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Cellular Chemotaxis Induced by Wear Particles from Joint Replacements

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Abstract

The destruction of bone around joint replacements (periprosthetic osteolysis) is an adverse biological response associated with the generation of excessive wear particles. Wear debris from the materials used for joint replacements stimulate a chronic inflammatory and foreign body reaction that leads to increased osteoclast differentiation and maturation, and decreased bone formation. Wear debris induces both local and systemic trafficking of inflammatory cells to the site of particle generation. Recent studies have shown that this effect is mediated primarily by chemotactic cytokines (chemokines) including macrophage chemotactic protein-1 (MCP-1, also known as CCL2), macrophage inhibitory protein-1 (MIP-1), Interleukin-8 (IL-8 or CXCL8) and others. These ligands migrate along a concentration gradient to interact with G-protein-linked transmembrane receptors on the cell surface. Chemokines are involved in the innate and adaptive immune responses, angiogenesis, wound healing and tissue repair. In vitro, in vivo and tissue retrieval studies have shown that chemokine-directed systemic trafficking of polymorphonuclear leukocytes and cells of the monocyte/macrophage lineage to wear particles results in the release of pro-inflammatory factors and subsequent bone loss. Modulation of the chemokine ligand-receptor axis is a potential strategy to mitigate the adverse effects of wear particles from joint replacements.

Keywords

Joint Replacement; Osteolysis; Wear; Particles; Chemokines

1. Biocompatibility of joint replacements

Long-term biocompatibility of total joint replacements for the treatment of end-stage arthritis is dependent on two premises: 1) initial integration of the implant within bone in satisfactory position, and 2) avoidance of subsequent adverse responses by the bone and surrounding tissues to the implant and its byproducts during usage. Although osseointegration and long-term functional stabilization of implants is readily achievable with modern joint replacements, avoidance of ensuing adverse biological reactions is still a significant challenge. This is due primarily to the generation of wear debris and byproducts from joint replacements. Despite the introduction of more wear resistant bearing surfaces, implant wear, periprosthetic osteolysis and prosthetic loosening are still of great importance [1].

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Wear particles are generated during normal usage of all joint replacements. For the hip and knee, it has been estimated that hundreds of thousands to millions of particles are generated with each step [2]. Given the fact that each person takes approximately 500,000 – 2,000,000 steps each year, the potential biological effects of wear debris are highly relevant.

In general, except for rare idiosyncratic immune responses to particles from metallic bearing surfaces, the biological reactions to polymers, ceramics and metallic wear particles constitute a non-specific foreign body and chronic inflammatory response [3]. The key cell lineages important to this response are the monocyte/macrophage cell line (including monocytes, macrophages, foreign body giant cells and osteoclasts), and cells of mesenchymal origin (osteoblasts, fibroblasts, other stromal cells and their progenitors). Although scattered lymphocytes are often present in retrieved tissues from loose joint replacements with osteolysis, their role is presumed to be immunomodulatory in nature, rather than primary [3–6].

The tissue interface surrounding loose joint replacements with osteolysis is not only composed of macrophages in a fibrous stroma, but there is heightened evidence of local bone deposition and turnover [7]. Recent studies have demonstrated that particles stimulate not only a local reaction but also a systemic response, culminating in cell homing to the local area of particle deposition [8,9]. The biological process by which systemically circulatory inflammatory and mesenchymal cells migrate to an area of high concentration of wear debris particles is the subject of this review.

2. Cytokines and Chemokines

Cytokines are protein, peptide or glycoprotein cell signaling immunomodulatory molecules that are primarily concerned with inter-cellular communication. Cytokines generally have autocrine and paracrine but not endocrine functions. Cytokines have a matching receptor on the cell surface that, when activated, results in a cascade of events leading to downstream signals that alter transcription factors, and up/downregulation of specific genes. There is great redundancy in cytokine functions; several cytokines often have very similar actions. Cytokines are often present in very small amounts, but can be increased by a factor of 1000 or more during acute stress such as infection, trauma, etc.

