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Review

Macrophage responses to implants: prospects for personalized medicine

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ABSTRACT

Implants, transplants, and implantable biomedical devices are mainstream solutions for a wide variety of human pathologies. One of the persistent problems around nondegradable metallic and polymeric implants is failure of macrophages to resolve the inflammation and their tendency to stay in a state, named "frustrated phagocytosis." During the initial phase, proinflammatory macrophages induce acute reactions to trauma and foreign materials, whereas tolerogenic anti-inflammatory macrophages control resolution of inflammation and induce the subsequent healing stage. However, implanted materials can induce a mixed pro/anti-inflammatory phenotype, supporting chronic inflammatory reactions accompanied by microbial contamination and resulting in implant failure. Several materials based on natural polymers for improved interaction with host tissue or surfaces that release anti-inflammatory drugs/bioactive agents have been developed for implant coating to reduce implant rejection. However, no definitive, long-term solution to avoid adverse immune responses to the implanted materials is available to date. The prevention of implant-associated infections or chronic inflammation by manipulating the macrophage phenotype is a promising strategy to improve implant acceptance. The immunomodulatory properties of currently available implant coatings need to be improved to develop personalized therapeutic solutions. Human primary macrophages exposed to the implantable materials ex vivo can be used to predict the individual's reactions and allow selection of an optimal coating composition. Our review describes current understanding of the mechanisms of macrophage interactions with implantable materials and outlines the prospects for use of human primary macrophages for diagnostic and therapeutic approaches to personalized implant therapy. *J. Leukoc. Biol.* 98: 953–962; 2015.

Abbreviations: COX = cyclooxygenase, DAMP = damage-associated molecular pattern, ECM = extracellular matrix, FBR = foreign body response, IRAK = IL-1R-associated kinase, M1 = classically (IFN-γ) activated M2 = alternatively (IL-4) activated, MMP = matrix metalloproteinase, MMR = macrophage mannose receptor (CD206), OPG = osteoprotegerin, PDGF = platelet-derived growth factor, PEG =

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Introduction

Implants, transplants, and implantable biomedical devices have become mainstream solutions for a wide variety of health problems, and their use in medical practices, for therapeutic applications, prevention, or diagnosis, is constantly increasing [1–3]. However, often adverse immune reactions against these foreign materials are observed in patients. These adverse reactions can lead to dramatic, immediate outcomes, such as intense pain, excessive inflammation, or rejection of the implanted material/tissue. Chronic inflammation and resulting pathologic changes in the implant microenvironment can be detrimental for the long-term function of implanted materials/tissues. Beside the inherent implant-related clinical problems of inefficiency or delayed recovery, adverse immune reactions also cause a significant deterioration of patients' quality of life, as 1) their health problems are not completely solved and affect their daily life, and 2) they must endure painful side-effects linked to rejection and/or inflammation. In addition, implantation and transplantation failures have a negative economic impact from the costs of additional surgery and/or treatment of side-effects, as well as prolongation of hospitalization and increased costs of healthcare. The development of strategies to avoid or exclude undesired side-effects in the use of biomedical devices and implants represents an important challenge.

To find solutions to such adverse immune reactions, there is a need to address this problem at an early stage of product development and preoperative tissue/material preparation. However, despite significant advances in recent decades in biomedical engineering, no safe and definitive technology to control a host's adverse immune reactions

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against biomedical devices, implants, and transplants is currently available.

Upon introduction of implantable material, it is recognized by the immune system as foreign, initiating a macrophage-mediated acute inflammatory phase, followed by resolution, proliferation of somatic cells, and tissue remodeling, leading to restoration of tissue homeostasis. However, a healing process that results in full function requires orchestration and satisfactory resolution of inflammation.

Macrophages play a pivotal role in the cascade of immunologic responses toward implants and biomedical devices. Recent years have witnessed an increased awareness in the biomaterials community regarding the importance of macrophages for healing of implant-related complications [4]. Tissue macrophages are among the first cells to react to any tissue injury and introduced foreign material, including implants. Macrophages are evolutionarily designed to initiate, orchestrate, and resolve inflammation by modulating their own phenotype as well as that of surrounding cells [5]. They derive from monocytes and show high levels of functional and phenotypic plasticity. Macrophages are versatile biochemical factories with a large arsenal of molecules to contain invading microorganisms or foreign bodies at the risk of collateral damage to surrounding tissue.

This review describes current understanding of the mechanisms of macrophage interactions with implanted materials and outlines the prospects for diagnosis and development of novel therapeutic approaches to limit resultant adverse reactions by implant modifications via nano/microscale coatings.

