Published in final edited form as:
Semin Immunol. 2008 April ; 20(2): 86–100.

FOREIGN BODY REACTION TO BIOMATERIALS

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Abstract

The foreign body reaction composed of macrophages and foreign body giant cells is the end-stage response of the inflammatory and wound healing responses following implantation of a medical device, prosthesis, or biomaterial. A brief, focused overview of events leading to the foreign body reaction is presented. The major focus of this review is on factors that modulate the interaction of macrophages and foreign body giant cells on synthetic surfaces where the chemical, physical, and morphological characteristics of the synthetic surface are considered to play a role in modulating cellular events. These events in the foreign body reaction include protein adsorption, monocyte/macrophage adhesion, macrophage fusion to form foreign body giant cells, consequences of the foreign body response on biomaterials, and cross-talk between macrophages/foreign body giant cells and inflammatory/wound healing cells. Biomaterial surface properties play an important role in modulating the foreign body reaction in the first two to four weeks following implantation of a medical device, even though the foreign body reaction at the tissue/material interface is present for the *in vivo* lifetime of the medical device. An understanding of the foreign body reaction is important as the foreign body reaction may impact the biocompatibility (safety) of the medical device, prosthesis, or implanted biomaterial and may significantly impact short- and long-term tissue responses with tissue-engineered constructs containing proteins, cells, and other biological components for use in tissue engineering and regenerative medicine. Our perspective has been on the inflammatory and wound healing response to implanted materials, devices, and tissue-engineered constructs. The incorporation of biological components of allogeneic or xenogeneic origin as well as stem cells into tissue-engineered or regenerative approaches opens up a myriad of other challenges. An in depth understanding of how the immune system interacts with these cells and how biomaterials or tissue-engineered constructs influences these interactions may prove pivotal to the safety, biocompatibility, and function of the device or system under consideration.

Keywords

Foreign body reaction; Macrophages; Foreign body giant cells; Biodegradation; Cytokines; Biomaterials

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Contract Grant Numbers: EB-00275
EB-000282

1. INTRODUCTION: INFLAMMATORY RESPONSE FOLLOWING MATERIAL IMPLANTATION

The perspective of this review originates from our long-standing clinical implant retrieval and evaluation program in the Department of Pathology at the University Hospitals of Cleveland. Simply put, our perspective is that derived from surgical pathology and the identification of inflammatory and wound healing responses as opposed to an immunology perspective, which focuses on innate and adaptive immunity. The consistent diagnosis of the foreign body reaction with macrophages and foreign body giant cells at tissue/material interfaces and the persistence of the foreign body response prompted our interest in subsequent investigation of various aspects of this phenomenon at the tissue/material interface of medical devices, prostheses, and biomaterials.

Host reactions following implantation of biomaterials include injury, blood-material interactions, provisional matrix formation, acute inflammation, chronic inflammation, granulation tissue development, foreign body reaction, and fibrosis/fibrous capsule development (Figure 1).[1–4] In the very early process of implantation, blood/material interactions occur with protein adsorption to the biomaterial surface and development of a blood-based transient provisional matrix that forms on and around the biomaterial. The provisional matrix is the initial thrombus/blood clot at the tissue/material interface. Obviously, protein adsorption and fibrin-predominant provisional matrix formation are intimately linked in their mechanistic responses. The injury to vascularized connective tissue not only initiates the inflammatory responses (innate immunity), it also leads to thrombus formation involving activation of the extrinsic and intrinsic coagulation systems, the complement system, the fibrinolytic system, the kinin-generating system, and platelets. These protein cascades may be intimately involved in the dynamic phenomenon of protein adsorption and desorption that is known as the Vroman Effect.[5] From a wound healing perspective, blood protein deposition on a biomaterial surface is described as provisional matrix formation. The provisional matrix furnishes structural, biochemical, and cellular components to the processes of wound healing and foreign body reaction. The presence of mitogens, chemoattractants, cytokines, growth factors, and other bioactive agents within the provisional matrix provides for a rich milieu of activating and inhibiting substances capable of modulating macrophage activity, along with the proliferation and activation of other cell populations in the inflammatory and wound healing responses. The provisional matrix may be viewed as a naturally derived, biodegradable sustained release system in which bioactive agents are released to control subsequent phases of wound healing.

Following the initial blood/material interactions and provisional matrix formation, acute and chronic inflammation occurs in a sequential fashion as expected. The extent or degree of these responses is controlled by the extent of injury in the implantation procedure, the tissue or organ into which the device is implanted, and the extent of provisional matrix formation. Neutrophils (polymorphonuclear leukocytes, PMNs) characterize the acute inflammatory response. Mast cell degranulation with histamine release and fibrinogen adsorption is known to mediate acute inflammatory responses to implanted biomaterials.[6,7] Interleukin-4 (IL-4) and interleukin-13 (IL-13) also are released from mast cells in a degranulation process and can play significant roles in determining the extent and degree of the subsequent development of the foreign body reaction.[8,9] Biomaterial mediated inflammatory responses may be modulated by histamine-mediated phagocyte recruitment and phagocyte adhesion to implant surfaces facilitated by adsorbed host fibrinogen. Both H1 and H2 histamine receptor antagonists greatly reduce the recruitment of monocytes/macrophages and neutrophils on implant surfaces. Protein adsorption and monocyte/macrophage adhesion are significant topics in the foreign body reaction and are discussed later in this review. The acute inflammatory response with

biomaterials usually resolves quickly, usually less than one week, depending on the extent of injury at the implant site.

Following acute inflammation, chronic inflammation is identified by the presence of mononuclear cells, i.e. monocytes and lymphocytes, at the implant site. Chronic inflammation is less uniform histologically than acute inflammation and this term has been used diagnostically to identify a wide range of cellular responses. The presence of mononuclear cells, including lymphocytes and plasma cells, is considered chronic inflammation. This chronic inflammatory response to biomaterials is usually of short duration and is confined to the implant site. Chronic inflammation also has been used to describe the foreign body reaction where monocytes, macrophages, and foreign body giant cells are present at the biomaterial interface. With biocompatible materials, early resolution of the acute and chronic inflammatory responses occurs with the chronic inflammatory response composed of mononuclear cells usually lasting no longer than two weeks. The persistence of the acute and/or inflammatory responses beyond a three week period usually indicates an infection. Following resolution of the acute and chronic inflammatory responses, granulation tissue identified by the presence of macrophages, the infiltration of fibroblasts, and neovascularization in the new healing tissue is identified. Granulation tissue is the precursor to fibrous capsule formation and granulation tissue is separated from the implant or biomaterial by the cellular components of the foreign body reaction; a one- to two-cell layer of monocytes, macrophages, and foreign body giant cells.