Chemokines are a family of chemotactic cytokines that provide key signals for trafficking and homing of specific subpopulations of cells in health and disease [10–13]. Chemokines are small molecules (8–10 kDa) that interact with G-protein-linked transmembrane receptors on the cell surface to guide cells towards the source of the chemokine via a concentration gradient. Chemokines are involved in the inflammatory and immune responses, angiogenesis and development, wound healing and tissue repair. They are essential to both the innate and adaptive immune systems.

Chemokines have up to 50% or more homology in their gene and protein structure. They are secreted as pro-peptides that are subsequently cleaved to form the active molecule. Chemokines have a unique 3-dimensional structure that contains four cysteine residues in specific locations. There are four groups of chemokines, including the C-C group, the C-X-C group, the C group, and the C-X₃-C group. The designation of the chemokine group is dependent on the location and spacing of the cysteine residues. Chemokines have a commonly used name, such as macrophage chemotactic protein-1 (MCP-1), but also have a more formal designation, such as CCL2 (for MCP-1), where the “L” in the formal designation refers to “ligand”. Importantly, because of protein homology, the chemokine ligands can often interact with multiple cell surface receptors. The receptors are designated as CCR (“R” stands for “receptor”), followed by a number.

Many chemokine receptor-ligand axes stimulate the migration and function of different subpopulations of leukocytes (See Table 1). The two chemokine groups most relevant to this review include members of the C-C and C-X-C family. In the C-C chemokine group, macrophage chemotactic protein-1 (MCP-1 or CCL2) and macrophage inhibitory protein-1 (MIP-1) are most important to this discussion (Figure 1). In the C-X-C group, Interleukin-8 (IL-8 or more formally CXCL8) is also highly relevant.

MCP-1 or CCL2 is a small cytokine of about 13 KDa and binds mainly to CCR2 but also may bind to CCR4 [14,15]. The gene for MCP-1 resides on chromosome 17. MCP-1 is produced by many cells including monocytes/macrophages, fibroblasts, osteoblasts, endothelial cells and others, especially in response to oxidative stress and other cytokines. MCP-1 regulates the migration and accumulation of monocyte/macrophages, dendritic cells, NK and memory T lymphocytes. Polymorphonuclear leukocytes and the majority of blood lymphocytes do not respond to MCP-1, however this chemokine also causes degranulation of basophils and mast cells. MCP-1 also stimulates interleukin-1 (IL-1) and IL-6 release from monocyte/macrophages, thereby contributing to autocrine and paracrine feedback loops linking chemokine and pro-inflammatory cytokine production. Regulation of gene expression of MCP-1 occurs primarily at the level of gene transcription by the inducible transcription factor NF- κ B.

MIP-1 is a chemokine with alpha (known as CCL3) and beta (CCL4) forms. MIP-1 is produced by cells similar for MCP-1. The gene for MIP-1 also resides on chromosome 17. Several chemokine receptors (CCR1, CCR3, CCR5, and CCR9) are postulated to mediate the effects of MIP-1 α , although this is controversial [16]. MIP-1 α is a potent chemoattractant for monocytes/macrophages and other leukocytes and is important for osteoclast recruitment and differentiation [10,13,16,17]. Interestingly MIP-1 α is primarily chemotactic for B lymphocytes, CD8+ T lymphocytes, NK cells, eosinophils, and causes histamine release from basophils, mast cell degranulation and ICAM expression, whereas MIP-1 β is chemotactic for CD4+ T lymphocytes. MIP-1 α stimulates the production of the pro-inflammatory cytokines IL-1, IL-6, and TNF- α , and appears to inhibit hematopoietic stem cell proliferation. MIP-1 α also has autocrine and paracrine effects similar to MCP-1, and is regulated by NF- κ B.

IL-8 also known as CXCL8 is a proinflammatory chemokine that is induced by stress, proinflammatory cytokines and steroid hormones [18–20]. The gene for IL-8 is found on chromosome 4. The ligand binds to two cell-surface G protein-coupled receptors, CXCR1 and CXCR2. These receptors are located on the surface of macrophages, endothelial cells, mast cells, epithelial cells and others. Activation of IL-8 promotes angiogenic responses in endothelial cells and the recruitment and migration of neutrophils. IL-8 and two other C-X-C chemokines including MIP-2 (CXCL2), and KC (CXCL1) are responsible for neutrophil mobilization from the bone marrow, rolling along and adherence to endothelial cells, and transmigration from the bloodstream into the interstitium.

