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Macrophages – Key Cells in the Response to Wear Debris from Joint Replacements

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Abstract

The generation of wear debris is an inevitable result of normal usage of joint replacements. Wear debris particles stimulate local and systemic biological reactions resulting in chronic inflammation, periprosthetic bone destruction, and eventually, implant loosening and revision surgery. The latter may be indicated in up to 15% patients in the decade following the arthroplasty using conventional polyethylene. Macrophages play multiple roles in both inflammation and in maintaining tissue homeostasis. As sentinels of the innate immune system, they are central to the initiation of this inflammatory cascade, characterized by the release of pro-inflammatory and pro-osteoclastic factors. Similar to the response to pathogens, wear particles elicit a macrophage response, based on the unique properties of the cells belonging to this lineage, including sensing, chemotaxis, phagocytosis, and adaptive stimulation. The biological processes involved are complex, redundant, both local and systemic, and highly adaptive. Cells of the monocyte/macrophage lineage are implicated in this phenomenon, ultimately resulting in differentiation and activation of bone resorbing osteoclasts. Simultaneously, other distinct macrophage populations inhibit inflammation and protect the bone-implant interface from osteolysis. Here, the current knowledge about the physiology of monocyte/macrophage lineage cells is reviewed. In addition, the pattern and consequences of their interaction with wear debris and the recent developments in this field are presented.

Keywords

Total joint replacement; Aseptic loosening; Osteolysis; Monocyte/macrophage; Wear particles; Inflammation; Tissue homeostasis

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INTRODUCTION

Total joint replacements (TJRs) are among the most successful surgical procedures developed during the 20th century. They provide predictable restoration of function in patients suffering from end-stage joint diseases, such as primary osteoarthritis, osteonecrosis, inflammatory arthropathies and other disorders. Although worldwide standards still need to be defined, the principles of TJR currently used were established years ago.[1] A recent 30 year-minimum follow up evaluation found that 88% of 110 total hip arthroplasties (THAs) were still in place and functioning well, illustrating the optimal long term behavior of the original low friction arthroplasty (LFA) concept.[2] Clinical success and increasing popularity in the surgical population have driven the indications of TJRs to more and more young and physically demanding patients. Recently, Kurtz *et al.*[3] estimated that more than 50% of all hip and knee TJRs are currently done in patients less than 65 years in the USA. Also, projections estimated that young patients would represent 52% and up to 62% of all hip and knee TJRs, respectively, in 2030. However, there is a consensus that survivorship of TJRs in patients less than 50 years is inferior as compared to patients over 50 years,[4–7] and, therefore, revision incidence rates are predicted to substantially increase over time.

Causes of implant failure are multifactorial, including implant design, surgical technique, method of fixation, infection and aseptic loosening.[8–11] Aseptic loosening secondary to periprosthetic osteolysis is the leading cause of revision procedures especially in patients with a hip and knee TJR in the long-term. In the context of joint replacements, osteolysis refers to bone destruction as seen on conventional radiographs and corresponds to bone defects seen during revision surgery. Recently, in a large series of THAs, Lübbeke *et al.* [12] reported femoral osteolysis in up to 24% of cases in the decade after the procedure, with more active patients at increased risk for developing osteolytic lesions. In total knee arthroplasty (TKA), osteolysis has been found in 5% to 20% of cases, at follow-up times ranging from less than 5 years to 15 years.[13] As a result, up to 15% patients are likely to be revised for aseptic loosening in the decade following a total joint arthroplasty.[14]

Today, there is a general agreement that the development of periprosthetic osteolysis is highly related to wear debris delivered continuously from an articulating surface of a TJR.[15] Routinely, wear of the bearing couple and the associated periprosthetic osteolysis are usually evaluated using sequential conventional radiographs with additional oblique views as needed, or by computed tomography imaging with metal supression. Analyses of periprosthetic tissues retrieved during revision of failed TJRs showed that ultra-high molecular weight polyethyelene (UHMWPE) wear debris is the most frequent type of debris around failed hip, knee and shoulder TJRs, whether the implants were cemented or not.[16] Several hundreds of thousands of UHMWPE particles may be generated during a single gait cycle,[17] and depending on their size, the periprosthetic tissues are exposed to a huge amount of wear debris.[18] Retrieved UHMWPE particles were mainly globular spheroids in shape, ranging from 0.1 to 2.0 μm in size, with a mean 0.5 μm diameter.[19] Noteworthy, 90% of particles are reportedly less than 1 μm [20,21]. While there is strong evidence the process of osteolysis involves different cell types, including osteoblasts, fibroblasts, lymphocytes, *etc.*, the inflammatory response to prosthetic wear debris is mostly driven by cells of the monocyte/macrophage lineage. Macrophages are multi-functional cells of the innate immune system. Their primary role is maintaining tissue homeostasis. This includes the clearance of necrotic and apoptotic cellular debris, tissue remodeling following injury of the host and defense against foreign invaders. Macrophages are considered innate effector cells, since they do not require previous exposure to a given antigen to initiate a response. These cells phagocytose microbes and debris, and protect the host from adverse noxious stimuli. A major role for the innate immunity is the “front-line” protection of organisms from invasion

by pathogenic microbes. However, this reaction is relatively nonspecific and quite limited compared to acquired immunity mediated by T cell receptors and immunoglobulins.[22–24]

Macrophages, upon activation by wear particulate debris, release an array of cytokines and pro-inflammatory mediators in the joint fluid that results in the recruitment, multiplication, differentiation, and maturation of osteoclast precursors. Subsequent bone resorption eventually leads to loosening of the implant. In this review, the basic facts of monocyte/macrophage lineage cellular physiology are reviewed, the interactions between macrophages and wear debris are detailed, and recent developments in this field are presented.

THE MONOCYTE/MACROPHAGE LINEAGE CELLS

Blood monocytes are circulating phagocytic cells with the ability to perform immune effector functions through chemokine receptors and pathogen recognition receptors. During inflammation, monocytes migrate into solid tissues where they can differentiate into resident macrophages or dendritic cells (DCs).[25] Migration to tissues and differentiation occur with the help of a survival signal, macrophage-colony stimulating factor (M-CSF), and the local microenvironment.[26,27] "Resident" monocytes participate in tissue homeostasis, homing to resting tissues where they can differentiate into resident macrophages.[28–31] "Inflammatory" monocytes are released from bone marrow in response to acute infection or injury. Their migration from bone marrow is dependent on the ligand-receptor interaction between monocyte chemoattractant protein-1/CCL2 (MCP-1) and the receptor CCR2, a well-known potent chemoattractant of monocytes.[32]