2. MONOCYTES, MACROPHAGES, AND FOREIGN BODY GIANT CELLS

2.1. Protein adsorption

2.1.1. Adsorption of plasma proteins—Biomaterials and medical devices immediately and spontaneously acquire a layer of host proteins prior to interacting with host cells. Thus it is highly probable that the types, levels, and surface conformations of the adsorbed proteins are critical determinants of the tissue reaction to such implants.[10] Conversely, the types, concentrations, and conformations of these surface-adsorbed proteins are dependent on biomaterial surface properties that dictate the adhesion and survival of cells, especially monocytes, macrophages and FBGCs, on protein-coated surfaces. The interaction of adsorbed proteins with adhesion receptors present on inflammatory cell populations constitutes the major cellular recognition system for implantable synthetic materials and medical devices. The presence of adsorbed proteins such as albumin, fibrinogen, complement, fibronectin, vitronectin, γ globulin, and others modulate host inflammatory cell interactions and adhesion and thus are linked to subsequent inflammatory and wound healing responses.[11–14] As previously indicated, these adsorbed proteins may desorb rapidly, i.e. the Vroman Effect, and thus present time-dependent variations in the type and level of proteins cells encounter in the *in vivo* environment.[15]

2.1.2. Complement activation on biomaterial surfaces—The complement system has long been recognized as a major host defense system for the interaction and removal of foreign substances *in vivo*. Complement activation and its subsequent reactions have been identified as causing adverse side-effects when blood/material interactions occur with devices such as hemodialyzers, oxygenators, catheters, prostheses, stents, vascular grafts, and other devices and materials. In blood/material interactions, there is tight cross-talk between the different cascade systems and platelets and leukocytes in the induction of clotting and inflammation. As complement and leukocytes are involved in biomaterial-associated thrombosis, as well as the more commonly identified coagulation factors and platelets, the true effect of a biomaterial surface on blood can only be identified when whole blood is used for interaction studies.[16, 17]

2.2. Macrophage adhesion

2.2.1. Macrophage recruitment—The progression of events in inflammation and the foreign body response requires the extravasation and migration of monocytes/macrophages to the implant site. The guided movement of monocytes/macrophages occurs in response to chemokines and other chemoattractants. Chemokines are cytokines that have chemoattractive properties and consist of 4 major families: CC, CXC, C, and CX_3C based on the spacing between the first 2 terminal cysteine residues.[18] Chemokines are not only involved in orchestrating cellular migration in inflammation and wound healing but play roles in hematopoiesis, angiogenesis, tumor metastasis, lymphocyte differentiation, and lymphocyte homing.[18–20]

Following blood-material interactions, platelets and the clot release chemoattractants, such as transforming growth factor (TGF-β), platelet-derived growth factor (PDGF), CXCL4 (Platelet Factor, PF4), leukotriene (LTB4), and interleukin (IL-1), that can direct macrophages to the wound site.[21] In addition, mast cell degranulation and release of histamine has been shown to play an integral role in recruiting phagocytes, including macrophages, to the site of the implanted biomaterial.[7] The assembly of macrophages at the implant site leads to further propagation of chemoattractive signals. Macrophage production of PDGF, tumor necrosis factor (TNF-α), IL-6, granulocyte-colony stimulating factor (G-CSF), and granulocyte macrophage colony stimulating factor (GM-CSF) call more macrophages to the wound site.[21] Rhodes et al. showed expression of CCL2 (Monocyte chemotactic protein, MCP-1) in exudate macrophages surrounding implanted polyethylene materials.[22] CCL2 (MCP-1) along with CCL5 (regulated upon activation, normal T-cell expressed and secreted, RANTES), CCL3 (macrophage inflammatory protein, MIP-1α), CCL4 (MIP-1β), CCL7 (MCP-3), CCL8 (MCP-2), and CCL13 (MCP-4) are chemokines known to attract monocytes/macrophages.[18,23] However, CCL2 (MCP-1) was shown not to influence the recruitment of monocytes to subcutaneous implant sites.[24] Utilizing our *in vitro* culture system of human blood-derived monocytes/macrophages we have demonstrated production of CCL4 (MIP-1β), CCL2 (MCP-1), CCL13 (MCP-4), CCL22 (MDC) by biomaterial-adherent macrophages.[25] Some of these products have the potential to recruit additional macrophages to the biomaterial-tissue interface. Once at the implant site or biomaterial surface, the macrophages can then adhere and engage in the subsequent events of the foreign body reaction (Figure 2).

2.2.2. Integrin receptors

The adsorbed blood protein-modified material surface is the substrate with which the recruited monocytes/macrophages encounter and interact. The various plasma and extracellular matrix proteins deposited onto the surface give cells a means of attaching via surface receptors. Integrins are a large family of cell surface receptors that mediate cell-extracellular matrix as well as intercellular interactions.[26,27] These adhesion molecules allow cells to migrate through the extracellular matrix and mediate signal transduction between the cell and its environments so that the cell can respond to its environment.[26] Integrins are heterodimers comprised of different α and β subunits. The partnering of different subunit chains confers variability to the specificity and function of the receptor.[28] Monocytes/Macrophages express integrins with 3 different types of β chains, β1, β2, β3. In monocytes/macrophages there are three β1 integrins, four β2 integrins, and one β3 integrin. β1 integrins include α4/β1 and α5/β1 which bind fibronectin and α6/β1 which binds laminin. Of the β2 integrins, there are αL/β2, αM/β2, and αD/β2 which are specific for intercellular adhesion molecules (ICAMs) and αX/β2 which binds complement fragment C3bi and fibrinogen. αM/β2 also interacts with a variety of other ligands such as fibrinogen, C3bi, and Factor X. Finally, monocytes/macrophages express αV/β3 of the β3 integrins which bind to vitronectin along with other RGD containing extracellular proteins.[28]

To determine monocyte, macrophage, and foreign body giant cell adhesion mechanisms, we have utilized human blood-derived monocytes in culture in a time-dependent fashion and on materials displaying different chemistries. To mimic the *in vivo* condition, we have added an additional 20% human serum to our culture media where adsorbed proteins provide ligands for integrin receptor binding and cellular adhesion. Initial monocyte adhesion is achieved through β2 integrins, in particular αM/β2(Mac-1, CD11b/CD18), by binding to various adsorbed protein ligands including fibrinogen, fibronectin, IgG, and complement fragment iC3b.[12,29] While our efforts have focused on complement components providing the initial adhesion ligands, others have focused on fibrinogen as being the principal adsorbed protein ligand. Recent studies have suggested that multiple protein ligands may participate in the receptor-ligand binding and monocyte adhesion. In particular, complement activation on fibrinogen-adsorbed surfaces has been suggested as the primary adhesion event.[16] In our more recent studies, β1 integrins have been determined to play a role in the subsequent adhesion and IL-4 induced macrophage fusion to form foreign body giant cells. This phenomenon is time-dependent as β1 integrins are not initially detected on adherent monocytes but begin to appear during macrophage development and are strongly expressed on fusing macrophages and foreign body giant cells with increased culture time.[30] Our studies have only used human blood-derived monocytes for several reasons. Others have used murine blood and peritoneal-derived monocytes/macrophages, knockout murine models, and tumor-derived cell lines. We believe that the respective phenotypes of these models and systems are not adequately characterized to model human leukocyte behavior.