3. Chemotaxis and Wear Debris – In vitro, in vivo and tissue retrieval studies

Although much is known about cellular chemotaxis in the case of inflammation, infection and cancer, we are only beginning to understand the implications of cell trafficking with respect to biomaterials and their byproducts. This topic is of obvious importance, as the function and longevity of any device in the body is dependent in part on the local and systemic cellular environment that a specific device incites.

3.1 Analysis of tissue and synovial fluid from retrieved implants

Periprosthetic tissues harvested from revised loose total hip replacements have demonstrated positive immunohistochemical staining for the C-C chemokines MCP-1 and MIP-1 α , but not

regulated upon activation normal T expressed and secreted protein (RANTES) [21]. High throughput protein chip analysis and organ culture of the periprosthetic tissues of revised hip replacements with osteolysis demonstrated increased levels of IL-6 and IL-8, as well as interferon- γ -inducible protein of 10 kDa (IP-10) and monokine induced by interferon- γ (MIG), both chemoattractants of activated Th1 lymphocytes [22]. MCP-1 was detected in six of thirteen samples from failed joint replacements with osteolysis, but in none of the control osteoarthritic tissues. Expression of the soluble form of ICAM-1 (sICAM-1), an inflammatory mediator expressed on activated monocytes that facilitates transendothelial migration of leukocytes and activated T-cells was also increased in tissues from revised implants with osteolysis. Cytokine and chemokine expression in the synovial fluid of patients undergoing revision total hip arthroplasty (metal-on-polyethylene) for loosening and osteolysis was compared to that from patients undergoing primary hip arthroplasty for osteoarthritis [23]. Flow cytometry was used to detect RANKL expression on periprosthetic bone marrow cells; enzyme-linked immunoassay and multiplex microsphere-based immunoassay was used to measure cytokine and chemokine levels. Revision arthroplasties demonstrated higher RANKL expression on osteoblastic stromal cells, higher levels of RANKL, IL-6, IL-8, IL-10, IP-10, MCP-1, MIG, and lower OPG/RANKL ratios in synovial fluid than primary arthroplasties. Moreover, there was a positive correlation between the levels of the above cytokines/chemokines, and RANKL levels in synovial fluid or RANKL expression on osteoblastic stromal cells.

3.2 Cell culture studies and chemokine expression

In vitro studies have shown that phagocytosable titanium alloy (Ti-alloy) and polymethylmethacrylate (PMMA) particles stimulated MCP-1 and MIP-1 α expression from monocytes/macrophages in a time- (1–72 hours) and dose- (0.003–0.75% volume/volume) dependent manner using ELISA (protein determination) and RT-PCR (gene expression) [21]. Cultures challenged with Ti-alloy particles had higher levels of chemokine release compared to PMMA particles. Using in vitro chemotaxis assays, culture medium collected from human monocytes/macrophages exposed to particles of Ti-alloy and PMMA also stimulated the migration of monocytes. Addition of neutralizing anti-human MCP-1 monoclonal antibody (5 μ g/ml) and anti-human MIP-1 α polyclonal antibody (30 μ g/ml) to the cultures inhibited this cell migration. There was no additive effect of combining these two antibodies. These studies confirm the importance of C-C chemokines in the foreign body and chronic inflammatory reaction associated with loosening and wear particles. Interestingly however, when similar studies were performed with human foreskin fibroblasts, only MCP-1, but not MCP-2, MIP-1 α or RANTES were increased in a time- and dose-dependent manner [24]. Ti-alloy particles upregulated MCP-1 release by 7-fold while PMMA particles increased MCP-1 levels 2-fold, when compared to unchallenged fibroblasts at 24 hours. Addition of pertussis toxin, an inhibitor of G protein activity suppressed the release of MCP-1 and the inflammatory marker interleukin-6 (IL-6) from the fibroblasts [25]. Thus, particle and cell type are important determinants of the specific chemokine response.