Resident tissue macrophages are highly specialized cells uniquely adapted to their location, such as type A synovial lining cells, liver Kupffer cell, microglia of the central nervous system, alveolar macrophages of lungs, osteoclasts (Figure 1) and connective tissue histiocytes. Their basic scavenging function is essential to homeostasis, housekeeping and remodeling of tissues following injury. The hallmarks of resident macrophage function include effective phagocytosis of apoptotic cells and cellular debris, host response to infectious/tumor diseases, induction/regulation of inflammation and subsequent tissue healing. Tissue resident macrophages are equipped with a broad-range of pattern recognition receptors (PRRs), which are required for the host response to pathogens. PRRs are important in innate immunity as a first-line defense for recognition of microbial patterns (pathogen-associated molecular patterns), so-called "PAMPs". Toll-like receptors (TLRs) were the first PRRs to be identified. TLRs recognize a wide spectrum of exogenous danger signals (PAMPs)[33] and endogenous (alarmins) danger signals. Globally, the PRRs promote the production and release of pro-inflammatory signals including cytokines such as IL-6, TNF-α, and IL-12.[34] Phagocytosis involves the entry into the cell of large particles, typically 1 μm or more, including particles as diverse as inert beads, apoptotic cells, and microbes.[22–24,35] Recognition of specific ligands on particles by cell-surface receptors, such as Fc receptors and complement receptors facilitates the process of phagocytosis. In addition to innate activation of macrophages induced by PRR-mediated recognition of microbial-associated molecular patterns (MAMPs), macrophages can also assume distinct phenotypical and functional activation states as a response to their local microenvironment.[25,36,37] In line with this, a concept of M1/M2/Mreg macrophages, after the Th1/Th2/Treg nomenclature, has been established.[26,37–40] The M1 phenotype ("M1 polarization") is characterized by high capacity to present antigen, and high production of interleukin 12 (IL-12) and IL-23.[28–31,41]. Production of inflammatory chemokines (CCL2-4, CXCL8-12, *etc.*) and distinct pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-23, *etc.*) are characteristic of M1 macrophages.[32,42] In contrast, the "alternatively activated macrophage" ("M2 macrophage") refers to mononuclear phagocytes activated upon exposure to IL-4, IL-13, IL-10 or glucocorticoids. [29,39,41,43,44] M2 polarization is

characterized by suppression of pro-inflammatory cytokines, intracellular killing and antigen presentation, and accompanied by increased production of IL-10.[31,39,45] Another macrophage phenotype is characterized by high IL-10 production and could be referred as "deactivated" [26] or "regulatory" macrophages ("Mreg").[37,46] The above classification is pertinent to the mouse macrophage phenotype; further subclassification of the M2 phenotype is ongoing in humans.

Dendritic cells (DCs) are predominantly known as potent inducers and modulators of the immune system. They derive from the mononuclear cell pool and are characterized by high expression levels of CD11c/MHC-II. Human DCs are divided into CD11c+ myeloid DCs ("conventional DCs/cDCs"), and CD11c− pDCs ("plasmacytoid DCs"), which have different TLR profiles.[47] Conventional DCs are capable of antigen presentation and reverse migration, *i.e.* are able to migrate to lymph nodes *via* afferent lymphatic vessels.[48] Immature progenitor conventional DCs are unable to prime T cells, but are equipped with high phagocytic activity[49]

Cells of the mononuclear phagocyte system originate from a self-renewing pool of multipotent hematopoietic stem cells (HSCs) in the bone marrow. HSCs give rise first to common lymphoid and myeloid progenitors, which further differentiate into mature lymphoid and myeloid lineage cells. The common lymphoid lineage generates T lymphocytes, B lymphocytes, and natural killer cells, whereas the common myeloid lineage generates either erythrocyte progenitors, or granulocyte/macrophage progenitors (GMPs), with monocytes arising from the latter. Monocytes will eventually differentiate into macrophages upon recruitment to a specific tissue site due to local inflammatory conditions. [29,43,50,51] Although DCs can be produced *in vitro* from GMPs, many macrophages and DCs subsets originate from macrophage/DC progenitors (MDPs), a subset of proliferating cells in the bone marrow that share phenotypic characteristics with myeloid precursors but cannot differentiate into granulocytes. However, MDPs and common DC progenitors (CDPs) have not been identified in humans.[52] Interestingly, multi-lymphoid progenitors (MLPs) are able to differentiate into monocytes and DCs, but also to cells of the lymphoid lineage, thus somewhat challenging the classical bifurcation of HSCs to separate myeloid and lymphoid arms.[53]

THE INTERACTIONS BETWEEN MACROPHAGES AND WEAR PARTICLES

Overview

The biologic response to wear debris is complex and often drives the process towards periprosthetic tissue destruction and implant loosening.[27,54,55] At the heart of this concept is that very small prosthetic particles (the size of micrometers and less) stimulate periprosthetic monocyte/macrophages to express pro-inflammatory/pro-osteoclastic cytokines, surface receptors and other substances that orchestrate increased formation, accumulation, activity, and survival of osteoclasts, and inhibit the osteogenic activity of osteoblasts. As a result, bone resorption predominates over osteogenesis at the bone-implant interface. According to this concept, the degree of bone loss is a function of the number, size and origin of prosthetic particles that influences the number and depth of resorption sites.[56]

As part of their innate immune function, macrophages play a pivotal role in wear particle recognition, and in the cascade of biological events leading to implant failure. They perform these roles *via* four basic innate functions: sensing, chemotaxis, phagocytosis and adaptive stimulation. Specifically, each inflammatory response consists of *inducers*, *sensors of inducers*, *inflammatory mediators*, *effectors,* and *regulators* of the immune response.[57]

The reaction of macrophages is in part dependent at least on wear particle size and origin. When the foreign particles are small (<10 μm), macrophages and foreign body giant cells adhere to and effectively phagocytose the particles. The particles accumulate and finally break down the endosomal membrane with spilling of cathepsins into the cytosol. For larger particles (20–100 μm) that cannot be effectively phagocytosed by a single macrophage or foreign body giant cells, foreing body granulomas will be formed. The nicotinamide adenine dinucleotide phosphate (NADPH) oxidase family (NOX) members and reactive oxygen species (ROS) are produced.[58,59] Osteoclasts are formed in bone adjacent to implants, whereas multinuclear foreign body giant cells are formed rather in the wear particle-rich periprosthetic tissues.[27,60] Particles ranging between 0.1–1.0 μm are thought to be the most biologically active, however there is controversy as to whether particles less than about 0.3 μm undergo pinocytosis, without cellular activation.[15]

Protein-associated particles do tend to clump however, and are are often presented to the cells as a much larger complex than a single particle. In the reaction to UHMWPE wear debris, monocyte/macrophage lineage cells predominate, but lymphocytes are scarce. On the other hand, with metallic wear debris and corrosion products, monocyte/macrophage infiltrates are seen but also T and B cells and plasma cells play a role with formation of so-called “aseptic lymphocyte dominated vasculitis associated lesions (ALVAL)”.[61,62]

In response to wear debris, bone resorption is mediated *via* cytokines such as TNF-α and IL-1β, which induce expression of receptor activator of NF-κB (RANK) ligand (RANKL), the key cytokine regulator of osteoclast generation and together with TNF-α in their activation.[63,64] Receptor activator of NF-κB ligand is expressed on the surface of osteoblasts, stromal cells, and immune cells within the bone marrow, and can be cleaved from the cell surface to form soluble RANKL.[65] $RANK^+$ osteoclast precursors fuse to form multinuclear cells in the presence of M-CSF and RANKL. This process is neutralized by the soluble decoy receptor osteoprotegerin (OPG), which binds RANKL and thus prevents its interaction with RANK.[66–68] As a result, the RANKL/OPG ratio is a critical parameter in the regulation of bone resorption, and has been correlated with a variety of bone disorders.[69]

Attachment of cathepsin-K positive monocytes/macrophages to the periprosthetic bone surface stimulates bone resorption.[70] Macrophages activated by titanium particles were shown to express cathepsin-K and absorb dentine discs *in vitro*.[54] In addition, osteoclast precursors expressing the RANK bind RANKL, which drives M0 macrophages to the multinuclear bone resorbing osteoclast. TNF-α and IL-1 potentiate this process, and a soluble RANKL neutralizer (OPG) inhibits it.