MACROPHAGE ACTIVATION AND POLARIZATION

Macrophages can be polarized by cytokines into "classical" (M1) and "alternative" (M2) states of activation. As opposed to IFN-γ-induced macrophages with proinflammatory and antimicrobial activity, IL-4 inhibits expression of inflammatory cytokines and enhanced mannose receptor-mediated endocytosis, reported by Stein et al. [6] in the Gordon laboratory. In 1999, Goerdt and Orfanos [7] extended the list of alternative activation inducers to include glucocorticoids, IL-10, IL-13, and TGF-β. Mantovani and colleagues [8] subdivided M2 macrophage phenotypes into 3 groups: M2a, induced by IL-4 and IL-13; M2b, by ligation of FcRs on IFN-γ-primed macrophages; and M2c, deactivation induced by IL-10, TGF-β, or glucocorticoids. M1 and M2 phenotypes are not terminal states of macrophage differentiation but rather, reversible, functional conditions that reflect the ability of these cells to respond promptly to exogenous danger signals and microenvironmental changes [9, 10]. The complexity of macrophage gene expression analysis and its apparent plasticity has resulted in refinements, in which prototypic M1 (IFN-γ induced) and M2 (IL-4 induced) macrophages are considered polar states in a spectrum of activation [11, 12]. In this model, each stimulus potentially induces characteristic macrophage transcriptional programs that partially overlap with those induced by related stimuli. Depending on the nature of such stimuli, these programs may reveal more or less similarity with prototypic M1 and M2 macrophages.

In general, prototypic M1 macrophages are characterized by activation of STAT1 and NF-κB transcription factors and elevated production of proinflammatory cytokines, such as TNF-α, IL-1β, IL-6, and IL-12 [5, 13]. These cytokines are able to induce rapid inflammatory and cytotoxic responses, characterized by activation of NK cells, $CD8^+$ cytotoxic lymphocytes, and recruitment of neutrophils. Elevated production of ROS and NO by M1 macrophages contributes to their enhanced antimicrobial properties. In contrast, prototypic M2 macrophages are characterized by activation of STAT6, elevated expression of endocytic receptors (such as stabilin-1 and mannose receptor), and increased production of anti-inflammatory factors, such as IL-10 and IL-1Ra [10, 14, 15]. M2 macrophages are involved in resolution of inflammation, wound healing, as well as pathologies, including allergy and cancer [5]. Although an M2 phenotype is considered to be favorable for implant function, some M2-released factors, such as CCL18, can support chronic inflammation and delay healing [16].

As the majority of studies in the area of macrophage/implant interactions uses M1/M2 terminology, in the current review, we will use the term "M1" for prototypic IFN-γ-stimulated macrophages and "M2" for prototypic IL-4-stimulated macrophages. In other cases, terms "M1-like" and "M2-like" will be used for macrophages with dominant pro- and anti-inflammatory phenotypes, respectively.

MACROPHAGE-PRODUCED CYTOKINES AS KEY FACTORS OF CHRONIC INFLAMMATION

Chronic inflammation is generally defined as a persistent inflammatory process, and it is a result of failure to resolve an acute inflammatory process or a result of an inadequate response to an injurious agent. The main cellular components at a chronic inflammatory site are monocyte-derived macrophages and lymphocytes. Inflammation at these sites is maintained as a result of an improper balance of secretion of pro- and anti-inflammatory cytokines.

Cytokines can be broadly grouped according to their function as pro- (TNF-α, IL-1β, IL-6, etc.) and anti-inflammatory (IL-1Ra, IL-10, and TGF-β). Macrophages, depending on their activation inducers, are able to secrete both types of cytokine. Additionally, macrophages secrete a large variety of chemokines to attract other immune cells to the site of inflammation (CXCL1, CXCL2, CCL5, IL-8, CXCL9, CXCL10, CXCL11) [17] or to promote fibrosis (CCL2, CCL3, CCL4, CCL11, CCL20, CCL22) [18].

A central role in the development of an inflammatory site is attributed to TNF-α, IL-1β, and IL-6. These cytokines are usually secreted in the acute phase of inflammation and play a role in the response to pathogens, recruitment of neutrophils, and differentiation and activation of B and T cells [17, 19, 20]. However, numerous studies also show their involvement in chronic inflammation, such as inflammatory bowel disease,

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polyethylene glycol, PET = polyethylene terephthalate, PLA = polylactic acid, PLL = poly(L-lysine), PMMA = polymethylmethacrylate, PVA = polyvinyl alcohol, RANK = receptor activator of NF-κB, RANKL = receptor activator of NF-κB ligand, ROS = reactive oxygen species, SEM = scanning electron microscopy, SR-A = scavenger receptor A, TiO_2 = titanium dioxide

rheumatoid arthritis, psoriasis, atopic dermatitis, chronic obstructive pulmonary disease, Alzheimer's disease, systemic lupus erythematosus, and cancer [21–23]. Conversely, CCL18, most strongly up-regulated by IL-4, was shown to be involved in chronic inflammation, as well as fibrosis [16, 24].

A number of other macrophage-secreted cytokines have also been associated with chronic inflammation. For example, IL-1α, IL-8, IL-18, and IL-32 have been linked to rheumatoid arthritis and atopic dermatitis; IL-3, IL-7, and IL-10 to allergic diseases and cancer; and IL-7, IL-8, IL-18, IL-19, IL-20, and IL-24 to psoriasis [19, 21].

Fibrosis is a common consequence of chronic inflammation, developing as a result of failed wound healing. Several studies suggest that M2 macrophages (stimulated by IL-4 or IL-13) play a key role in wound repair [25, 26]. They secrete TGF-β1, PDGF, MMPs, CCL7, and CCL8 to stimulate proliferation, migration, and activation and increase collagen synthesis in myofibroblasts, consequently promoting fibrosis [27].