MIF is a lymphokine released by activated lymphocytes that suppresses macrophage migration and inhibits cytokine release from activated macrophages. Macrophages also secrete and respond to this cytokine. Phagocytosable PMMA particles were shown to stimulate the release of MIF, MCP-1 and MIP-1 α from human monocyte/macrophages; addition of MIF inhibited the migration of macrophages to particle challenge [26].

Analysis using protein chip arrays has been used in studies exposing human primary macrophages to submicron sized particles of UHMWPE, TiAlV alloy, CoCr alloy, and alumina in vitro [27]. TiAlV particles were the most stimulatory (5- to 900-fold higher cytokine expression compared with non-stimulated cells), CoCr and alumina were mildly stimulatory

(two- to fivefold greater levels than non-stimulated cells), and UHMWPE particles were the least stimulatory. Macrophages secreted detectable levels of Interleukin-1 α (IL-1 α), tumor necrosis factor- α (TNF- α), IL-1 β , MCP-1, IL-8, IL-6, GM-CSF, IL-10, and IL-12p40. MCP-1 was the only cytokine/chemokine that was stimulated by all four particle types, at varying levels: TiAlV (18-fold), CoCr (5-fold), alumina (2-fold), and UHMWPE (1.5-fold). High levels of IL-8 elicited by the metallic and polymer particles suggested an important role for IL-8 in the early response to wear debris.

In vitro studies have been carried out comparing the cytokine and chemokine response of human THP-1 human monocytes to phagocytosable particles averaging 2.6 micrometers in diameter versus titanium discs of comparable surface roughness [28]. Expression of key cytokines and chemokines was monitored over a 72-hour period. In general, expression levels increased with culture time, particle concentration, and LPS stimulation. The levels of the chemokines MCP-1 and MIP-1 α gradually increased in expression as a function of time up to 72 hours. For TNF- α , MIP-1 α , MCP-1, VEGF and IL-1 α , the expression levels for titanium discs were significantly higher than the corresponding expression levels for titanium particles and tissue culture plastic alone at 72 hours, possibly reflecting “frustrated phagocytosis”. Other researchers showed that “Ceridust” UHMWPE particles (mean particle size was 5.72 μ m), or ambient pressure of 0.0345 MPa (5Psi) singularly or together had no effect on MIP-1 α and MCP-1 release by monocytes isolated from healthy blood donors [29]. M-CSF and PGE2 levels were increased by both stimuli, and their application together was synergistic. These findings suggested that cyclical pressure may be an important factor in the development of osteolysis around loosened implants.

Chemokine release by osteoblasts exposed to particles is an acute stress response to adverse stimuli that induces immediate cell recruitment. Human MG-63 osteosarcoma cells and human bone marrow derived primary osteoblasts were cultured with clinically relevant, phagocytosable, commercially pure titanium particles less than approximately 5 micrometers. The particles stimulated a time- and dose-dependent release of IL-8 (primarily a neutrophil chemokine) and MCP-1 protein and gene expression at doses as low as 0.05% volume/volume [30]. Interestingly, gene transcription was independent of protein synthesis. Titanium particles also induced increased binding of the transcription factor NF- κ B to the IL-8 promoter, and increased ERK, JNK, and p38 activation in MG-63 osteoblasts [31]. IL-8 protein release was suppressed by specific inhibitors of the ERK and p38 MAPK pathways, indicating that particle-induced NF- κ B-mediated transcriptional activation is controlled by the MAPK signal transduction pathway [31]. Addition of N-acetyl-L-cysteine (Nac, an anti-oxidant inhibitor of NF- κ B) and MG-132 (a 26S proteasomal inhibitor preventing I κ B α degradation) suggested that titanium particle activation of NF- κ B activity and IL-8 chemokine expression in human bone marrow osteoblasts involves oxidant signaling and I κ B α -proteasomal degradation [32]. Cytochalasin D, an inhibitor of phagocytosis, decreased IL-8 protein production in human bone marrow osteoblasts but not MG-63 osteosarcoma cells. Thus particle induced chemokine release is mediated by phagocytosis-dependent and independent mechanisms of gene activation. IL-8 and MCP-1 secretion from osteoblasts may help amplify and sustain osteoclastic bone resorption at the prosthetic interface, thereby promoting the progression of osteolysis.

