDMs	Ti Ti, LPS	Melatonin (0.4 mg/ml in drinking water) Butyrate?	-Reduced osteolysis -Improved bone erosion markers (BV/TV, BMD, and total porosity) -Reduced osteoclast activation regulation of gut microbiota function in the activation of butyrate and its receptor GPR109A - Modulated protein levels of IL-1β NLRP3, and caspase-1
Li et al. (2021)	In vivo Female C57BL/6 J mice In vitro BMSCs RAW264.7 cells	UHMWPE RANKL	EV local injection	-Reduced generation of inflammatory mediators -Decreased osteolysis -Promoted the osteogenic differentiation -Decreased pro-inflammatory factor production and osteoclastic activity

Ti titanium, *UHMWPE* ultrahigh molecular weight polyethylene, *PMMA* polymethyl methacrylate, *IP* intraperitoneal, *BMDMs* bone marrow-derived macrophages, *BV/TV* bone volume to tissue volume ratio, *BMD* bone mineral density, *EVs* extracellular vesicles, *VEGF* vascular endothelial grow factor, *IL* interleukin, *TNF* tumor necrosis factor, *CPK* cathepsin K, *MMP-9* matrix metalloproteinase-9, *TNF-α* tumor necrosis factor-α, *TRAP* resistant acid phosphate, *NF-κB* nuclear factor-kappaB, *RANK* receptor activator of NF-κB, *MCP1* monocyte chemoattractant protein 1, *MIP1α* macrophage inflammatory protein 1-alpha, *RANKL* receptor activator of NF-κB ligand, *OPG* osteoprotegerin, *NBD* NEMO-binding domain

(Willert et al. 2005b; Hallab et al. 2008). Moreover, high concentrations of local metal debris in patients with failed MOM-THA were noted to increase metal reactivity and allergic reactions along with peri-prosthetic T cell-mediated inflammation (Thomas et al. 2009). In order to induce direct reactions, wear debris also activates lymphocytes to regulate the secretion of pro-inflammatory and osteoclastogenic mediators, including macrophage colony-stimulating factor (M-CSF), activator NF-κB ligand (RANKL), and IL-17A (Chen et al. 2019). On the other hand, a variety of substances are secreted by macrophages in response to implant materials, including chemotactic mediators (e.g., IL-8, CCL3, and CCL2), pro-inflammatory cytokines (e.g., IL-1β, IL-6, tumor necrosis factor-alpha [TNF-α], and prostaglandin E2), and growth factors (e.g., M-CSF and vascular endothelial growth factor [VEGF]). These factors are involved in the RANKL-mediated osteoclastogenesis, leading to bone resorption (Holt et al. 2007; Goodman and Ma 2010; Fuller et al. 2002). Osteoclastogenesis is a multi-complex procedure accompanied by the formation of osteoclasts from monocyte/macrophage precursors and overexpression of both RANK and RANKL genes (Collin-Osdoby and Osdoby 2012; Xu and Teitelbaum 2013). Osteoprotegerin (OPG) is a soluble decoy receptor for RANKL secreted by osteoblasts. It can suppress RANKL signaling pathways (Boyce and Xing 2007). Therefore, specific profiles of inflammation mediators play an essential role in the pathogenesis of metal debris-induced osteolysis.

Several studies have been investigated primarily on cell lines or murine macrophages. Wear debris-stimulated immune cells prominently produce chemokines and

cytokines, promoting osteoclastogenesis and osteolysis (Jämsen et al. 2020). Previous in vitro and in vivo studies demonstrated that TNF-α could boost osteoclast differentiation from precursor cells by the upregulation of RANKL (Kitaura et al. 2022, 2004; Wei et al. 2005). Furthermore, IL-8 is a chemokine that contributes to the migration of monocytes/macrophages to the peri-prosthetic region (Gu et al. 2012). Particulate debris-induced macrophage activation and resorption loss are also controlled by CCL2 (C–C motif chemokine ligand 2)-CCR2 (C–C Motif Chemokine Receptor 2)/CCR4 axis (Gibon et al. 2012a).