Wear particle sensing by macrophages

Implanted biomaterials are immediately coated with proteins from blood and interstitial fluids, and through this adsorbed layer of proteins, cells sense and respond to foreign surfaces.[71] A variety of adsorbed proteins including fibronectin, vitronectin, albumin, fibrinogen, von Willebrand factor, complement, and others have been shown to play a pivotal role in the macrophage response to biomaterials.[72,73] Macrophages bind to coated foreign surfaces *via* integrin-mediated interactions, Fc receptors, complement receptors and scavenger receptors, which mediate binding with the particle surface-adsorbed, cell-adhesive proteins.[74,75]

Macrophage receptor with collagenous structure (MARCO) is one of the scavenger receptors not normally found in human monocytes, and is only expressed in a very restricted manner such as in chronic foreign body inflammation. MARCO expression is induced by wear debris *in vitro* and *in vivo*.[76,77] MARCO enhances the expression of IL-12 and nitric oxide (NO) production.[77] Implant-derived wear particles may lead to harmful over-

expression of MARCO.[75] This could play an important role in the first line of host defense against unopsonized and opsonized particles in macrophages in periprosthetic tissues.[75,76]

The response to wear particles is not only due to their phagocytosis by monocyte/macrophages, but also due to PRR-mediated sensing.[78–80] Wear debris are often combined with endogenous ligands being thus potent danger signals in tissues around loose implants.[81–83] A current hypothesis suggests that PAMPs produced by subclinical levels of bacteria contribute to particle-induced osteolysis in aseptic loosening of orthopaedic implants.[78] Therefore, TLRs are thought to play an important role in the periprosthetic tissues associated with aseptic loosening (Figure 2). TLRs -1 to -9 were detected in synovial-like membranes surrounding loose implants in monocyte/macrophages and some fibroblast-like cells by immunohistochemistry, immunofluorescence and reverse transcription polymerase chain reaction.[71,80,83–85] High expression of TLR4 in monocyte/macrophages of interface tissues is potentially very important as the primary ligand of this receptor is lipopolysaccharide (LPS).[71,80,85]

As a hydrophobic lipid molecule, LPS has a high affinity to wear particle surfaces where it easily attaches.[86] The particles provide a high-surface area foreign body platform, to which bacterial structural components, such as LPS can adhere. PAMPs or alarmins may also act as haptens, which attach especially to metallic particles. The bacterial component-particle complexes are recognized by monocyte/macrophages *via* the TLR pathway.[78,79] LPS-free titanium particles did not induce strong expression of pro-inflammatory cytokines, whereas LPS-coated particles led to elevated production of such cytokines *in vitro*.[87–89] LPS has been found in periprosthetic tissues.[90] In this line, the high expression of TLRs in the periprosthetic tissues could be potentially important, as they can reflect occurrence of subclinical biofilms on the prosthetic surfaces. By this way bacteria can contribute to resorption of bone-implant binding leading to “aseptic” loosening of TJRs.[79,84,91,92] TLR9 which recognizes bacterial-derived DNA in endosomal membranes might play a role in the host response to phagocytosed wear particles by recognizing bacteria or their DNA remnants.[71,80,93] Although extensively expressed in the periprosthetic tissues, TLR3,7, and 8 recognize viral-derived RNA structures and likely play other role in periprosthetic osteolysis because they can also sense endogenous ligands.[71,94,95]

The adaptor molecules of TLRs, such as MyD88, play important roles in intracellular signaling pathways. These adaptor molecules have been proven to be relevant to aseptic loosening.[89,96] Hence, inhibition of MyD88 decreased polymethylmethacrylate (PMMA) particle-induced production of TNF-α in RAW 264.7 murine macrophages, whereas TRIM inhibition increased TNF-α, compared to wild type macrophages. As a result, MyD88−/− mice developed less particle-induced osteolysis than wild type mice. This suggests that the biological response to PMMA particles is dependent in part on MyD88 signaling.[96] Hirayama *et al.*[89] reported that mRNA expression of TLR4, TLR5, TLR9, MyD88, IRAK1, and IRAK4 were down-regulated after phagocytosis of titanium particles with LPS by rat macrophages, suggesting self-protective mechanisms to regulate excessive host response.

C-type lectin receptors (CLRs) recognize PAMP and initiate innate and adaptive immunity in the presence of infection, similar to TLRs. However, the function of CLRs and their relevance to implant loosening is poorly understood.[97] On the other hand, the evoked signals from inflammasome sensors such as RLRs (RIG-I-like receptors) and NLRs (NOD-like receptors) can promote either the activation and nuclear translocation of transcription factors such as NF-κB or the assembly of the caspase-1 inflammasome.[98–100] In addition, implant-derived wear debris including UHMWPE, silica, chromium, cobalt, titanium and PMMA bone cement activate the NALP3 inflammasome as determined by cathepsin and cytosolic release *in vitro* (NALP = NACHT-, LRR- and pyrin-doman-containing protein 3; NACHT =

NAIP/neuronal apoptotis inhibitory protein – CIITA/MHC class II transcription activator – HET-E/incompatibility locus protein from Podospora anserine – TPI/telomerase-associated protein). Both large and small sized particles activate the NALP3 inflammasome pathway; subsequently, the proinflammatory cytokine precursors pro-IL-1 β, pro-IL-18 and pro-IL-33 are cleaved by caspase-1 activation.[83,101,102]

Wear particle phagocytosis by macrophages

Wear particles with or without endogenous proteins in the synovial-like implant interface membrane are recognized and phagocytosed by monocyte/macrophages which then produce pro-inflammatory cytokines, such as TNF-α, IL-1, IL-6, IFN-γ and others.[55,103] Although macrophages are able to phagocyte wear debris particles without any opsonizing proteins, particles with attached proteins, such as DAMP, stimulate more effectively inflammatory foreign body reactions to wear debris. This occurs through scavenger receptor and PRRs, in particular TLRs.[104] On the other hand, prosthetic particles can influence processes leading to periprosthetic bone resorption without phagocytosis.[105]