We have recently demonstrated expression and co-localization of α3, α5 or αV with β1 on fusing macrophages/FBGC at day 7 of culture as well as the strong co-localization of αM and αX with β2 in FBGC and at macrophage fusion interfaces. Therefore, IL-4-induced FBGC are characterized by the expression of αM/β2, αX/β2, α5/β1, α5/β1, α2/β1, and α3/β1, which indicates the potential interactions of complement C3b fragments, fibrin, fibrinogen, fibronectin, factor X, and vitronectin at sites of biomaterial implantations.[31]

2.2.3. Integrin signaling and cytoskeleton remodeling—Macrophage integrin binding to the material surface adherent protein layer provides intracellular signals that can modulate macrophage behavior. Downstream signaling transduction pathways affect cytoskeletal rearrangements and formation of adhesion structures.[27,32] Following adhesion, macrophages undergo cytoskeleton remodeling in order to spread over the material surface. Podosomes are specialized macrophage adhesion structures that form in the early stages of cell adhesion and consist of punctate f-actin on plasma membrane extensions. Podosomes consist of a central core of actin surrounded by a ring of vinculin, talin, α-actinin, paxillin and other proteins and also contain proteins that regulate actin polymerization such as gelsolin.[33–35] Using our *in vitro* monocyte culture system, we have shown that podosomes are present in actively fusing macrophages on glass.[36] Macrophage podosomes are associated with the recruitment of β2 integrins[35] β2 integrins are necessary for initial monocyte adhesion to a surface and αM/β2 may play a role in podosome assembly necessary for macrophage adhesion.[30] αM co-localizes with β2 in fusing macrophages.[31] αM/β2 integrin podosomes co-localize with paxillin, talin, and vinculin after β2 integrin ligation causes intracellular signaling via a proline rich tyrosine kinase 2 (PYK2) which is a member of the focal adhesion kinase (FAK) family.[37]

There is extensive interplay between intracellular signaling molecules, such as focal adhesion kinase (FAK), src-family kinases, and extracellular signal regulated kinase (ERK 1/2), and cytoskeletal proteins such as vinculin, talin, paxillin, and actin.[38,39] FAK becomes activated following integrin binding and is responsible for regulating cytoskeletal dynamics and in turn the assembly and disassembly of focal adhesions[40] FAK is recruited to the focal adhesion complex and is tyrosine phosphorylated. After FAK activation, other protein tyrosine kinases,

such as src are activated. The cytoskeletal protein, paxillin, binds FAK and acts as a docking partner between the cytoplasmic domains of integrin receptors and other cytoskeletal proteins such as vinculin.[41] Integrins also regulate ERK signaling which ultimately results in the phosphorylation of transcriptions factors that can regulate the cell cycle.[42]

Cell adhesion to a biomaterial is dependent on the proteins that adsorb onto the surface. Surfaces with varying properties promote differential cellular integrin binding to the absorbed protein layer[43–46] Subsequent material dependent differences in cell adhesion and cytoskeletal rearrangement correlate to differences in phosphorylation of FAK and ERK[47, 48] and differences in recruitment of talin, α-actinin, paxillin.[49] This indicates that differences in downstream integrin signaling account for morphological differences in adherent cells on material surfaces.

2.2.4. Apoptosis/Anoikis of adherent cells—Integrin signaling is also responsible for controlling the cell cycle. Integrins are important in regulating cell death which is necessary for cell detachment and tissue remodeling.[50] Anoikis is a term for apoptosis induced by cell detachment from its supportive matrix.[51] When a cell is properly adhered to a surface, FAK mediates survival signaling. Disruption of adhesion signals promotes anoikis.[52] Monocytes initially adhere to most surfaces quite well, but fail to maintain adhesion over time.[30] Biomaterial surface chemistry influences apoptosis of adherent macrophages both *in vitro* and *in vivo*.[12,53–55] Caspase-3, a protein involved in apoptosis signaling, is activated by neutrophils under shear stress and leads to detachment from biomaterials.[56] Caspases are involved in cleaving gelsolin, a protein involved in regulating actin polymerization, and this in turn disrupts adhesion.[52] The disruption of adhesion leads to anoikis. Material surface chemistry can influence both adhesion and apoptosis. Materials that do not promote adhesion lead to cell detachment and anoikis. The induction of apoptosis is inversely related to fusion and we have hypothesized that macrophage fusion to form foreign body giant cells is an escape mechanism to avoid apoptosis.[53]

2.3. Macrophage fusion: foreign body giant cell formation

2.3.1 Induction of fusion—Cell-cell fusion requires a series of highly orchestrated events.[57] Biomaterial surface adherent macrophages fuse to form foreign body giant cells (FBGCs). Our laboratory has established an *in vitro* model for the induction of human monocyte-derived macrophage fusion and foreign body giant cell formation using IL-4.[58] By using IL-4 neutralizing antibody, our laboratory also confirmed that IL-4 is important in the induction of macrophage fusion on biomaterial surfaces *in vivo*.[59] IL-13 was found to induce the fusion of monocyte-derived macrophages as potently as IL-4.[60] Both IL-4 and IL-13 were found to upregulate mannose receptors on fusing macrophages with localization of the receptor at fusion interfaces[60]. Inhibitors of mannose receptor activity prevented or reduced macrophage fusion indicating that this receptor is integral in foreign body giant cell formation.[61] Mannose receptors are expressed on macrophages and dendritic cells and mediate endocytosis and phagocytosis.[62] We have demonstrated that FBGC formation exhibits features of phagocytosis such as the detection of the endoplasmic reticulum proteins, calnexin and calregulin, at fusion interfaces co-localized with actin.[63] However, phagocytosis and fusion can be decoupled by using an inhibitor of rac1 activation. Inhibition of rac1 activation did attenuate fusion but did not affect the phagocytotic abilities of the macrophages.[64] Purified α-tocopherol (vitamin E) also induces the formation of FBGCs through the activation of diacylglycerol kinase.[65]