Molecular investigations demonstrated that bone implantation particles upregulated TNF-α and promoted the function of osteoclasts in the productions of matrix metalloproteinase-9 (MMP-9), resulting in a significant inflammatory reaction (Laquerriere et al. 2004; Dapunt et al. 2014). IL-1β promotes osteoclast function and involves the pathogenesis of aseptic loosening (Shiratori et al. 2018). In another study, it was shown that the upregulation of TNF-α, RANK, and RANKL was correlated with peri-prosthetic bone loss following THA (Holding et al. 2006). The secretion of IL-1β is mediated by activation of NLRP3 protein and subsequent aggregation of an intracellular complex of NLRP3 inflammasome (Nikmehr et al. 2017). The interactions between the components of the NLRP3 inflammasome, including NLRP3 protein, adaptor proteins ASC (apoptosis-associated speck-like protein containing a caspase-recruitment domain), and pro-Casp1, causes cleavage and activation of Casp1. Finally, active Casp1 converts pro-IL-1β and pro-IL-18 into the mature form of IL-1β and IL-18 (Bazrafkan et al. 2018). The NLRPs can be activated by a wide range of danger-associated molecular patterns (DAMP) and pathogen-associated molecular patterns (PAMP) (Dostert et al. 2009). During priming stimuli, toll-like receptors (TLRs), a family member of pattern recognition receptors, are able to recognize DAMP/DAMP, leading to the activation transcription factors, e.g., NF-κB (Yang et al. 2020). One pathway that contributes to the inflammasome activation is related to NF-κB signaling pathways. Additionally, NF-κB itself mediates the synthesis of pro-IL-1 β, pro-IL-18, and NLRP3 (Kelley et al. 2019). NLRP3, a sensor of cellular stress, recognizes different DAMPs in the cytosol of antigen-presenting cells and directly activates the inflammatory cascades following contact with metal debris (Caicedo et al. 2009; Jacobs et al. 2006). It was reported that some particulate materials, e.g., silica and asbestos, can stimulate the NLRP3 aggregation and activation of the inflammasome complex, mediating the production of IL-1β and IL-18 (Jo et al. 2016). A growing body of literature has emphasized the important role of the NLRP3 inflammasome activation in wear particle-induced inflammation. The exposure of human monocytes to alkane polymers generated by implant wear led to lysosomal damage. Consequently, the enzymatic leakage activated the NLRP3 inflammasome and resulted in Casp1-medicated IL-1β and IL-18 production (Maitra et al. 2009). Recent research has made it increasingly apparent that the NLRP3 inflammasome activation plays an essential role in wear debris-triggered immune response in macrophages (Jämsen et al. 2020). Co/Cr/molybdenum alloy particles also could stimulate macrophages to secrete IL-1β via the NLRP3 signaling pathways. The upregulation of nicotinamide adenine dinucleotide phosphate (NADPH), Casp1, NLRP3, and ASC was proven (Caicedo et al. 2009). In another study, titanium (Ti) particles were proven to activate NLRP3 inflammasome components (e.g., NLRP3, ASC, and Casp1) and increase IL-1β release (Manzano et al. 2018). Furthermore, polymethylmethacrylate particle phagocytosis could trigger Casp1-dependent secretion of IL-1β in mouse macrophages and human monocytes. Moreover, mice lacking Casp1 exerted decreased wear particle-induced osteolysis. In addition, NLRP3 inflammasome components also showed a critical role in altering osteoclasts (Burton et al. 2013). Besides, the results of an in vitro study on the primary human macrophages and human macrophage cell line and an in vivo study on a murine model of inflammatory osteolysis showed that Co alloy implant particles stimulated inflammatory cascades and bone absorption primarily via DAMP, not TLR4 activation (Samelko et al. 2016). In a previous in vivo experimental model, Ni allergy was observed following exposure of the dorsal side of the ears to Ni in mice. These reactions were dependent on IL-1 receptor/myeloid differentiation factor 88 (MYD88) signaling pathways without involving TLR4 (Vennegaard et al. 2014). Genomic DNA analysis showed that THA aseptic loosening earlier than 15 years after primary operation was related to NLRP3 rs35829419 and caspase recruitment domain-containing protein 8 (CARD8) rs2043211 polymorphisms, emphasizing the critical role of NLRP3 in the pathogenesis of aseptic loosening (Mavčič et al. 2020).