Depending on the stimulus, macrophages are able to adopt a distinct phenotype with a different cytokine secretion profile. However, these distinct macrophage populations were obtained in vitro, whereas macrophage populations are likely to be mixed in vivo, as distinct stimuli are present at the same time at an inflammatory site. Moreover, many studies have been conducted in mouse models, and the results are not always analogous to those on human macrophages [28]. Thus, specific profiles of inflammation mediators, released in response to implant materials and coatings, are required to define individual patient responses and possible therapeutic improvement of implant compatibility.

IMPLANT-INDUCED INFLAMMATORY COMPLICATIONS

In recent years, implants and biomedical devices have become common solutions to a variety of medical problems. From dental implants and artificial knees to ventricular assist devices and artificial eye lenses, biomedical devices have been implemented successfully in medicine to restore functions of damaged organs. Besides the common perioperative and postoperative complications of surgery, implant-specific inflammatory complications often develop. In some patients, adverse immune reactions to implanted devices lead to chronic inflammation, pain, and on occasion, implant failure. These, in turn, may cause additional costs, further surgical intervention, and most importantly, a decrease in quality of life of the patient. Examples of inflammation-related implant failures are listed in **Table 1**.

Implants for total knee or hip replacement are among the most commonly used in medicine. In the United States alone, there are >1 million such surgical operations performed each year [34]. Some of these patients need to undergo a revision surgery, usually related to aseptic loosening associated with periarticular osteopenia, focal osteolysis, and infection [35]. At the heart of these complications is inflammation. It usually starts with the accumulation of wear particles (microscopic particles of implanted material formed during friction of articulating surfaces) at the implant-tissue interface. These induce a cellular response through phagocytosis or through direct interactions at the cell surface [36]. Host cells, primarily resident macrophages and fibroblasts, upon recognition of the wear particles, start to produce a wide range of proinflammatory cytokines and growth factors, such as TNF-α, IL-1α, IL-1β, IL-6, IL-8, IL-11, IL-15, TGF-α, GM-CSF, M-CSF, PDGF, and epidermal growth factor [37, 38]. These inflammatory factors are able to induce osteoclast formation through the RANKL/RANK/OPG pathway, which stimulates osteolysis, as well as recruits inflammatory macrophages and lymphocytes [34, 36, 39, 40]; these cells produce additional proinflammatory and pro-osteoclastogenic factors, thus enhancing the reaction. On the other hand, wear particles inhibit the differentiation of mesenchymal stem cells into osteoblasts and induce apoptosis. Furthermore, osteoblasts start to secrete proinflammatory cytokines and chemokines that recruit inflammatory macrophages and lymphocytes, as well as secrete osteoclastogenic factors to promote osteolysis [41]. Additionally, a number of oxidative stress molecules, such as high-mobility group protein B1, COX-2, iNOS, 4-hydroxynonenal, and nitrotyrosine, have been found elevated in periprosthetic tissue associated with osteolysis, suggesting a role for ROS in wear particle-induced osteolysis [42].

Although the main role in mediating the response to wear particles belongs to macrophages, several other cells are also involved. Osteoclasts are multinucleated cells of the monocyte/macrophage lineage involved in bone resorption and osteolysis [37]. In the periprosthetic tissue of patients with osteolysis, elevated levels of CCL2 and CCL4 may increase osteoclast

TABLE 1. Reasons for implant failure associated with inflammation

Type of implant	Commonly used material	Cause for implantation	Reasons for failure
Teeth [29]	Titanium, zirconium, Ti-Ni alloy	Tooth loss	Peri-implantitis, osteolysis, fibrosis at the implant-bone interface
Knee [30]	Co-Cr alloy, polyethylene, titanium alloys, stainless steel	Osteoarthritis, rheumatoid arthritis	Aseptic loosening, infection, periprosthetic fracture, arthrofibrosis
Hip [31]	Co-Cr alloy, polyethylene, Titanium alloy, ceramic, stainless steel	Osteoarthritis, osteonecrosis, inflammatory arthritis	Aseptic loosening, infection, periprosthetic fracture
Spine [32]	Titanium, stainless steel, plastic	Spinal deformity, scoliosis, osteoporosis	Pseudoarthrosis, infection, pain
Left ventricular assist device [33]	Titanium	End-stage heart failure	Coagulation disorders, wound infections, stroke

recruitment [43]. Wear particles can inhibit anti-osteoclastogenic signaling through IL-6 and IFN-γ, and as mentioned earlier, through proinflammatory cytokines, they can activate osteoclasts via the RANKL/RANK/OPG pathway [44]. Thus, wear particles promote osteolysis through recruitment and activation of osteoclasts and inhibition of anti-osteoclastogenesis signals. Additionally, fibroblasts are also involved in osteolysis by promoting osteoclastogenesis. In response to wear debris particles, fibroblasts up-regulate expression of CCL2, IL-1β, IL-6, IL-8, MMP1, COX-1, COX-2, LIF, TGF-β1, and TGF-βR1, which promote generation of osteoclasts from bone marrow cells [45].