The exact molecular mechanisms that lead to macrophage fusion have not been fully elucidated. Besides the mannose receptor, several receptors participate in the fusion phenomenon. IL-4 induced fusion is dependent on β1 integrin receptors whereas β2 integrins are involved in the

initial monocyte adhesion process.[30] CD44 and CD47 are highly induced in macrophages at the onset of fusion and promote fusion and multinucleation, respectively.[66,67] Dendritic cell-specific transmembrane protein (DC-STAMP) is necessary for fusion in the formation of FBGCs. Macrophage fusion was completely abrogated in DC-STAMP deficient mice.[68] The expression of DC-STAMP is not needed on every fusing cell, but rather on the master fusing cell. The DC-STAMP ligand is not known, but CCL2 is a candidate.[69] CCL2 is involved in foreign body giant cell formation. Kyriakides et al. showed that foreign body giant cell formation was reduced in CCL-2 null mice implanted with biomaterial. Blockade of CCL2 *in vitro* also reduced FBGC formation further confirming that CCL2 is a critical participant in macrophage fusion.[24] Other inflammatory mediators besides CCL2 can also impact fusion. Osteopontin (OPN) is an extracellular matrix protein that is upregulated at inflammatory sites such as biomaterial implant sites. OPN knockout mice had more foreign body giant cells than their wildtype counterparts and OPN added to monocytes *in vitro* led to reduced fusion. Therefore, OPN appears to play an inhibitory role in foreign body giant cell formation.[70] Molecules that impact macrophage fusion are summarized in Table 1.

When multiple macrophages come in contact with each other in order to fuse, the necessary binding molecules must be present. IL-4 induced molecules are needed on both fusing partners in order for fusion to occur.[71] These findings indicate that all cells that undergo fusion to form FBGC have been phenotypically altered by an IL-4 stimulus or other necessary fusion inducing stimulus such as IL-13. However, expression of necessary fusion promoting molecules is not enough to undergo fusion. The surface needs to support fusion. Macrophage fusion on biomaterial surfaces is material dependent[55] indicating that surfaces must have an appropriate array of absorbed proteins in order for adherent cells to undergo the necessary phenotype to fuse into foreign body giant cells. After culturing human monocytes on polystyrene coated with different protein substrates (i.e. complement C3bi, collagen I and IV, fibrinogen, plasma fibronectin, fibroblast fibronectin, laminin, thrombospondin, vitronectin, or von Willebrand factor), it was found that vitronectin strongly supported macrophage adhesion and fusion. This suggests that surfaces that favor vitronectin adsorption also favor FBGC formation.[72] Foreign body giant cell formation on biomaterials in plasma fibronectin knockout mice was increased compared to control mice. This suggests that plasma fibronectin adsorption can also modulate FBGC formation.[73] Therefore, the complicated events that lead to FBGC formation are dependent on two main criteria: the presence of appropriate fusion inducing stimuli and a material surface with the appropriate adherent proteins.

2.3.2. Phenotypic characteristics of foreign body giant cells—Foreign body giant cells display an antigenic phenotype similar to monocytes and macrophages, reflecting the fact that FBGCs are formed from the fusion of monocyte-derived macrophages.[74] Current medical implantations such as arthroplasties along with testicular and breast implants have provided a means of studying the characteristics of foreign body giant cells in the human response to implanted materials. Foreign body giant cells in tissue removed from human implant surgeries have been shown *in situ* to express macrophage-associated membrane molecules such as CD45 (leukocyte common antigen), CD13, CD14, CD15A (Hapten X), CD37, CD39, CD43, and HLA-DR; receptors such as CD16 (FcRIII), CD31 (FcRII), CD35 (C3b receptor), CD71 (transferrin receptor); and adhesion molecules such as CD11a,b,c, CD18 (leukocyte function associated, LFA, antigen family), CD54 (ICAM-1), and CD44; while CD68 was strongly stained in the cytoplasm of FBGCs.[74–77] Additionally, α and β integrin subunits for the vitronectin receptor (CD51/CD61), very late antigen receptor (VLA-2, CDw49b/CD29) and VLA-4 receptor (CDw49d/CD29) were detected on foreign body giant cells.[78] Expression of osteoclast markers tartrate-resistant acid phosphatase (TRAP), and vitronectin receptor were also found on FBGCs derived from tissue surrounding total joint arthroplasties.[79] Osteoclasts are phenotypically different multinucleated giant cells found in bone. The foreign body giant cells formed near bone interfaces or in joint capsules would be

expected to differ from those formed in soft tissues as the surrounding environmental signals would be dissimilar.

Foreign body giant cells have the potential to be responsive to cellular signals via cell surface receptor expression as well as actively participate in the inflammatory response through the production of cytokines. Foreign body giant cells derived from human arthroplasties were shown to express cytokine receptors on the cell membrane such as gp130, IL-1R type 1, IL-2Rα, IL-2Rγ, IL-6R, TNFR, M-CSFR, and SCFR, while receptors for IL-4 and GM-CSF were weakly detected and receptors for IL-3 and IL-8 were not present.[74,80] FBGCs, derived from a murine model injected with nitrocellulose particles, showed production of IL-1α and TNF-α only during the first month of the foreign body reaction and subsequently initiated the production of transforming growth factor-β (TGF-β), but did not show the production of macrophage inflammatory proteins (MIP).[81] Although derived from a non-human source, the study shows the capability for FBGCs to influence the tissue response. Like macrophages, foreign body giant cells show the ability to engage in cell-cell as well as cell-matrix interactions.

As mentioned previously, materials implanted into varying types of tissues would be expected to evoke varying responses. The described investigations into the phenotypic characteristics of foreign body giant cells involved responses to particulate materials. The tissue surrounding total joint prosthesis often is exposed to wear particles of micrometer sizes, including polyethylene, acrylic cement, and metal, which can lead to a foreign body reaction. Macrophages are capable of phagocytosing very small particles (< 5 μm) while larger particle sizes (> 10 μm) induce the formation of foreign body giant cells. Obviously in soft tissue environments with minimal mechanical forces, implants will tend to stay intact and macrophages and foreign body giant cells will adhere and respond to material surfaces. Therefore, tissue location as well as material form and size, are factors that can influence the foreign body reaction to materials introduced into the body.