Pro-inflammatory factor production by wear particle-activated macrophages (Figure 3)

It is not possible to mention here all pro-inflammatory molecules expressed in periprosthetic tissues exposed to implant-induced danger signals. Hence, the cytokines listed below are only a part of the total activation network that could be switched on due to the presence of an implant. TNF-α is a master cytokine during inflammation and a potent inducer of other pro-inflammatory chemokines and cytokines. Macrophages exposed to prosthetic particles of different origin (PMMA, UHMWPE, metal) increase the expression of TNF-α predominantly *via* the NF-κB pathway.[106] Based on this fact, Fisher *et al.*[107] introduced the concept of *in vitro* measurement of functional biological capacity for a specific type of particle. TNF-α expression can be suppressed in macrophages by TNF-α inhibiting factor (TIF) *via* induction of p50 from the NF-κB family and also by several cytokines (IL-4, IL-10, TGF-β).[108] TNF-α can also increase its own expression *via* a positive feedback loop, which boosts the overall response of effector cells.[109]

IL-1 possesses multiple and diverse properties mediating especially the acute phase response to endogenous and exogenous stimuli acting on macrophages and other cell populations.[110] Before release from the cell in a biologically active form, precursors of IL-1β and IL-18 (pro-IL-1β and pro-IL-18) must be cleaved by caspase-1 activated by the inflammasome (a multiprotein complex of more than 700 kDa). Recently, it was also demonstrated that metal particles mediate the release of inflammatory cytokines *via* activation of inflammasomes (*e.g.* NALP3) in macrophages.[101,102] *De novo* synthesis of pro-IL-1β could be associated at least partially with stimulation of TLR1 and TLR2 by short oxidized C12-C16-long alkane polymers produced as a result of UHMWPE breakdown.[111]

IL-6 is a multifunctional cytokine strongly involved in the regulation of inflammation and bone metabolism, and therefore plays an important role at the bone-prosthesis interface. Several studies demonstrated increased expression of IL-6 after stimulation of monocyte/macrophage populations with prosthetic particles and also in periprosthetic tissues from failed THAs.[112,113] Using high-throughput protein chips to profile a set of inflammatory cytokines in tissues from failed THAs, Shanbhag *et al.*[114] found that IL-6 and IL-8 could be the primary drivers of end-stage osteolysis, while TNF-α and IL-1β may not play as important a role in the end-stage osteolysis.

Osteopontin (OPN) is a pleiotropic cytokine expressed by activated T cells, DCs and macrophages. It contains the specific integrin binding sequence (RDG, Arg-Gly-Asp) through which it interacts with several integrin receptors, *e.g.* the αVβ3-integrin.[115] OPN is

involved in chronic inflammation and osteolysis.[116] Increased expression of OPN was found in macrophages, regardless of their site, in interfacial membranes retrieved from patients with aseptically loosened implants.[117] In the absence of OPN, wear debris-induced osteolysis was found to be diminished.[118]

IL-12 and IL-23 are important factors contributing to the differentiation of naive $CD4^+$ T cells toward Th1 and Th17 phenotype, respectively. These cells could be important to "particle disease" because they are highly associated with induction and perpetuation of chronic inflammatory conditions. Both Th1 and Th17 effector T cells can drive immune-mediated changes; the disease induced by either T cell population is distinct in terms of the type of inflammatory leukocytes recruited to the site of inflammation, and in terms of the preferential location in the tissues.[119] The Th17 subset is a potent producer of IL-17A and IL-17F that target various cell groups including macrophages to express a number of pro-inflammatory cytokines (such as IL-1, IL-6, TNF-α), chemokines (monocyte chemoattractant protein-1/MCP-1/CCL2, MIP-2), and matrix metalloproteinases (MMPs) that could potentially influence the periprosthetic tissue response to danger signals and overall stability of the bone-implant interface.[120] Additionally, Th17 cell-secreted IL-17 appears to be a strong inducer of RANKL expression leading to distortion of the RANKL/OPG balance in favor of osteoclastogenesis.[121]

The role of dendritic cells in the response to wear debris

In comparison to macrophages, little is known on the role of dendritic cells in the processes of particle disease. Inflammatory DCs can be found in interface tissues around loose implants,[59] and may account for up to 30% cellular infiltrates.[83] Upon contact with purified and oxidized UHMWPE wear debris, a two-stage inflammatory response was evoked *in vitro* in GM-CSF-produced conventional DCs. First, oxidized UHMWPE stimulated MHC class II expression and IL-12 production, probably *via* direct stimulation of TLR1/2 on the DC surface.[111] This also activated transcription and synthesis of pro-IL-1β and pro-IL-18. Secondly, DCs phagocytosed but failed to degrade small UHMWPE particles, leading to phagolysosomal damage, release of the cathepsin S and B into cytosol and activation of other PRRs engaged in the NALP3 (or cryopyrin) inflammasome. Activated NALP3 inflammasome catalyzes caspase-1 dependent activation and subsequently IL-1β and IL-18 are released from the cells. Such enzymes and cytokines released to the extracellular environment contribute to the digestion of extra-cellular matrix (ECM), periprosthetic inflammation, osteoclast-mediated bone resorption and ultimately osteolysis.[83] Apart from their role in innate immunity, mature DCs in interface tissues might act as antigen presenting cells (APCs) and participate in delayed-type (cell-mediated) hypersensitivity induced by metal ions. On the other hand, resident DCs can play important role in tissue homeostasis *via* at least low expression of MHC class II, costimulatory molecules, and proinflammatory cytokines.[122]

RECENT DEVELOPMENTS

Systemic trafficking of macrophages to wear particles

The local tissue reaction to wear debris has been studied for over 4 decades. Recently, details concerning a systemic response to wear particles have been elucidated and have indicated that wear particles initiate systemic migration of monocyte/macrophage precursors to the local site of particle generation.[123–125] Monocyte/macrophages have been shown to migrate from the intravascular compartment to the remote site containing wear particles.[123,125–127] The systemic recruitment of macrophages involves signaling mechanisms, which represent a unique avenue for regulation of the inflammatory response associated with the generation of wear debris.

Ren *et al.*[123,125] used a murine model of particle-induced osteolysis to examine the role of systemic macrophage recruitment *in vivo*. The authors used immunodeficient "nude" mice, which cannot mount an immune response against the exogenous, genetically-altered, reporter macrophages which were injected into the systemic circulation. Clinically relevant PMMA or UHMWPE particles were injected into the femoral canal. Then, 5–7 days later reporter macrophages were injected intravenously through the tail vein. Using the techniques of bioluminescence, fluorescent microscopy and immunohistochemistry, reporter macrophages were shown to selectively migrate from the intravascular compartment to the remote site of particle implantation in the femoral canal. Together, these studies showed that systemic macrophages undergo preferential trafficking to a site of inflammation induced by PMMA or UHMWPE particles. However, the chemoattractants governing macrophage recruitment to wear particles remained unknown. If these factors were to be identified, this might provide a potential biological intervention to reduce the inflammatory reaction and adverse events associated with wear debris.