3.3 Animal studies of chemokine expression in the presence of wear particles

A murine model was developed in which particles were placed with a stainless steel rod in retrograde manner in the femur, providing specimens for analysis using histology, ELISA of organ culture explants and RT-PCR for protein and gene expression respectively [33,34]. Addition of a single bolus of commercially pure titanium particles resulted in chronic inflammation and scalloping of the endosteum, and increased expression of IL-6 and MCP-1

protein. When IL-1 receptor knockout mice were used instead of wild type mice in the same model, the inflammatory membrane and markers were blunted at the 2-week harvesting period [34,35]. When clinically relevant UHMWPE particles were substituted for commercially pure titanium particles in wild type mice, an inflammatory membrane also formed; IL-1 β and MCP-1 mRNA increased linearly over a 10-week time period [33].

4. Discussion

Orthopaedic surgical procedures using implants for joint replacement, fracture fixation, spinal surgery and other indications are associated with an acute inflammatory reaction due to the surgical trauma alone. This subsides over days to weeks and subsequently the implant-tissue construct attains long-term biological and functional stability [36–40]. Thus, acute inflammation usually subsides, leading to a state of repair and eventual biocompatibility. However, adverse tissue responses may also occur; the acute inflammatory reaction may persist and progress to a chronic inflammatory state. If these adverse events resolve, the end result may be fibrosis; the implant may or may not achieve its intended biological and mechanical function. For joint replacements, optimal long-term function is associated with appropriate patient, prosthesis and material selection, optimal surgical technique and patient usage, and avoidance of infection. In the case of cementless joint replacements, initial osseointegration is of paramount importance to avoid the development of fibrous interfaces, interfacial motion and loosening. Fibrous interfaces can also function as a conduit for migration of wear debris and synovial fluid around the implant, facilitating bone destruction and subsequent loosening [41,42].

For total joint replacement, after implant stabilization occurs, wear of the bearing surfaces is the major issue limiting longevity of the prosthesis [43]. The inflammatory and foreign body reaction to wear particles leads to chronic synovitis and periprosthetic osteolysis, undermining the bony prosthetic bed. This results micromotion, macromotion and eventual gross failure of fixation.

The above events occur in the context of complex cellular and molecular interactions due to the surgical trauma and implantation procedure. Local tissue injury initiates the release of numerous inflammatory factors (cytokines, chemokines, prostanoids, nitric oxide and oxygen metabolites) and growth factors, providing a biological and mechanical environment for inflammation and repair. Thereafter, wear and the biological effects of wear particles can change the homeostatic bone-prosthetic environment to one of dysregulation, chronic inflammation and continued bone loss [44,45].

The presence of wear debris stimulates both local and systemic cellular reactions. Chemokines such as IL-8, MCP-1, MIP-1 α and others are released by acute and chronic inflammatory cells, cells of mesenchymal origin and others. These chemokines normally amplify the inflammatory response in order to effect containment of potentially harmful stimuli (such as bacteria and other toxins) and provide a mechanism for resolution and repair. However, cytokines and chemokines acting in both autocrine and paracrine fashion may intensify the reaction to wear debris in an unfavorable way. In the latter case, very aggressive osteolytic lesions may be the end result [46–48]. The final outcome is ostensibly determined by the type, amount and physicochemical characteristics of the wear particles, and genetic background of the host [49].

Given the fact that wear particles are continuously generated with ongoing use of joint replacements, and that these particles induce local and systemic inflammatory cell migration and activation, strategies can be directed to minimize potential adverse reactions. Improved bearing surfaces should decrease the overall particle burden, however, the characteristics and

biological reactions of the particles subsequently generated should be closely monitored [49–51]. Pharmacological therapies targeted at specific inflammatory factors have had some success in in vitro studies and animal models [52–54]. However, anti-TNF therapy and the use of bisphosphonates to treat osteolysis have largely been unsuccessful in human clinical trials [53,55]. This may be due to the fact that inflammatory pathways are very redundant, as well as issues related to timing and dosing of specific pharmacological agents, which would probably have to be continued indefinitely [53,56]. Furthermore, many of the inflammatory mediators are important to general immune surveillance and tissue homeostasis, making their use controversial for a non-life threatening condition such as periprosthetic osteolysis. Perhaps the most promising therapies include the use of erythromycin (an inhibitor of the transcription factor NF κ B [57]), agents that interfere with the RANK/OPG axis [53,56,58], and statins (inhibitors of the mevalonate pathway [59,60]).