2.4. Consequences of foreign body giant cell formation

2.4.1. Mediators of degradation—The activation of macrophages with the subsequent release of a myriad of bioreactive agents has been extensively studied in a wide variety of *in vitro* and *in vivo* models. The adhesion of macrophages and foreign body giant cells at the surfaces of biomaterials produces a privileged microenvironment that exists between the cell membrane and the surface of the biomaterial. In a process described by Henson as frustrated phagocytosis, macrophages and foreign body giant cells can release mediators of degradation such as reactive oxygen intermediates (ROIs, oxygen free radicals), degradative enzymes, and acid into this privileged zone between the cell membrane and biomaterial surface such that immediate buffering or inhibition of these mediators is delayed or reduced.[82,83] It is known that phagolysosomes in macrophages can have acidity as low as pH 4.[84] Biomaterial surfaces in this privileged microenvironment are thus susceptible to high concentrations of these degradative agents. Therefore, the chemistry of the biomaterial surface will dictate its susceptibility to biodegradation. For example, addition polymers such as polyethylene used in artificial joints or polypropylene used as a suture material may undergo surface oxidation by the ROIs. Medical devices and prostheses composed of addition polymers usually contain small amounts of antioxidants to inhibit this oxidative process. Resorbable sutures are polyesters that are specifically designed to undergo degradation and complete resorption into monomer units that can be degraded in the Krebs' cycle. Examples of these include polylactic acid, polyglycolic acid, polycaprolactone, and others. Enzymatic degradation also has been implicated in the degradation of polyester biomaterials.[85] Not all polyesters undergo degradation and there are only rare examples of the degradation of polyethylene terephthalate (Dacron®) whose use in vascular graft prostheses has demonstrated any clinical biodegradation. Polyurethanes are condensation polymers whose specific chemistries

determine their potential or probability of degradation. Polyester polyurethanes undergo degradation. The soft segment of polyether polyurethanes is known to undergo degradation. [86–98] This phenomenon will be discussed in the next section.

The adhesion of macrophages and foreign body giant cells as well as other inflammatory cells has been shown to exhibit a reduced bacteriocidal capability following adhesion to biomaterial surfaces. In part, this is related to a respiratory burst that occurs upon adhesion and leaves the adherent cell exhausted and incapable of further producing bacteriocidal molecules. In addition, the surface chemistry of the biomaterial may facilitate apoptosis (programmed cell death) that, in turn, leaves the macrophage incapable of attacking foreign organisms that may be adherent to the biomaterial.[53] We have demonstrated that biomaterial-adherent cells can undergo material-dependent apoptosis both *in vitro* and *in vivo*, thus rendering macrophages nonfunctional while the surrounding environment of the implant or biomaterial remains unaffected. Adherent inflammatory cell apoptosis has been described as an important mechanism for the persistence of cardiovascular device infection where apoptosis is induced by shear stress in cardiovascular devices.[54]

2.4.2. Device failure

Adherent macrophages and foreign body giant cells in the foreign body reaction are now known to lead to degradation of biomaterials with subsequent clinical device failure. Figure 3 illustrates the progression of the foreign body reaction with resulting damage to the underlying material surface. Polyether polyurethane (PEU) elastomers replaced silicone rubber as pacemaker lead insulation, because they offered superior mechanical properties, were biocompatible, and were thought to be biostable. In the late 1980's, clinical device failure with pacemakers using leads having the PEU Pellethane-2363–80A® was investigated. Retrieved clinical specimens were evaluated and two phenomena were suggested as leading to the degradation of the Pellethane PEU. These were ESC (environment stress cracking) that was facilitated by zones of stress concentration on the pacemaker lead with subsequent degradation of the material, and MIO (metal ion oxidation) where the polyether soft segment component of the PEU was identified as undergoing chemical degradation with chain cleavage leading to lower molecular weights of the polymer and a reduction in mechanical property performance. While numerous mechanisms were proposed for the failure of PEU pacemaker leads, it was not until 1990 that our group in a seminal study demonstrated that adherent macrophages and foreign body giant cells were responsible for the *in vivo* cracking of pre-stressed Pellethane 2363–80A. In this study and others, we clearly identified the *in vivo* correlation between macrophage and FBGC adhesion and environmental stress cracking on the surface of the material.[86,87] Adherent and spread cells were necessary as *in vivo* studies using enhanced and persistent chronic inflammation; and studies in which steroids inhibited macrophage adhesion and spreading showed no environmental stress cracking. We subsequently identified an oxidative chain cleavage mechanism that was facilitated by the adsorption of α2-macroglobulin onto the polyurethane and catalyzed the oxidation and chain cleavage of the polyether soft segments.[88] Infrared analysis of these specimens clearly identified oxidation as a key process in the degradation and implicated ROIs such as superoxide anion and/or hydroxyl radicals, as potential participants in this oxidative process.[89] Studies of this phenomenon by Labow and Santerre have focused on the ability of macrophage-derived enzymes to facilitate degradation of polyurethanes.[90–95]

These studies clearly identified the importance of the use of antioxidants in these polymers to inhibit the oxidation process that occurs with the foreign body reaction. The persistence of the foreign body reaction and the fact that it is present at the interface between the tissue and the device for the lifetime of the device, suggests that the oxidation process is continuous, albeit at low levels. In general, chemical degradation and physical damage in pacemaker leads most

probably have a synergistic effect on the failure of the insulation, in that, as chemical degradation proceeds the polymer surface becomes brittle and more susceptible to physical damage and as physical damage proceeds, cracks open on the surface and into the bulk of the material, exposing new surfaces to oxidants released by macrophages and foreign body giant cells. The chemical and molecular composition of the primary structure of the polyurethane polymer is known to modulate or inhibit the process of environmental stress cracking and degradation.

Our studies led to a third generation of polyurethanes for biomedical application. Polycarbonates were used as the soft segments in these polymers and exhibited a marked reduction in degradation.[96] A fourth generation of polyurethanes is currently under investigation. These polyurethanes have soft segments that are either polyether or polycarbonate but, more importantly, have short chain molecules attached to the polymer chain ends (SME, surface modifying endgroups) such that when fabricated, these adhesion inhibiting molecules are present at the surface of the biomaterial at the tissue/material interface.[97–100] Significant efforts to molecularly engineer the polyurethanes such that they are biostable and do not undergo biodegradation are being carried out. The excellent biocompatibility and superior mechanical properties of segmented polyurethane elastomers support these efforts to molecularly design non-biodegradable biostable polyurethanes.

3. CROSSTALK BETWEEN MACROPHAGES/FBGCS AND INFLAMMATORY/WOUND HEALING CELLS

3.1. Macrophage/FBGC cytokine secretion

3.1.1. Macrophage activation and cytokine secretion—Macrophages secrete an array of inflammatory mediators following activation. A resting macrophage becomes activated in response to microbial products, immune complexes, chemical mediators, certain extracellular matrix proteins, and T lymphocyte-derived cytokines. Activated macrophages are capable of secreting a wide range of cytokines such as IL-1, IL-6, IL-10, IL-12, IL-18, TNF-α, TGF-β, IL-8, MCP-1, and MIP-1α/β.[101] Adherent macrophages on biomaterials become activated in an attempt to phagocytose the biomaterial. Subsequent cytokine secretion directs the inflammatory and wound healing response to the biomaterial.