Osteoblasts are also involved in the formation of the immune reaction to implants. In physiologic conditions, there is a balance between bone formation and bone resorption, with osteoblasts responsible for bone formation, whereas osteoclasts promote bone resorption. In inflammatory conditions, this balance is altered. In response to wear particle stimulation, osteoblast ability to secrete osteoid is impaired [41], and collagen I synthesis is decreased [46]. Additionally, wear particles induce production of IL-1, IL-6, IL-8, TNF-α, CCL2, and MMP1 in osteoblasts [41, 46], in addition to osteoclastogenesis factors, RANKL and M-CSF [47].

Lymphocytes may also play a role in the immune reaction toward wear particles. The subtype of T cells that are predominantly present in the periprosthetic tissue is Th1 cells. It has been suggested that lymphocytes cooperate with macrophages through the interaction of IL-15, IL-15Rα, and IL-2Rβ and take part in the type IV delayed hypersensitivity response. Upon activation, they release IL-3, GM-CSF, IFN-γ, lymphotoxin-α, and macrophage migration inhibitory factor to attract and activate macrophages, which in turn, secrete IL-2 and activate more Th cells. This represents a possible immune mechanism in patients with hypersensitivity to metal ions [38].

MACROPHAGE RESPONSES TO IMPLANTS

All implanted materials are able to induce a FBR, which is primarily mediated by macrophages. The severity of reaction may depend not only on the nature of the implanted material, its structure, and surface topography but also on individual reactions of the implant recipient. In general, the standard sequence of immune events after implantation includes protein adsorption on the surface of the implant, macrophage recruitment, and adhesion on the surface, followed by the release of chemokines that recruit additional macrophages and other immune cells and induce acute inflammation. Unsuccessful resolution of acute inflammation can result in chronic inflammation, accompanied by fusion of macrophages, formation of foreign-body giant cells, and fibrous encapsulation of implanted material [48]. The severity of these reactions, the phenotype, and cytokine profile of implant-associated macrophages predetermine the fate (function vs. failure) of implanted devices. Implant-associated infections strongly amplify inflammatory responses and induce implant failure [49]. Excessive fibrosis, resulting in the formation of a thick, fibrous capsule, also affects implant function. Thus, control of inflammatory responses by preventing implant-associated infections and manipulating the macrophage phenotype may improve implant acceptance by the patient. In this part of the review, we will focus primarily on the macrophage phenotype induced by interaction with implants.

The nature of the implanted material plays a critical role in the amplitude and type of macrophage reaction. For example, an in vitro study compared the effects of 4 different biomaterials on human macrophage phenotype; 2 (Parietex Composite and multifilament PET) induced a more pronounced, proinflammatory response, detected by production of TNF-α, MCP-3 (CCL7), IL-1β, IL-6, and MIP-1α (CCL3), and a higher pro/anti-inflammatory cytokine ratio, referred to as an "M1/M2 index" [50]. Moreover, the inflammatory environment, simulating bacterial infection, increased proinflammatory cytokine production by macrophages cultured with PET. In contrast, macrophages cultured with polypropylene responded with CCL18 production and demonstrated a low pro/anti-inflammatory cytokine ratio [51]. These studies suggested that choice of biomaterial may be critical when implant-associated infection is possible.

In general, titanium and titanium alloys are considered to be highly biocompatible materials for implantation.A layer of TiO_2 on the surface of implants has beneficial effects on its biocompatibility. For example, TiO_2-coated silicone inhibited production of reactive oxygen species and IL-6 by mouse macrophages [52]. However, titanium implants are not completely devoid of inflammatory responses, and adverse reactions to titanium are indeed observed. One complication is caused by the ability of macrophages to engulf implant-released particulate wear debris; this results in activation of proinflammatory programs in human macrophages, including release of TNF-α, IL-1β, IL-6, MIP-1α, and MCP-1 (CCL2) [43, 53]. The pattern of cytokine response and concentrations of released cytokines may vary strongly between individuals, indicating that individualized approaches are required for treatment. Therefore, modulation of macrophage phenotype toward an M2-like state can be considered as a therapeutic approach [54, 55]. Overall, a moderate proinflammatory response to titanium particles was exacerbated in IFN-γ (M1)-predifferentiated human macrophages (including increased production of TNF-α, IL-1β, CCL3, CCL4, GM-CSF, and G-CSF) and suppressed in IL-4 (M2)-treated macrophages [56]. Thus, M1 polarization of macrophages during bacterial biofilm formation on the surface of implants may enhance adverse reactions to titanium, whereas M2 polarization can potentially diminish them.

Despite numerous observations that implanted biomaterials recruit proinflammatory macrophages, in some cases, the phenotype of implant-associated macrophages cannot be strictly characterized as M1 or M2 but combines M1 and M2 features, indicating that an extensive panel of markers is needed to define the implant-specific macrophage phenotype. Moreover, in porous biomaterials, polarization of macrophages depends on their spatial distribution. For instance, in a recent in vivo mouse study, macrophages located in the pores of polyhydroxyethylmethacrylate-based hydrogels revealed a M1-like phenotype, whereas M2-like macrophages were found on the implant surface [57].