Monocyte chemoattractant protein-1 (MCP-1/CCL2) is one of the critical chemokines known to regulate macrophage trafficking.[55,128] MCP-1 acts through its receptor CCR2.[128] Gibon *et al.*[129] disrupted the MCP-1 ligand-CCR2 receptor axis thereby mitigating macrophage migration towards the site of UHMWPE infusion *in vivo*. This disruption was associated with a decrease in the particle-associated adverse effects on bone mineral density, using microCT scanning. Other chemokine ligand-receptor axes have yet to be explored including macrophage inhibitory factor (MIF) with CXCR2,[130] or MCP-1 interaction with CCR4.[131–133]

Another clever model describing the systemic trafficking of macrophages to wear particles from joint replacements was recently reported by Yang *et al.*[134] In this model, periprosthetic tissues and bone chips obtained at revision surgery performed for loosening in humans were placed into the muscles of SCID (severe combined immunodeficiency) mice. Peripheral blood monocytes harvested from the same patients undergoing surgery were fluorescently labeled and exposed to PMMA or titanium alloy particles *in vitro*, prior to intra-peritoneal injection into the mouse. Human monocyte/macrophages were found in abundance in the transplanted human bone chips, which exhibited marked erosions and decreased bone mineral density. In addition to particle-induced bone destruction, homeostatic mechanisms attempt to effect repair of bone in the periprosthetic tissues. Genetically altered reporter osteoprogenitor cells, introduced through a left ventricular puncture, were also shown to migrate systemically to the femoral canal into which UHMWPE particles were continuously infused.[135] Thus, it would appear that signaling mechanisms for both bone resorption and bone formation are initiated by wear particle-induced inflammation.

Wear particles and macrophage polarization

A current hypothesis suggests that macrophage activation in osteolysis may lead to macrophage polarization.[37,136] This hypothesis suggests that wear particles initially activate M0 macrophages and polarize them towards a pro-inflammatory M1 phenotype, promoting active inflammation (Figure 4). The M1 dominated response subsequently moves to a more chronic inflammation, which includes fibrosis and attempts at repair and tissue restoration. In this phase, M2 and/or Mreg macrophages may play an anti-inflammatory role, controlling ongoing tissue damage and walling off granuloma-like structures in an attempt to isolate non-degradable materials.

Co-authors of the current report[137] explored the association between wear particles from joint replacements and macrophage polarization using human tissue retrieval and *in vitro* studies. First, they hypothesized that there was a higher ratio of M1/M2 macrophages in tissues harvested from patients undergoing revision joint replacement compared to synovial

tissues from patients undergoing primary joint replacement. Second, they hypothesized that the conversion of monocyte/macrophages to the M2 phenotype by exposure to IL-4 was more effective after the uncommitted macrophages had first passed through the M1 stage.[138] They tested these hypotheses using immunohistochemistry, Western blot analysis, flow cytometry, and enzyme-linked immunosorbent (ELISA) assay of culture supernatants. A higher expression of M1 macrophages was found in the revision tissues, than in synovial biopsies from patients undergoing primary joint replacements (M1/M2=2.87 *vs* 0.46, respectively, p=0.0008). This is consistent with the hypothesis that particles produced from wear of prosthetic joints activate macrophages and polarize them to an M1 profile. This activates a cascade of release of various pro-inflammatory factors, which contribute to inflammation, osteolysis and potentially loosening of the implant.[15] The ability to polarize this response to wear particles towards an anti-inflammatory phenotype with a predominance of M2 macrophages could help to mitigate these adverse events, possibly prolonging implant longevity.

Using an *in vitro* model of murine macrophages cultured with PMMA particles, LPS, and IL-4, the authors found that IL-4 administration alone to undifferentiated macrophages was not sufficient to polarize the macrophages towards an M2 profile.[137] However, after priming the macrophages with LPS and/or PMMA particles to induce an M1 profile, IL-4 administration was sufficient in both cases to increase polarization of M1 to M2 macrophages. This was reflected in their cytokine profile with IL-1RA and other anti-inflammatory cytokines.

Paul *et al.*[139] showed that microstructured, rather than nanostructured, topography on polyvinylidene fluoride induced human macrophages to an activated state that had the characteristics of both M1 and M2 macrophages based on the expression of surface molecules, chemokine and cytokine release and gene analysis. The results of their study suggest that the macrophage response to biomaterial surfaces can be modulated through different cellular processes and that tuning of the macrophage phenotype to M1 or M2 with biomaterials is possible.

With respect to implant-derived wear particle-induced responses, it appears that the M1 macrophage response would lead to chronic inflammation, whereas the M2 macrophage response might suppress this reaction. It is clear that macrophages play a pivotal role not only in inflammation, but also remodeling/wound healing responses and therefore biomaterials can be designed to affect those responses.[140]

Host factors influencing the response to wear particles

A high variability in the survivorship of THA implants, and the incidence of aseptic loosening and size of the periprosthetic osteolytic lesions has been observed between individuals with similar UHMWPE wear rates even with the identical implant.[141] Engh *et al.*[142] estimated that both volumetric wear and patient propensity to osteolysis might account for 53% of the variance in the total area of osteolysis. How does one explain such a high degree of inter-patient variability?

This could be caused, for example, by differences in surgical technique (*e.g.* positioning of the implants, quality of bone-implant interface, protection of bone bed from joint fluid access). Furthermore, variations related to biomaterial and design properties of particular implants and due to patient-related factors (*e.g.* age, co-morbidities, medications, level of activity and differences in mechanical loading) could play a role. Additionally, genetic factors can contribute to the risk for aseptic loosening. In line with this, there is a question as to which genes (genotype) could influence the fate of an implant in terms of premature aseptic loosening/periprosthetic osteolysis (phenotype).

Wilkinson *et al.*[143] first published a study on the association between single nucleotide polymorphisms (SNP) in the gene encoding for TNF-α and risk of periprosthetic osteolysis in hip replacement patients. Subsequently, several studies described other molecules as candidates involved in the processes of aseptic loosening/osteolysis.[141,144–146] Structurally and functionally, these include receptors, intracellular mediators, enzymes, cytokines and other proteins (Figure 5). In addition, detailed knowledge of the hierarchy of regulatory networks could help with the identification of other yet hidden targets. For instance, NF-κB1 (p50 in its active form) represses the gene encoding TNF-α. Hence, mutations or polymorphisms that reduce the expression/binding of NF-κB1 could contribute to chronic inflammation associated with TNF-α hyperactivity around implants *via* reduced repression of TNF-α.[109]

A recently published systematic review on genetically determined susceptibility to aseptic loosening of hip replacements revealed several areas of potential agreement (SNPs of TNF-238A allele, IL1RA +2018C allele, polymorphisms in genes for IL-6, MMP-1, *etc*.). However, this review also demonstrated major sources of heterogeneity between studies, underlining the need for large multi-center prospective studies that should provide stronger evidence for genetic predisposition to aseptic loosening/osteolysis.[147] These studies will require both more sophisticated research strategies and advanced statistical methods (*e.g.* improved risk-analysis models) to overcome the challenges. Additionally, such studies will require multiple adjustments for numerous important variables such as age, gender, time from surgery, and type of implant thus enabling more precise clinical phenotyping.