In our laboratory, we began investigating cytokine release from human adherent macrophages on biomedical polymers in the late 1980's as an indicator of the extent of macrophage activation as determined by biomaterial surface chemistry. Differential IL-1 production from macrophages cultured on biomaterials allowed us to assess the reactivity of the polymer as a measure of biocompatibility.[102,103] IL-1 secretion was found to be dependent on the biomedical polymer and the protein pre-adsorbed on the surface.[104] IL-6 and TNF-α *in vitro* macrophage secretion was also found to be differential on variant biomedical polymers.[105] Secretion of the pro-inflammatory cytokines, IL-1β[106], IL-6, and TNF-α[107,108], from *in vitro* adherent macrophages on a wide range of materials has been studied extensively.[109–117] These studies have shown that macrophage activation can be modulated by the surface properties, such as material surface chemistry and surface topography[118], of the biomedical polymer.

In order to further our understanding of how surface chemistry can affect macrophage activation, we analyzed *in vitro* cytokine expression (IL-1α, IL-1β, IL-6, IL-8, IL-10, and TNF-α) of adherent macrophages using semi-quantitative RT-PCR. It was found that macrophages on surfaces that inhibited monocyte adhesion and IL-4 mediated macrophage fusion had a different cytokine expression profile than surfaces that promoted fusion.[119] Cytokine expression of biomaterial adherent macrophages *in vivo* was also found to be dependent on

surface chemistry.[120] However, mRNA expression may not reflect the functional level of the cytokine due to potential transcriptional regulations.

The use of a protein array method allows for screening a multitude of cytokines secreted from monocytes cultured on biomaterials.[121] We have recently begun using proteomic analysis (i.e. cytokine array screening followed by ELISA quantification) in order to investigate the effect of material surface chemistry on adherent macrophage and FBGC cytokine production. We have found that macrophages on a biomaterial surface that does not promote fusion secrete higher levels of pro-inflammatory cytokines, IL-1β and IL-6, per cell. Also, adherent macrophages/FBGCs underwent a phenotypic switch over time going from a more classical activation state to a more alternative activation state.[25]

Activated macrophages have several heterogeneous phenotypes. Classical macrophage activation occurs after induction by IFN-γ and exposure to microbial products such as LPS.[122] Classically activated macrophages, whose main function is the killing of intracellular pathogens, upregulate pro-inflammatory cytokines, inhibit anti-inflammatory cytokines, and produce nitric oxide. Alternatively activated macrophages are stimulated by IL-4, IL-13 and glucocorticoids, inhibit pro-inflammatory cytokines, promote anti-inflammatory cytokines, and upregulate mannose receptors.[123,124] Alternatively activated macrophages play a role in allergic responses, the elimination of parasites, and matrix remodeling.[125]

A phenotypic switch in biomaterial adherent macrophages to a more alternatively activated macrophage phenotype over time is expected because in order to induce fusion IL-4 is added to our culture system on days 3 and 7[58] IL-4 is known to induce an alternative activation phenotype in macrophages inclusive of the upregulation of mannose receptors[123] which has been found to be necessary for the formation of foreign body giant cells.[61] The biomaterial adherent macrophage phenotype does not become entirely alternative because of the continued secretion of the chemokines, RANTES and MCP-1. Using our monocyte *in vitro* cell culture, adherent macrophages/FBGCs have a differential cytokine profile than either classically or alternatively activated macrophages indicating that biomaterial activation is unique (Table 2).[25] However, the utilization of a classification system to identify macrophage activation states should be used as a framework considering the myriad of macrophage phenotypes in response to variable inflammatory mediators and pathogenic signals.[126]

In vitro testing of cytokine profiles released by adherent human macrophages/FBGCs can be an initial means of assaying biocompatibility. In depth *in vitro* proteomic analysis concomitant with biomaterial development can be exploited.[127] However, prior to carrying out these assessments, researchers should be aware of contaminating adherent endotoxin (LPS) and the effect on macrophage cytokine secretion. Removal of adherent endotoxin on orthopedic wear particles almost completely eliminated IL-1β, IL-6, and TNF-α production from human monocytes.[128] LPS is recognized by toll like receptor 4 (TLR4)[129] and can stimulate macrophages to become classically activated. Therefore, proper sterilization and processing prior to evaluating adherent macrophage cytokine secretion is warranted.

Proteomic analyses are needed to analyze complex cytokine networks in order to further assess how adherent macrophages/FBGCs can modulate the foreign body response. Biomaterial adherent macrophages/FBGCs are considered to be the main mediators of the foreign body response and can influence the behavior of other leukocytes (i.e. neutrophils, monocytes, lymphocytes) and wound healing cells (i.e. fibroblasts, keratinocytes) through the secretion of soluble mediators. Also, the secretion of soluble mediators by other inflammatory/wound healing cells can impact macrophage behavior. Most notably IL-4 and IL-13 are inductors of macrophage fusion[58,60] and TNF-α is known to be responsible for biomaterial adherent macrophage apoptosis.[130]

To further understand the complex cell-cell interactions in the foreign body response, investigation of cytokine secretion following implantation *in vivo* is warranted. Brodbeck et al. studied the cytokine expression profiles by semi-quantitative RT-PCR of exudate leukocytes and biomaterial adherent macrophages at biomaterial implant sites.[120] IL-1α, IL-1β, TNF-α, and IL-10 were quantified at biomaterial implant sites by enzyme linked immunosorbent assay (ELISA).[3,131] We have recently started using high throughput immunoassays to quantify a multitude of cytokines/chemokines at biomaterial implant sites (unpublished results).

3.1.2. Extracellular matrix remodeling—Macrophages are capable of secreting growth and angiogenic factors that are important in the regulation of fibro-proliferation and angiogenesis.[132] Alternatively activated macrophages overexpress certain extracellular matrix (ECM) proteins, such as fibronectin, and are believed to be involved in tissue remodeling during wound healing.[133] Alternatively activated macrophages also produce pro-fibrogenic factors which enhance fibrogenesis by fibroblasts opposed to classically activated macrophages which inhibit fibrogenesis.[134] Human macrophages activated by biomedical polymers *in vitro* have been shown to stimulate fibroblast activity. Also, the fibroblast stimulatory potential has been shown to correlate to the *in vivo* fibrotic response.[135,136] Biomaterial adherent macrophages therefore can secrete proteins that modulate fibrosis and in turn the fibrous capsule that develops around a material following implantation. This fibrous capsule can interfere with biomaterial function, depending on the intended use of the medical device, prosthesis, or biomaterial.