Polarization of macrophages during implant-induced reactions involves the recognition of foreign materials by surface receptors. However, the specific macrophage receptors and intracellular

signaling upon recognition of biomaterials are poorly characterized. Proteins adsorbed on the surface of biomaterials (fibrinogen, fibronectin, vitronectin, complement component C3b, etc.) play a major role in implant recognition and initiation of FBR [48]. These proteins are recognized by several macrophage integrins, including macrophage-1 antigen (CD11b/CD18) and arginine-glycine-aspartic acid-binding integrins αvβ3, αvβ5, and α5β1 [58, 59]. Integrins are not only involved in the initial adhesion to biomaterials but also mediate inflammatory responses and regulate the extent of fibrotic encapsulation [58]. In human macrophages, the CD11b/CD18 receptor recognized titanium alloy particles, followed by signaling through transcription factors NF-κB and induction of TNF-α and IL-6 expression [60]. Potential involvement of TLR signaling in the response to implant wear debris was also reported. Mouse bone marrow-derived MyD88 knockout macrophages demonstrated an impaired TNF-α response after exposure to PMMA particles. In addition, particle-induced osteolysis was reduced in MyD88$^{-/-}$ mice [61]. Another study that uses TLR4 knockout mice suggested that monocyte/macrophage adhesion on the surface of PET implants is inhibited in the absence of TLR4 [62]. TLRs are able to recognize certain types of biomaterial directly [59]. However, accumulation of endogenous DAMPs on the surface of biomaterials and their subsequent recognition by TLRs upon initial tissue injury are another proposed mechanism [59]. Overall, a central pathway implicated in the release of multiple proinflammatory factors upon biomaterial contact involves activation of NF-κB downstream of TLR and integrin stimulation by biomaterial surfaces coated with pathogen-associated molecular patterns and DAMPs. This mechanism is especially well characterized in the case of wear debris-induced osteolysis [63]. Moreover, particles of a different nature (such as titanium or PMMA) are able to trigger NF-κB activation, resulting in the release of proinflammatory mediators. Upstream molecular cascades leading to NF-κB activation upon wear particle recognition involve common members of TLR signaling pathways, including MyD88, IRAK2, IRAK4, and TNFR-associated factor 6 [63]. However, much less is known about signaling pathways induced by direct recognition of implant surfaces and whether biomaterials of a different nature can differentially trigger downstream signaling events. Besides integrins and TLRs, scavenger receptors on macrophages (SR-A, macrophage receptor with collagenous structure) are also involved in the recognition of biomaterial particles, including TiO_2. Interestingly, expression of SR-A may appear beneficial during exposure to implant-derived debris, as SR-AI/II$^{-/-}$ mice demonstrated exacerbated lung inflammation after challenge with TiO_2 particles [64]. Known pathways of biomaterial recognition by macrophages are summarized in **Fig. 1**.

Overall, the majority of studies has demonstrated that unwanted macrophage-mediated inflammatory responses upon implantation lead to poor function of implanted medical devices. To date, several approaches have been explored to modulate implant-induced inflammation through manipulation of the macrophage phenotype. These approaches include local re-polarization of macrophages toward an anti-inflammatory phenotype, modification of implant surface topography, as well as application of anti-inflammatory implant coatings