CONCLUSION

Wear particles stimulate biological reactions resulting in chronic inflammation and bone destruction, that ultimately result in implant loosening in some patients. Macrophages, as sentinels of the innate immunity system, are central to the initiation of this inflammatory cascade *via* the release of pro-inflammatory and pro-osteoclastic factors. The current scheme includes numerous biological steps that have been in part clarified, but comprehensive knowledge on osteolysis is still in progress. Periprosthetic osteolysis was originally considered as a local disease, however recent developments indicated that wear particles initiate systemic migration of monocyte/macrophage precursors to the local site of particle generation. Furthermore, macrophages are able to polarize into an inflammatory phenotype in response to wear debris. On the other hand, there exist strong and effective regulatory networks that inhibit wear-debris induced inflammatory pathways. Many of the findings are based on studies in mice and may not be easily transferred to humans. With better understanding of the biologic response to wear debris, new concepts have emerged, such as the role of individual biological and genetic factors in the modulation of particle-induced osteolysis. Taken together, these new insights should result in potential strategies to mitigate the adverse events related to wear particles.

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ABBREVIATIONS

ALVAL	Aseptic lymphocyte dominated vasculitis associated lesions
AP-1	Activator protein-1
APC	Antigen presenting cell
CCL2,3,4,…	C-C chemokine ligand 2,3,4,…
CCR2,4	C-C chemokine receptor 2,4
CDP	Common dendritic cell progenitor
CLR	C-type lectin receptor
CXCL1,2,…	Chemokine (C-X-C motif) ligand 1,2,…
DAMP	Danger-associated molecular pattern
DC	Dendritic cell
ECM	Extracellular matrix
FIZZ1	Found in inflammatory zone 1
GM-CSF	Granulocyte-macrophage colony stimulating factor
GMP	Granulocyte/macrophage progenitor
GP	Gene polymorphism
HSC	Hematopoietic stem cells
IFN-α/β	Interferon α/β
IFN-γ	Interferon-gamma
IL-1 RA	IL-1 receptor antagonist
IL-1,2,3,…	Interleukin-1,2,3,…
IRAK1,4	Interleukin-1 receptor-associated kinase-1,4
IRF	Interferon regulatory factor
KLF4	Krüppel-like factor 4
LFA	Low friction arthroplasty
LPS	Lipopolysaccharide
LT-α	Lymphotoxin-α
M-CSF	Macrophage-colony stimulating factor
MAMP	Microbial-associated molecular patterns
MAPK	mitogen activated protein kinase
MARCO	Macrophage receptor with collagenous structure
MCP-1	Monocyte chemoattractant protein-1
MDP	Macrophage/dendritic cell progenitor
MHC	Major histocompatibility complex
MIF	Macrophage inhibitory factor
MIP-2	Macrophage inflammatory protein-2

MLP	Multi-lymphoid progenitor
MMP	Matrix metalloproteinase
MyD88	Myeloid differentiation primary response protein 88
NACHT	NAIP/neuronal apoptotis inhibitory protein
CIITA/MHC	class II transcription activator
HET-E	incompatibility locus protein from Podospora anserine
TP1	telomerase-associated protein
NADPH	Nicotinamide adenine dinucleotide phosphate
NAIP	Neutral apoptosis inhibitor protein
NALP3	NACHT-, LRR- and pyrin-doman-containing protein 3
NF-κβ	Nuclear factor-kappa β
NFAT	Nuclear factor of activated T-cells
NK	Natural killer
NLR	NOD-like receptor
NO	Nitric oxide
NOD	Nucleotide-binding oligomelization domain
NOX	NADPH oxidase
OL	Osteolysis
OPG	Osteoprotegerin
OPN	Osteopontin
PAMP	Pathogen-associated molecular patterns
pDC	Plasmacytoid dendritic cell
PGE2	Prostaglandin E2
PMMA	Polymethylmethacrylate
PRR	Pattern recognition receptor
RAGE	Receptor for advanced glycation endproducts
RANK	Receptor activator of NF-κB
RANKL	RANK ligand
RIG	retinoid acid inducible gene
RDG	Arginine-glycine-aspartic acid
RLR	RIG-I-like receptor
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SCID	Severe combined immunodeficiency
SNP	Single nucleotide polymorphisms
STAT1,6	Signal transducer and activator of transcription 1,6

TAK1	Transforming growth factor-activated kinase 1
TGFβ	Transforming growth factor-β
THA	Total hip arthroplasty
TIF	TNF-α inhibiting factor
TJR	Total joint replacement
TKA	Total knee arthroplasty
TLR1,2,3,4,…	Toll-like receptor1,2,3,4,…
TNF- α	Tumor necrosis factor- α
TRIM	Tripartite motif
UHMWPE	Ultra-high molecular weight polyethylene

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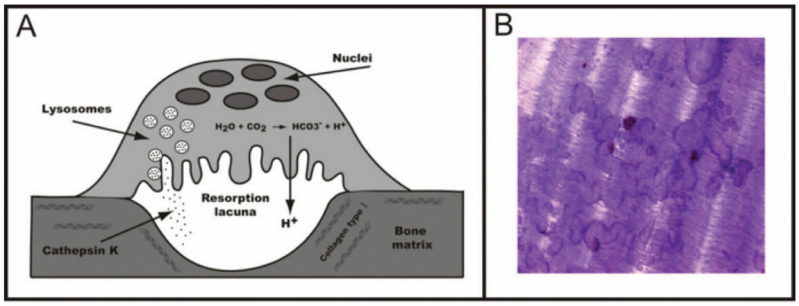

Figure 1.

A) Bone resorption by the osteoclast is a two-phase process. Bone is acid demineralized, followed by degradation of the demineralized collagen type I-rich matrix by secreted cathepsin K and other acidic proteinases. B) After one cycle, osteoclasts either undergo apoptosis or initiate a new cycle by moving further. This figure shows toluidine blue stained osteoclast trails (resorption pits) on dentine discs, formed by M-CSF- and RANKL-induced human osteoclasts. M-CSF = macrophage-colony stimulating factor. RANKL = receptor activator of nuclear factor kappa- ligand.