In order to further understand how macrophages can influence extracellular matrix (ECM) remodeling and wound healing, we have recently begun studying the differential secretion of matrix metalloproteinases (MMPs) and their inhibitors from adherent macrophages and foreign body giant cells.[137] Matrix metalloproteinases are proteolytic proteins that hydrolyze components of the extracellular matrix. MMPs also can affect cell behavior by cleaving circulating, cell surface and pericellular molecules. MMPs can facilitate release of cell surface and matrix bound growth factors and cytokines and can also cleave cell surface receptors. MMPs directly influence the composition of the ECM and in turn can impact cell movement, growth, differentiation and survival.[138] Tissue inhibitors of metalloproteinases (TIMPs) are specific inhibitors that bind MMPs in a 1:1 ratio and directly determine the level of MMP activity.[139]

We found that adherent human macrophages/FBGCs on biomaterials produce MMP-9, TIMP-1, and TIMP-2 *in vitro*. MMP-1, MMP-2, MMP-3, MMP-8, MMP-10, MMP-13, TIMP-1, and TIMP-4 were not detected in cell cultures. MMP-9 concentration increased over time whereas TIMP concentrations remained constant. Furthermore, MMP-9, TIMP-1, and TIMP-2 concentration per cell were increased on surfaces that inhibited adhesion. Pharmacological inhibition of MMP-1, -8, -13, and, -18 did not affect adhesion but did reduce fusion.[137] These data indicate that adherent macrophages/FBGCs secrete MMPs and TIMPs in a material dependent manner and MMPs may play a role in macrophage fusion; however, further research is needed in this area. The adherent macrophages/FBGCs on a biomaterial surface can modulate ECM remodeling/fibrosis and therefore affect biomaterial performance.

3.2. Lymphocyte/macrophage interactions

Our investigation into the role monocytes and macrophages play in response to biomaterials led to the discovery that IL-4 and IL-13 are potent inducers of foreign body giant cells formation from adherent macrophages.[58,60] The transient presence of lymphocytes at the implant site along with lymphokine involvement in macrophage fusion implicate the lymphocyte as playing a critical role in the foreign body reaction. Lymphocytes have been shown to adhere to

biomaterial surfaces *in vitro*.[140,141] In lymphocyte/macrophage co-cultures, lymphocytes have been observed to associate with macrophages and foreign body giant cells.[142,143] To determine the role of lymphocytes in the foreign body reaction to synthetic biomaterials, we have utilized human blood-derived lymphocytes and monocytes in co-cultures. The lymphocytes and monocytes are cultured directly as well as separated by a membrane via a transwell insert when exposed to biomaterial surfaces in order to investigate the interactions between lymphocytes and macrophages during the foreign body reaction.

In our investigations, we found that adherent lymphocytes predominantly associated with macrophages or FBGCs rather than the surface itself.[143] We demonstrated that in co-cultures, lymphocytes enhanced macrophage adhesion and fusion while the presence of macrophages stimulated lymphocytes to proliferate. These responses occurred primarily through paracrine-mediated mechanisms.[143] Moreover, these interactions and responses were differentially influenced by material surface chemistry.[144]

Because of the importance of soluble factors, we subsequently investigated the production of inflammatory mediators from lymphocytes and macrophages in response to biomaterial surfaces utilizing protein arrays as a screening tool and ELISA for quantification. Undetected lymphokines such as IL-2 and IFN-γ indicated the lack of classic T lymphocyte activation. However, the production of cytokines, chemokines, and extracellular matrix proteins were biomaterial surface chemistry dependent.[145] Utilizing the *in vitro* co-cultures and the transwell system for isolating paracrine interactions, lymphocytes, via paracrine and juxtacrine means, enhanced adherent macrophage/FBGC activation in terms of inflammatory cytokine production (unpublished results). Therefore, our laboratory has demonstrated that both direct (juxtacrine) and indirect (paracrine) mechanisms of interactions between lymphocytes and macrophages may play an integral part in the inflammatory, foreign body reaction, and wound healing events that occur at the tissue/material interface. However, the specific mechanisms for these observations are still unknown.

4. CONCLUSIONS

The development of novel biomaterials, biomedical devices, or tissue-engineered constructs necessitates a thorough understanding of the biological responses to implanted materials. Once a biomaterial is introduced into the body, a sequence of events occurs in the surrounding tissue and ultimately ends in the formation of foreign body giant cells at the tissue/material interface. The consequences of the reaction to the material surface can be devastating. Our laboratory has focused on gaining a mechanistic understanding of the foreign body reaction, how adherent macrophages can impact the overall inflammatory response to biomaterials, and how these events can be modulated by material surface chemistry. We have shown that surface chemistry can impact macrophage behaviors such as adhesion, apoptosis, fusion, and cytokine secretion. Broadening our understanding of the complex cell/material interactions will contribute to the development of novel biomaterials and tissue-engineered constructs that direct biological responses.

As the fields of tissue engineering and regenerative medicine expands, biomaterials will be combined with cells, proteins, and/or other biological components creating hybrids appropriate for functional regeneration of diseased and damaged tissues. One of the unique issues for any tissue-engineered device is the interactions between the host and the syngeneic, allogeneic, or xenogeneic cells or possibly stem cells of the implanted construct. At the implant site, the tissue-engineered device would be subjected to inflammatory mediators and signaling molecules such as cytokines, growth factors, and extracellular matrix enzymes and proteins which is different than the native environment of the construct cells. Depending on the cell type in the implant, these mediators could evoke variable responses such as activation,

differentiation, proliferation, or migration. Additionally, cells near or on the material surface would be subjected to an environment of low pH, ROS, and degradative enzymes which are specific to the foreign body reaction. The engineered material-cell hybrids must maintain its properties and functions, and regenerate tissue in the midst of a “compromised” environment. In order for the material-cell hybrids to perform optimally, specific modulation of the foreign body reaction would be required. The material must provide the appropriate biomimetic environment to ensure cell survival. Also, the material can be used to direct desired cell behaviors such as orientation and migration to ensure that the appropriate cells migrate to and/or adhere to the implant. Therefore, an in depth understanding of the host response to biomaterials is needed in order to engineer materials that perform suitably in their applications.