Another approach to preventing particle-induced osteolysis is to design a “smart” prosthesis for surveillance and modulation of the cell populations near and remote from the prosthesis. Surface coatings that promote the migration of selected cell populations and discourage chronic inflammation could potentially optimize prosthesis integration and minimize fibrous tissue ingrowth. After osseointegration has been accomplished, ongoing wear may lead to local and systemic trafficking of unwanted inflammatory cells. Sensors physically associated with the prosthesis could monitor the peri-implant environment and facilitate the release of specific chemokines in a time- and dose-related fashion to discourage inflammatory cell infiltration. In this way, knowledge of the biological events associated with joint replacement and ongoing wear of the bearing surfaces could be monitored and modulated to facilitate implant longevity.

5. Conclusion

Wear debris and byproducts from joint replacements induce both local and systemic trafficking of inflammatory cells to the site of particle generation. These processes are controlled primarily by chemokines such as MCP-1, MIP-1, IL-8 and other factors released from cells at the surgical site. Modulation of these chemokines and their receptors may potentially enhance initial osseointegration of prostheses for joint replacement, and mitigate the adverse effects of wear debris at the bone-implant interface.

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Wear particle induced chemotaxis of bone marrow cells to bone tissue

N: Neutrophil; HSC: Hematopoietic Stem Cell; MSC: Mesenchymal Stem Cell

Figure 1.

This figure depicts some of the biological processes involved in wear particle-induced cell trafficking of bone marrow cells. The generation of wear particles stimulates the local release of chemokines from inflammatory cells along a concentration gradient. This mobilizes more inflammatory cells (primarily polymorphonuclear leukocytes and monocyte/macrophages) and mesenchymal stem cells (for repair) to the site of particle deposition. Similar cell signaling processes have been found to occur during traumatic injuries to bone, including fracture.

Table 1**Expression of Chemokine Receptors in Human Leukocyte Populations**

Receptor	Main Ligands	Main Expressing Cells
CCR1	CCL3 (MIP-1a), CCL4, CCL5 (RANTES), CCL20 (MIP-3),	CCL7 (MCP-3), CCL8 (MCP-2), M ϕ , DC, peripheral lymphocytes, eosinophils, EO, BAs, PMN
CCR2 b/a	CCL-2 (MCP-1), CCL7, CCL8, CCL16	M ϕ , DC, T, NK
CCR3	CCL3, CCL5, CCL7 (MCP-3), CCL8	DC, Eo, Ba, Th2
CCR4	CCL2, CCL3, CCL5, TARC, MDC	DC, Th2
CCR5	CCL2, CCL3, CCL4 (MIP-1b), CCL5, CCL8	M ϕ , Th1, DC
CCR6	LARC	T, DC (CD34), Th17
CCR7	CCL19, CCL21	T, M ϕ
CCR8	CCL1, CCL16	Th2, M ϕ
CCR9	CCL3, CCL25	T
CCR10	CCL27, CCL28	T
CXCR1	IL-8, CXCL6, CXCL8	PMN
CXCR2	CXCL1 (KC), CXCL2 (MIP-2a), CXCL3-8	PMN
CXCR3	CXCL-3 (MIP-2), CXCL9-11	Th1, NK
CXCR4	CXCL12 (SDF-1)	Widely expressed
CXCR5	CXCL13	B
CXCR6	CXCL16	T
CX3CR1	CX3CL1	T

M ϕ = Monocytes; DC=dendritic cells; DC (CD34)=DC-derived from CD34 cells in vitro; PMN=neutrophils; Eo=eosinophils; Ba=basophils; Th=T helper; Tc=T cytotoxic;

This is an evolving list as of the time of writing. Ongoing scientific investigations will outline more details of the different chemokine receptor-ligand axes.