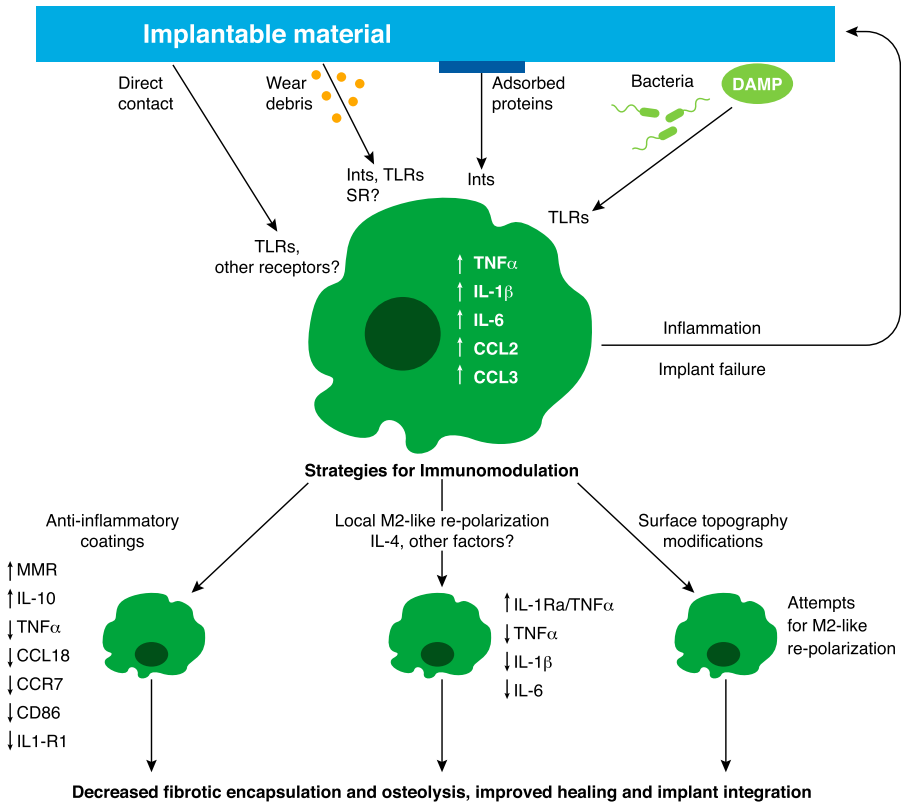

Figure 1. Adverse reactions of macrophage to implantable materials and strategies for immunomodulation. In response to direct contact with implant, implant-derived wear debris, adsorbed proteins (fibronectin, fibrinogen, complement component C3b, etc.), bacteria, and DAMPs, macrophages up-regulate expression and secrete proinflammatory factors that result in chronic inflammation and implant failure. Anti-inflammatory implant coatings, local M2-like repolarization of macrophages, and biomaterial surface-topography modifications are current strategies for immunomodulation, which were shown to decrease fibrotic encapsulation of implants and improve healing and implant function. Ints, integrins.

[65–67]. Local administration of IL-4 prevented an inflammatory response and reduced osteolysis caused by polyethylene particles in a mouse calvaria model [68]. In line with another study demonstrating the suppressive effect of IL-4 on titanium-induced inflammatory responses in human macrophages, these results are consistent with the therapeutic potential of anti-inflammatory cytokines in implant-induced inflammation [56].

An emerging, additional strategy is modulation of the macrophage phenotype by modifying the implant surface [66]. Microstructured topographical modification of polyvinylidene fluoride was shown to induce production of pro- and anti-inflammatory factors by human primary macrophages [69]. Moderate effects of surface topography modifications on the production of TNF-α, MCP-1, MIP-1α, and vascular endothelial growth factor were detected in murine RAW 264.7 macrophages, cultured on poly(dimethylsiloxane) films [70]. Overall, surface roughness, porosity, as well as the pattern and dimensions of surface modifications (e.g., microstructure vs. nanostructure modifications) were shown to be important factors that affect macrophage polarization. However, the effects of surface topography are complex, and the resulting macrophage phenotype combines pro- and anti-inflammatory properties [66]. Moreover, it is still unclear which topography pattern is optimal for induction of a healing macrophage phenotype during implantation. Despite being a supportive factor to improve implant acceptance, topography modification is insufficient to solve a key problem, and coating of the implant surfaces by biocompatible, degradable, and immunotolerogenic biomaterials is the most promising strategy today. Immunomodulatory approaches to reduce macrophage-mediated inflammatory responses to implants are summarized in Fig. 1.

IMPLANT COATING AND IMMUNE REACTIONS

A common problem in biomedical engineering is that the best surface and bulk properties for a given biomedical application do not usually reside in the same material. For example, metals provide the best mechanical properties for load-bearing applications, but even the most biocompatible metals, such as titanium, cannot be remodeled by the host or degraded by the immune system, and the response to them compared with more natural biomaterials is generally inferior [1]. In some cases, poor integration of an implant or chronic inflammation can lead to catastrophic problems, such as peri-implantitis, osteolysis, aseptic loosening, and abrupt implant failure. Therefore, thin biomaterial coatings are commonly used to improve implant success, as they provide a more biocompatible surface without significantly modifying the bulk properties of the implant [71]. One of the main needs for surface coatings in the context of immunomodulation is to decrease inflammation and an immune response [72].

To decrease the immune response to the implant, a common method is to coat its surface with biomaterials that can improve its integration significantly. To this end, natural polymers, such as collagen, hyaluronan, alginate, chitosan, etc., are generally used [48]. Another approach is to provide a coating that minimizes protein adsorption and in turn, limits the interaction of host immune cells with the surface. Recently, it has been shown that the attachment and maturation of cells are related directly to their adhesion properties; depending on the substrate, ECM, the cytokine-release profiles can show significant differences and affect Th1/Th2 induction of $CD4^+$ T cells [73]. Furthermore, for more specific control of the interaction, such surface modifications were done by immunomodulatory molecules (e.g., CD200), which resulted in a significant decrease in a foreign-body response in a subcutaneous model [74]; other possible targets, such as immunoreceptor tyrosine-based inhibitory motif-containing receptors, have also been proposed [75].

Nevertheless, the composition of a biomaterial coating should be taken into account to prevent unwanted reactions [76], and in some cases, exclusion of protein adsorption might be a more viable route [77]. The biomaterials of choice for this approach are generally highly hydrophilic synthetic polymers, such as PEG, polyethylene oxide, or PVA. Such materials can also prevent implant-related infection and biofilm formation [78]; for example, peptidomimetic polymers—designed to contain a short region with strong, water-resistant attachment to surfaces (mimicking the high L-3,4-dihydroxyphenylalanine content mussel adhesion proteins), whereas the remainder is composed of an *N*-substituted glycine (peptoid) oligomer of variable length to provide resistance to biofouling—resemble the use of methoxyethyl side-chains in PEG [79]. For natural polymers, the problem is generally