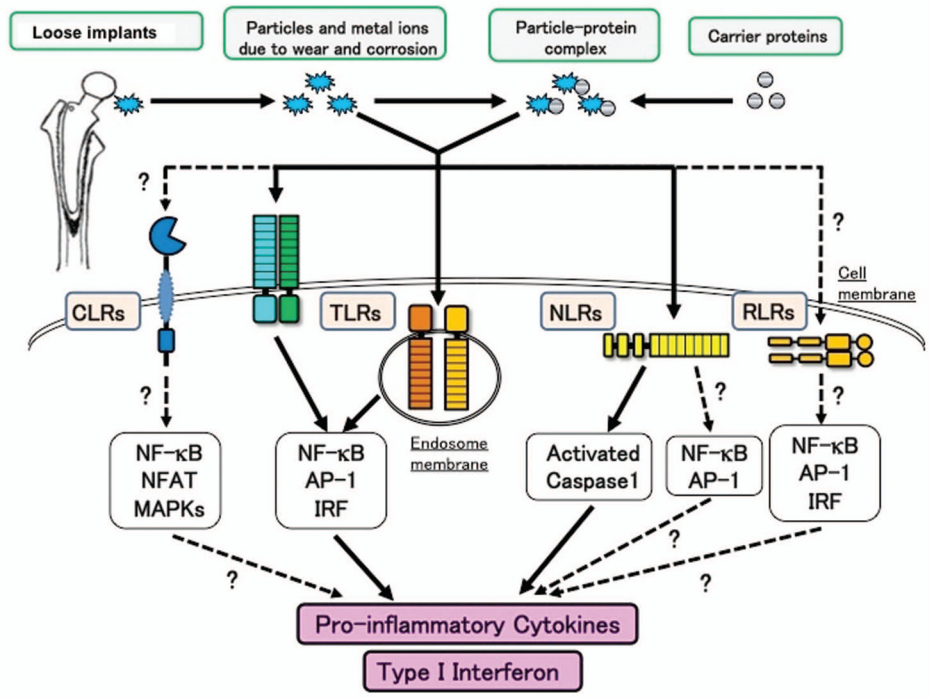

Figure 2.

Pattern-recognition receptors (PRRs) recognize wear debris around loose implants. Wear particles are generated from articulating and non-articulating surfaces of artificial joints. Particles with/without carrier proteins are recognized, as such or after phagocytosis, by pattern-recognition receptors (PRRs) including C-type lectin receptors (CLRs), Toll-like receptors (TLRs), nucleotide-binding oligomelization domain (NOD)-like receptors (NLRs) and retinoid acid inducible gene (RIG)-I-like receptors (RLRs) which finally leads to the production of pro-inflammatory cytokines [*e.g.* tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-8, interferon (IFN)-γ and type I IFN]. *In vitro*, implant-derived wear debris was reported to induce NALP3 inflammasome [the neutral apoptosis inhibitor protein (NAIP), MHC class II transcription activator (CIITA), heterokaryon incompatibility locus E protein from *Podospora anserine* (HET-E) and telomerase-associated protein (TP1) (=NACHT), leucine-rich repeat and pyrin-domain-containing protein 3 or NALP 3 inflammasome]. Wear particles activate the NALP3 inflammasome pathway so that the proinflammatory cytokine precursors pro-IL-1-β, and pro-IL-18 are proteolytically activated by caspase-1. NF-κB = nuclear factor kappa B; NFAT = nuclear factor of activated T-cells; MAPKs = mitogen activated protein kinases; AP-1 = activator protein 1; IRF= interferon regulatory factor.

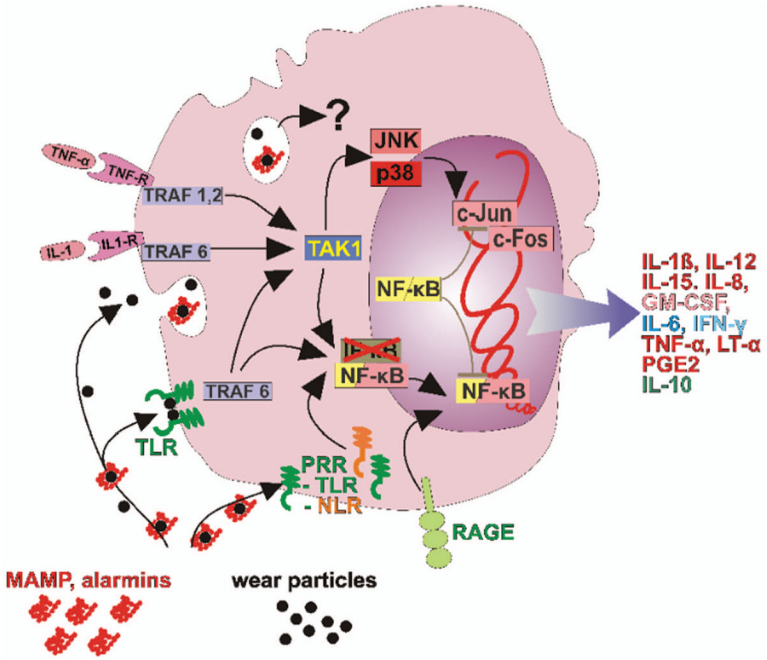

Figure 3.

Initiation and amplification of the inflammatory response is associated with secretion of several cytokines and other substances from cells stimulated by pathogen/microbial-associated molecular patterns (PAMP/MAMP) or alarmins such as LPS, bacterial cell wall structures, bacterial DNA, damaged cell components, *etc.* recognized through pattern-recognizing receptors (PRRs) such as cell surface or intracellular Toll-like receptors (TLRs) and strictly intracellular nucleotide oligomerisation domain-like receptors (NLRs), or cellular damage sensing receptor for advanced glycation endproducts (RAGE) and others. Wear particles, once coated with host-related danger signals or other opsonins particles, could contribute substantially to the above inflammatory stimulation predominantly by increasing the expression of several pro-inflammatory cytokines such as IL-1, TNF-α, and IL-6. Intracellular pathways responsible for inflammatory responses to TLR, IL-1 receptor and TNF-α receptor stimulation use several common crucial factors such as transforming growth factor-activated kinase 1 (TAK1), which is involved in the activation of canonical pro-inflammatory transcription factors NF-κB and c-JUN member of AP-1. Both transcription factors are responsible for transcription initiation of pro-inflammatory cytokines and mediators (IL-1β, IL-6, IL-12, IL-15, IL-8, TNF-α, LT-α, PGE2) but also for the expression of growth factors (GM-CSF) and Th1 stimulators IFN-γ. Two factors are important for modulation of the inflammatory response: homodimeric form of NF-κB (p50/p50) and p38. For example p50/p50 could suppress the expression of TNF-α. The role of p38 can both support inflammation by promoting expression of proinflammatory cytokines and prevent inflammatory responses for example by p38 controlled expression of important anti-inflammatory factors that limit inflammation and contribute to its resolution (IL-10).