It seems that implant wear debris undergoes phagocytosis by macrophages or induces frustrated phagocytosis. A reasonable hypothesis is that NLRP3 activation represents a major role in the pathogenesis of peri-prosthetic osteolysis. Therefore, any approaches that inhibit the activation of NLRP3 inflammasome will be considered the potential treatment for peri-implant osteolysis. In this study, we first presented a detailed review of the inflammatory signaling pathways involved in the pathogenesis of particulate debris-triggered peri-implant osteolysis, emphasizing the recent findings associated with the NF-κB/NLRP3 axis. Secondly, anti-inflammatory-based therapy as a potential promising treatment strategy against implant-related adverse reactions was summarized.

Targeting NF-κB/NLRP3 axis for management of aseptic loosening

According to the literature, several therapeutic approaches have been examined to manage the implant debris-induced inflammation with the preventive purpose of aseptic loosening of orthopedic implants in both in vitro and in vivo investigations. There are limited studies to show that the suppression of NLRP3 can alleviate implant-induced osteolysis. Key details and results were summarized in Table 1.

Blockage of pro-inflammatory signaling pathways via inhibitors

A previous study showed that erythromycin could successfully inhibit osteoclastogenesis induced by wear debris, including polymethyl methacrylate (PMMA) and ultrahigh molecular weight polyethylene (UHMWPE). This inhibitor of the cytochrome P450 system regulated the expression of cathepsin K (CPK), NF-κB, IL-1β, and TNF-α, not RANK in RAW cells. Moreover, erythromycin suppressed the osteoclast formation in the RANKL-induced bone marrow-derived macrophages (BMDMs) (Ren et al. 2004).

Double-stranded oligodeoxynucleotides (ODN) containing an NF-κB binding element have been used for the treatment of different inflammatory diseases. ODN is able to mimic the microbial/viral DNA function (De Stefano 2011). In a preliminary study, the anti-inflammatory effects of NF-κB decoy ODN could successfully suppress the UHMWPE wear debris-triggered chemokine and cytokine production in primary macrophages and macrophage-like cell lines, including monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1-alpha (MIP1α), and TNF-α (Ping et al. 2017). In another study, suppression of NF-κB signaling by decoy ODN with high affinity to NF-κB was shown to mitigate UHMWPE wear particle-induced inflammatory response through regulating MCP-1, MIP1α, and TNF-α in the macrophage cell lines and BMDMs (Tzu-hua Lin et al. 2014). Furthermore, local injections of NF-κB decoy ODN blocked the polyethylene particle-induced inflammation via mitigation of TNF-α and RANKL expression and induction of IL-1 receptor antagonist (anti-inflammatory cytokine) and OPG (anti-resorptive cytokine) in a murine calvarial model (Sato et al. 2015).