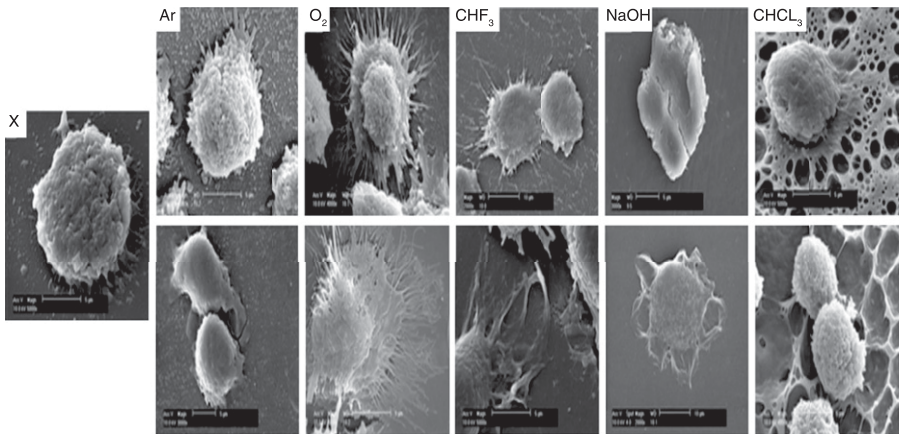

Figure 2. An example of the macrophage behavior on different surfaces (SEM images). Polymeric surfaces were treated with plasma or chemically etched (etching conditions are denoted at top left corners). The physical effects of the surface treatment have a significant effect on macrophage morphology, particularly with respect to the number of filopodia and level of cell spreading. Reprinted with permission from Damanik et al. [83].

TABLE 2. Benefits and deficiencies of existing implant coatings

Coating type	Method of deposition	Mechanical properties	Biocompatibility, specific functions	Antibacterial properties and interaction with immune system	Key pathologic adverse effects
Polyelectrolyte multilayers (PLL/HA, PAH/PSS, Col/Alg, Col/CS, etc.)	Dipping robots, manual build-up, microfluidic systems	Soft, nanoscale, gel-like structures; attachment to the surface depends on implant surface properties	Carrier of bioactive molecules; nanofibrillar structure of SEM can be mimicked	Certain polyelectrolytes, such as chitosan, have antibacterial properties; the films can be loaded with antibacterial agents.	Individual polyelectrolytes can be taken in by immune cells that can trigger inflammatory reactions; as a result of their highly charged nature under certain conditions, the individual components can be cytotoxic after film degradation.
Hydrophilic polymer brushes (PVA, PEG) [89]	Covalent linking to the surface	Direct attachment to the implant, hard to remove	Prevention of nonspecific protein adsorption on implant surfaces, limiting adverse immune reactions by providing a bio-inert surface	As a result of their bio-inertness, they are generally bacteriostatic, but biofilm formation is possible after the contamination of the brush layer. Conjugation of antimicrobial agents is possible.	Does not induce any interaction between the implant and the host tissue
Natural polymer-based film coatings (collagen, gelatin, alginate, hyaluronic acid, etc.) [90]	Sol-Gel methods, in crosslinked hydrogel form	Depends on the surface properties of the implant, batch-batch variation as a result of the natural polymers' inherent property variations	Most of the natural polymers are conducive to cell attachment and proliferation; they tend to improve implant/host tissue interactions.	Most of the natural polymers are just as prone to bacterial attachment, and "race to the surface" between bacteria and the host cells determines the outcome.	As the natural polymers are, by definition, xenogeneic or allogeneic, they can induce strong immune reactions, but on average, they are tolerated well by the immune system.
Synthetic polymer-based coatings (PLLA, PLGA, PCL, PEEK, etc.) [78]	Solvent casting	Depends on the surface properties of the implant; can be tailored by changing the properties of the synthetic polymer (MW, tacticity)	They are biocompatible, although less conducive to cell adhesion compared with the natural polymers.	Similar to the natural polymers, race to the surface is the dominant factor, with a slightly more advantageous conditions for the bacteria. Incorporation of antimicrobial agents is possible.	Degradation products of some synthetic polymers can lower the pH around the implant and can induce inflammatory reactions.
Nanoscale deposition techniques (for molecules, such as calcium phosphate) [91]	Plasma spray deposition, ion beam-assisted deposition, magnetron sputtering, physical vapor deposition	Deposition condition and the underlying implant material dependent	Coatings, such as calcium phosphate or hydroxyapatite, render the surface more biocompatible; however, the processes are not suitable for all biocompatible materials.	No direct antimicrobial activity; can be rendered antimicrobial by impregnation with silver and other suitable antimicrobial agents	Abrupt delamination of the coating material can induce acute inflammation.

HA, Hyaluronan; PAH, poly(allylamine hydrochloride); PSS, poly(styrene sulfonate); Col, collagen; Alg, alginate; CS, chondroitin sulfate; PLLA, poly(L-lactic acid); PLGA, poly(lactide-*co*-glycolide); PCL, polycaprolactone; PEEK, polyetheretherketone.

degradation and loss of the effect over time and batch-to-batch variability. Although synthetic, nonfouling polymers offer more control over the physical and chemical properties, the effect they provide is mostly passive, i.e., they basically evade the immune system and do not provide an active interface between the implant and the host. The coating method can be selected with respect to 1) necessity to release bioactive agents, 2) control over the thickness of the coating, and 3) requirements pertaining to topography or surface chemistry [66].