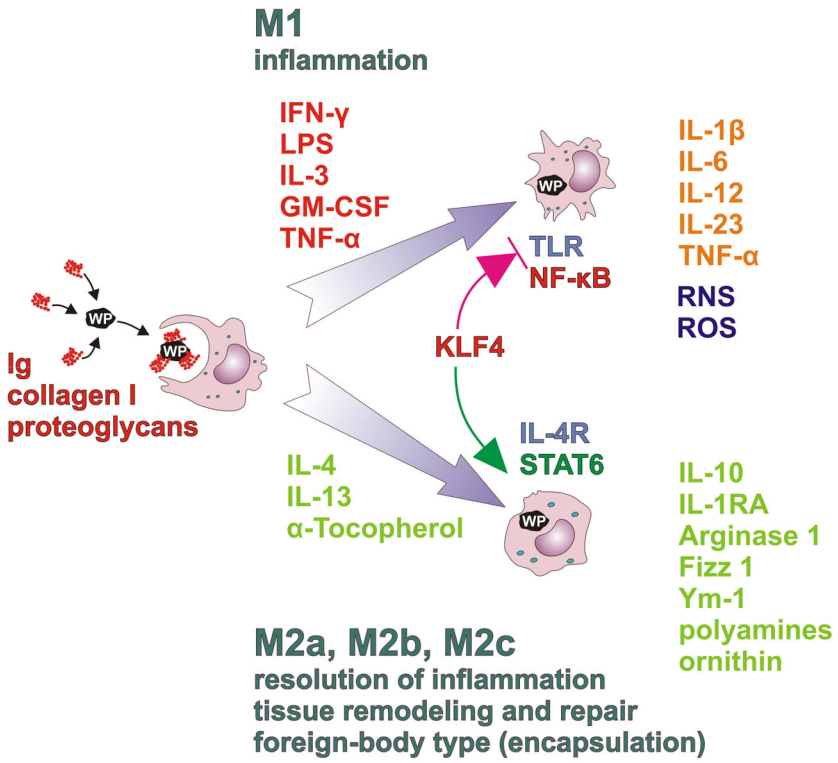

Figure 4.

Wear particles (WP) or pathogen-associated molecular patterns like lipopolysaccharide (LPS) together with IFN-γ produced by NK cell and several cytokines (IL-3, GM-CSF, TNF-α) induce macrophage polarization toward the classical M1 phenotype, characterized by the production of pro-inflammatory cytokines IL-1β, IL-6, Th1-polarizing cytokine IL-12, Th17 maturation-inducing cytokine IL-23, reactive oxygen species (ROS), and reactive nitrogen species (RNS) promoting and perpetuating thus inflammation. Other factors like IL-4, IL-13, α-tocopherol stimulate macrophage polarization toward alternatively activated - M2 macrophage, characterized by production of IL-10, IL-1 receptor antagonist (IL-1RA), arginase 1, Fizz 1, chitinase-like protein (Ym-1), polyamines, ornithin, factors involved in antiinflammatory response or resolution of inflammation, tissue remodeling and repair, foreign-body type response (encapsulation), anti-parasite defense (Ym-1), and generally suppression of Th1 functions. During macrophage polarization Krüppel-like factor 4 (KLF4) plays a decisive role. KLF4 expression is increased in M2 macrophages and dramatically reduced in M1 macrophages. KLF4 cooperates with STAT6 to induce an M2 polarization and to inhibit an M1 *via* sequestration of coactivators of NF-κB. Wear particles deliberated from the prosthetic surfaces coated by type I collagen, aggrecan, proteoglycans and immunoglobulins serve as strong facilitators during macrophage polarization.

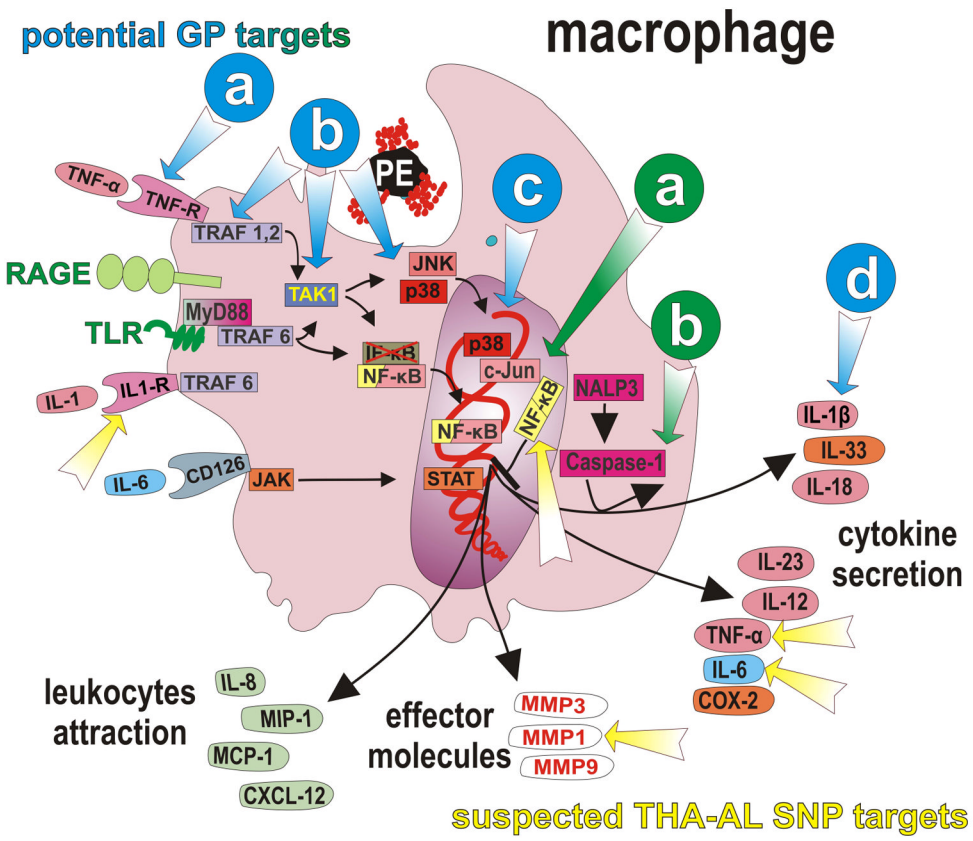

Figure 5.

Simplified overview of the potential targets influencing macrophage-signaling pathways related to periprosthetic osteolysis (OL) and total hip arthroplasty aseptic loosening (THA-AL). In blue - gene polymorphisms (GP) affecting: receptors (a); individual proteins of intracellular signaling pathways (b); non-coding sequences of involved genes (promoter and response elements, enhancers, introns, polyadenylation signal) (c); GP affecting structure and activity of chemokines, cytokines and effector molecules (d). In green - posttranscriptional regulation (e.g. regulatory miRNA, epigenetic regulation of gene-expression) (a); GP affecting processing enzymes and proteins involved in posttranslational modifications, intracellular transport, and processing (b). In yellow - currently described SNP targets supposed to be associated with increased risk of AL (IL-1 receptor; matrix metalloproteinase 1 (MMP-1); IL-6 and TNF-α; SNP in TNF-α promoter associated with reduced binding of inhibitory p50 homodimers). Note that when one or even several of proposed “pro-osteolytic GPs” (even in the key molecules) are found in a patient, it does not automatically mean that large osteolysis develops around his or her TJR. Such abnormalities may be well compensated by other pathways involved in complex signaling network running in periprosthetic tissues.