An 11-amino acid peptide containing the NF-κB essential modulator (NEMO)-binding domain (NBD) has been considered a unique inhibitor of NF-κB signaling that target inhibitor of kappa B (IκB) kinase (IKK) complex. IKK is the master activator of NF-κB, containing two subunits, IKKα and IKKβ (Zhao et al. 2018; Karin 1999). It was reported that NBD could inhibit PMMA particle-induced osteolysis in the murine calvaria model (Clohisy et al. 2006). In another research, mutant CCL2 proteins such as 7ND, a decoy agent to suppress the CCR2 activity and decrease immune cell migration, could mitigate UHMWPE particulate debris-induced bone destruction. It could successfully increase bone healing and bone mineral density via reducing osteoclasts and inflammatory cells in a murine calvaria model of osteolysis (Xinyi Jiang et al. 2016). Likewise, tetracycline, a MMP-9 inhibitor, suppressed the Ti particle-induced inflammatory osteolysis through downregulating MMP-9 receptor, TNF-α, RANK, and RANKL. It also reduced the number of osteoclast-like cells in the murine osteolysis model (Chen et al. 2012). Blockade of VEGF via VEGF inhibitor (VEGF R2/Fc chimera) was reported to suppress UHMWPE-induced inflammatory osteolysis in a mouse model. It could successfully inhibit the membrane proliferation, inflammatory cells, and expression of TNF-α and IL-1β in UHMWPE-stimulated pouch tissues. VEGF inhibitor also reduced the number of tartrate-resistant acid phosphatase $(TRAP)^+$ cells and bone resorption of implanted calvaria (reduced loss of bone collagen content and bone erosions) (Ren et al. 2007).

siRNA targeting CXC chemokine receptor type 2 (CXCR2), a coupled receptor of IL-8 involved in the maturation of osteoblasts, alleviated Ti particle-associated osteolysis in the mouse calvaria model. Additionally, siRNA targeting CXCR2 inhibited the formation of osteoclastic cells via both direct effects on osteoclasts and indirect effects through regulating the gene expression of RANKL and OPG in osteoblasts in vitro (Wang et al. 2016). Previously, it was demonstrated that melatonin attenuated wear particle-induced bone loss and enhanced bone formation (Ping et al. 2017). Melatonin also was proven to attenuate the number of osteoclasts ($TRAP^+$ cells) and regulate inflammatory responses via reducing the number of TNF-α-, IL-1β-, and IL-6-positive cells. In addition, melatonin could moderate the activation of NF-κB via downregulating the protein levels of p-IκBα, p65, and p-p65 in an animal model of Ti particle-triggered osteolysis. Moreover, melatonin dose-dependently reduced RANKL-osteoclastogenesis, osteoclastic resorption, and F-actin ring formation in BMDMs (Ping et al. 2017). In an animal study, the effects of melatonin on Ti nanoparticle-induced osteolysis were investigated. The results showed that the oral supplementation of melatonin could attenuate osteolysis-associated alterations, including bone erosion and osteoclast activation. Melatonin regulated the production of gut microbiota-derived butyrate, which could modulate protein levels of IL-1β, NLRP3, and Casp1 in lipopolysaccharide- and Ti-particle-stimulated BMDMs (Wu et al. 2021).

Blockage of pro-inflammatory signaling pathways via stem cells

The ability of stem cells, particularly mesenchymal stem cells (MSCs), to migrate into the injured tissues showing inflammation, has been proven. MSCs are able to secret several mediators with anti-inflammatory and immunosuppressive properties (Schmitt et al. 2012). The application of MSCs to differentiate into osteoblast and replace bone tissue for treating aseptic loosening of TJA has been discussed in several studies (see review by Jukka Pajarinen et al. 2017). However, there are limited studies to show the anti-inflammatory effects of stem cells or their derivatives in preventing the aseptic loosening caused by wear debris-induced inflammation. The regulation of the innate immune system via MSCs plays a critical role in treating several diseases (Le Blanc and Mougiakakos 2012). It was presented that the conditioned supernatants collected from MSCs decreased TNF-α, IFN-γ, IL-6, and IL-12p70, but increased IL-10 and IL-12p40 production in LPS-induced macrophages (Maggini et al. 2010). Additionally, it was demonstrated that MSCs injected into the systemic circulation could migrate to the area of inflammation induced by UHMWPE particles in an in vivo model of continuous intramedullary particle infusion (Gibon et al. 2012b). A pivotal crosstalk between MSCs and macrophages has been reported in all bone diseases with inflammatory backgrounds. This process is also involved in the bone-healing procedure (Pajarinen et al. 2019). In a pre-conditioning protocol, short-term exposure of MSCs to LPS or TNFα regulated immunomodulatory responses via prompting monocyte polarization toward M2 macrophages with anti-inflammatory phenotypes and suppression of M1 and improved bone regeneration in an in vitro co-culture model. This protocol showed potential for treating inflammatory bone abnormalities (Lin et al. 2017). Extracellular vehicles (EVs), secreted by stem cells, are membrane-bounded structures with the ability to deliver biologically active agents (Jousheghan et al. 2021). Recently, EVs were reported to regulate intercellular communications and directly promote tissue repair and regeneration. A recent study demonstrated that EVs isolated from human urine-derived stem cells attenuated UHMWPE debris-induced bone loss. The results presented that EVs promoted BMSC osteogenic differentiation, reduced inflammatory cytokines, and regulated differentiation of RAW264.7 cells into osteoclasts. Furthermore, a study on an animal model showed that the local injection of EVs around the central regions of the calvaria reduced the production of inflammatory mediators, regulated osteolysis, and resulted in increased bone volume (Li et al. 2021).