One of the most common coating structures is hydrogels, which provide a 3-dimensional network of defined thickness, are well hydrated, and allow transfer of nutrients, bioactive molecules, and gases [80]. A recent study in mice demonstrated that zwitterionic [poly(carboxybetaine methacrylate)] hydrogels were resistant to fibrotic encapsulation in vivo, favoring a healing phenotype of macrophages with decreased expression of proinflammatory markers (iNOS, IL-1R1, TNF-α, CCR7, IL-12) and elevated expression of anti-inflammatory markers (MMR, arginase 1, IL-10, and SR-BI/II) [67]. Likewise, ECM-based hydrogel implant coatings decreased the pro/anti-inflammatory ratio during an in vivo response to implanted polypropylene mesh in rats [65]. It is possible to preload hydrogels with drugs and growth factors to achieve controlled delivery around the implant; the rate of release can be adjusted by changing the physical properties of the gel, such as mesh size, degree of crosslinking, or interactions with the bioactive agents to be released. Another possibility is phospholipid-based mimicry of cell-membrane components on the surface of the implant to resemble its "self" nature; however, here, degradability is again a problem, and control of crosslinking, thickness, and hydration of hydrogels is not easy.

The crosslinking of the coating to increase its stability might be material specific, requiring specific enzymes; chemical agents, such as glutaraldehyde, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide/N-hydroxysuccinimide for protein-based materials, etc.; or physical methods (dehydrothermal treatment, cryogelation) [81]. Physico/chemical modification of the surface is possible by plasma treatment, chemical etching, or other thin film deposition methods, such as physical vapor deposition or low-energy plasma spraying [82] (**Fig. 2**)

Polyelectrolyte multilayers are composed of sequentially deposited polyanions and polycations to form thin, ordered, hydrated structures with specific surface properties. These thin coatings can also be loaded with bioactive molecules to act as delivery systems [84, 85]. They can be produced with nanoscale precision, up to several tens of micron-thick constructs, and they can conform to any kind of surface topography, making them a good candidate for implant coating. For example, Schultz et al. [86] covalently incorporated an anti-inflammatory, synthetic analog of α-melanocyte-stimulating hormone into PLL/poly(L-glutamic acid) multilayer films on porous titanium surfaces. Upon implantation of the modified titanium implants in rats, they observed an increase in IL-10 levels compared with a control analog, following 3 mo of implantation [86]. Previously, it has been shown that cationic surface coatings, such as poly(β-amino alcohols), can decrease the level of the foreign-body response to implanted materials [87]. The main problems related to thin coatings are fast enzymatic or erosan-based degradation under physiologic conditions, possible adverse effects of degradation products, limited control over the release of incorporated bioactive agents over long periods, and maintenance of their activity in the dynamic environment of the implantation side. Current focus on smart, responsive coating can provide some solutions to these problems [88]. Furthermore, more in-depth, real-time monitoring of biomaterial clearance by macrophages can improve our understanding of the role of these crucial cells to the dynamic response to the implanted materials. Benefits and deficiencies of existing implant coatings are presented in **Table 2**.

The first step to identify the macrophage response to implanted materials can be done ex vivo by exposure of patient-derived monocytes to the uncoated or coated biomaterials in various culture conditions. In a recent study, we have demonstrated an approach to choose an appropriate implantable material based on individual patient responses [92]. We used different modifications of PLA as an implant material and measured type I and type II inflammatory cytokines (TNF-α and CCL18, respectively) and histologic markers (CD206 and stabilin-1) to determine individual patient responses to the PLA types. Based on the extent of macrophage inflammatory responses, we predicted potentially compatible PLA modification for each donor. Our system can be refined further by addition of parameters, indicating the bias to chronic inflammatory and fibrotic reactions, and can be used as a diagnostic platform for rapid prediction of patient-specific inflammatory responses to implants and optimization of novel-coating materials [92].

CONCLUSIONS AND PERSPECTIVES

Currently, there is no reliable approach to avoid adverse immune responses to implants and biomedical devices, independent of drugs. Commonly used anti-inflammatory agents or immunosuppression techniques can have life-threatening side-effects and not necessarily guarantee the success of implantation/transplantation (i.e., effective function of the transplanted tissue, implant, or medical devices). One of most promising solutions to overcome this problem is to develop coatings that can actively decrease the adverse immune responses. Personalization of these coatings can be achieved by 1) precise definition of macrophage-released factors as biomarkers and pretesting of coatings by use of individual monocyte-derived macrophages in vitro (innovative diagnostic system) and 2) stabilization of macrophage phenotype by use of biomaterials as coatings for the implant surface to modulate macrophage interaction with the implant. In the future, such systems can significantly improve the outcome of clinical application of implants and biomedical devices.

AUTHORSHIP

J.K. designed, structured, and wrote the manuscript. A.G. wrote part of the manuscript and Table 1. V.R. wrote part of the manuscript and designed Fig. 1. C.D. and P.L. wrote part of the manuscript. N.E.V. wrote part of the manuscript and designed the project.

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DISCLOSURES

The authors declare no competing financial interests.

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