Blockage of pro-inflammatory signaling pathways via herbal medicine

Herbal products have been used traditionally for the prevention and treatment of several diseases (Mokhtari et al. 2020; Bagheri et al. 2017; Khazaei et al. 2018). The efficiency of herbal products as active molecules was established in bone tissue engineering, biomaterial science, and orthopedics (Tang et al. 2021). Recently, it was revealed that *Angelica sinensis*, a traditional Chinese herb, could successfully alleviate UHMWPE debris-induced inflammatory osteolysis. *Angelica sinensis* reduced TNF-α and IL-1β both in vivo and in vitro. Moreover, the number of osteoclasts and osteolysis areas were reduced in calvaria harvested from the mouse model (Yang et al. 2012). In another study, the flavonoid quercetin was reported to suppress Ti dioxide-induced chronic arthritis in mice (Borghi et al. 2018). Besides, puerarin, a type of polyphenol isolated from *Pueraria lobata*, recognized to induce an inhibitory effect on Ti debris-induced osteolysis. This bioactive agent could regulate the gene expression of TNF-α and IL-1β, moderate the extracellular signal-regulated kinase1/2 (ERK1/2), and reduce the number of $TRAP^+$ cells in a mouse model of calvarial osteolysis. Furthermore, puerarin dose-dependently attenuated RANKL-triggered bone resorption, osteoclast activation, and F-actin ring formation in vitro (Yang et al. 2019). Therefore, using plants or their derivatives with antioxidant and anti-inflammatory properties may help to alleviate the particulate debris-induced osteolysis, leading to the management of aseptic loosening of joint prostheses.

Conclusion

In summary, aseptic loosening is associated with inflammatory response-induced osteolysis. It is well established that wear debris activates pro-inflammatory signaling associated with NF-κB/NLRP3 axis within macrophages, resulting in the production of inflammatory cytokines and the activation of osteoclasts. Therefore, inhibition of these molecular mechanisms may alleviate the inflammatory responses and reduce particulate debris-induced osteolysis in peri-prosthetic tissues. Several novel pharmacological approaches have been introduced to suppress the progress of osteolysis. Biological inhibitors, herbal products, stem cells, and stem cell-driven EVs have been suggested to suppress the activation or production of mediators involved in inflammatory responses, mainly target NF-κB/NLRP3 axis. Studies on both in vitro and in vivo reported that such approaches could successfully inhibit wear particle-induced osteolysis by reversing the activation of macrophages and regulating the inflammatory mediators. Although these strategies might be effective in treating osteoclastic disorders, e.g.,

wear debris-triggered osteolysis, further studies are needed to utilize such products in clinical trials.

Author contribution M. Q. and S. S. J. conceived of the presented idea. M. Q., M. P., O. D., N. G., and S. S. J. equally participated in drafting the article. M. Q. and S. S. J. participated in revising it critically for important intellectual content. All authors gave final approval of the version to be submitted and any revised version. The authors declare that all data were generated in-house and that no paper mill was used.

Availability of data and materials No datasets were generated or analyzed during the current study.

Declarations

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