Our perspective has been on the inflammatory and wound healing response to implanted materials, devices, and tissue-engineered constructs. The incorporation of biological components of allogeneic or xenogeneic origin as well as stem cells into tissue-engineered or regenerative approaches opens up a myriad of other challenges. Considerations into how the immune system interacts with these cells and how biomaterials influence these interactions will be covered in the following reviews.

Acknowledgements

Contract Grant Sponsors: National Institute of Health (NIH)

National Institute of Biomedical Imaging and Bioengineering (NIBIB)

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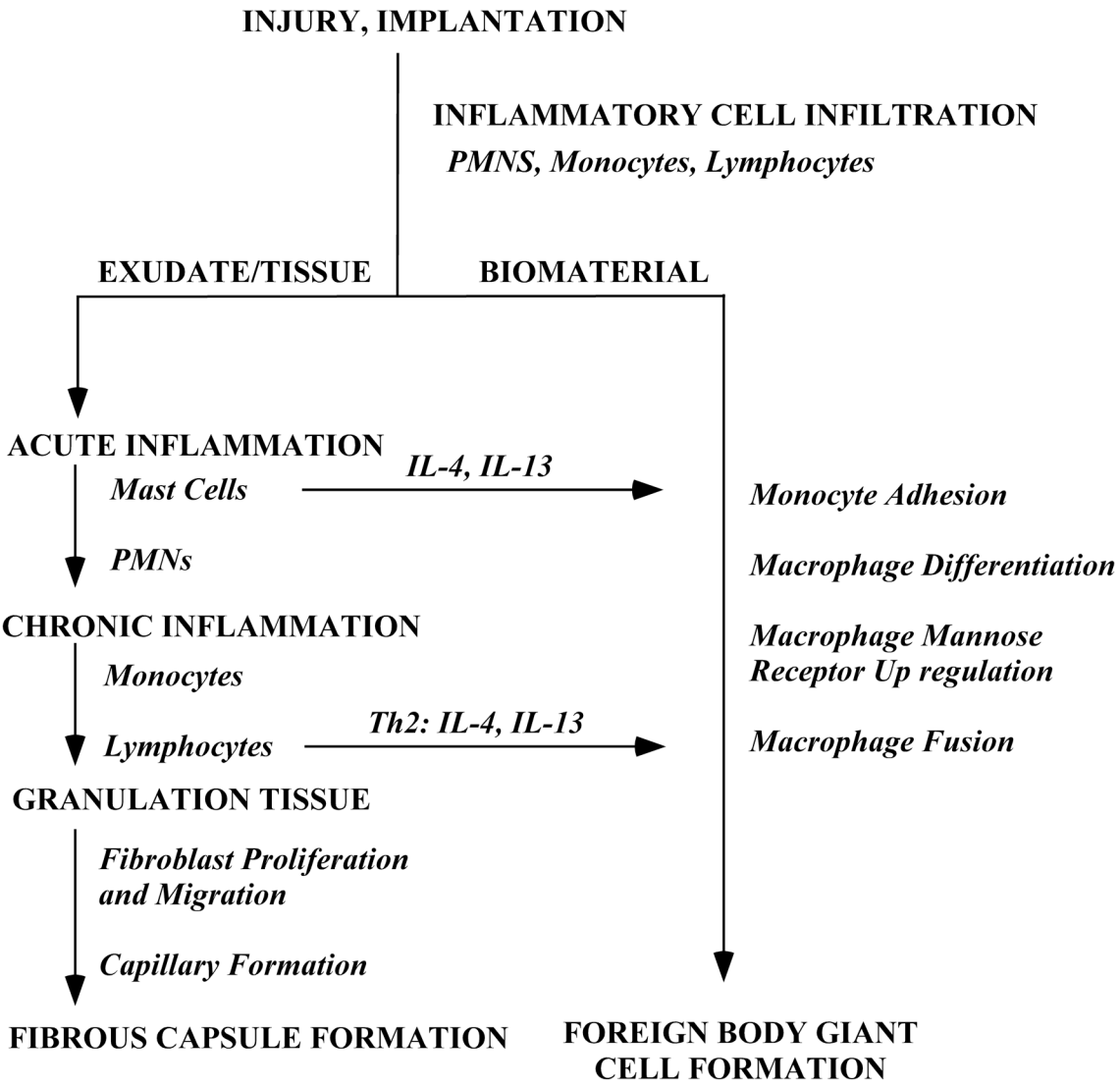

Figure 1.

Sequence of events involved in inflammatory and wound healing responses leading to foreign body giant cell formation. This shows the potential importance of mast cells in the acute inflammatory phase and Th2 lymphocytes in the transient chronic inflammatory phase with the production of IL-4 and IL-13, which can induce monocyte/macrophage fusion to form foreign body giant cells.

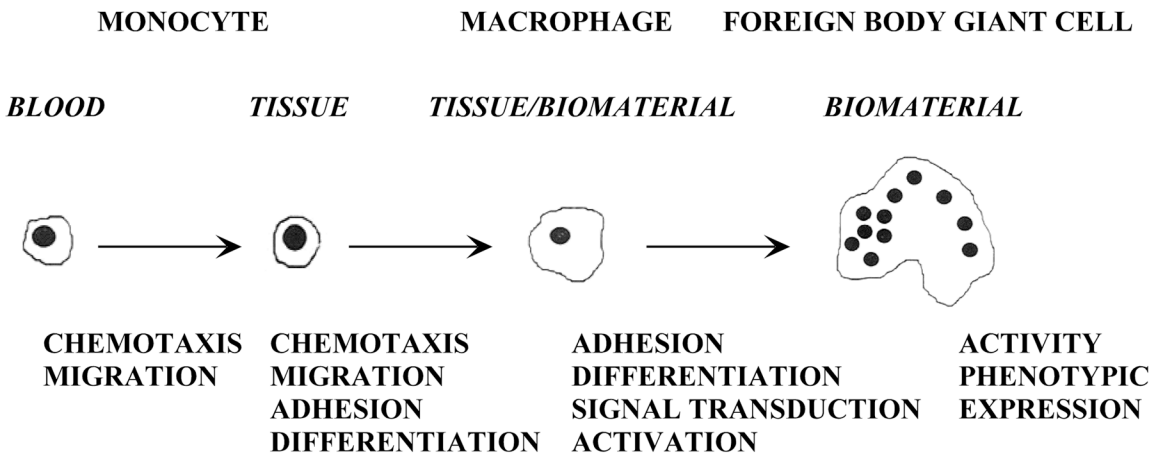

Figure 2.

In vivo transition from blood-borne monocyte to biomaterial adherent monocyte/macrophage to foreign body giant cell at the tissue/biomaterial interface. There is ongoing research to elucidate the biological mechanisms that are considered to play important roles in the transition to foreign body giant cell development.

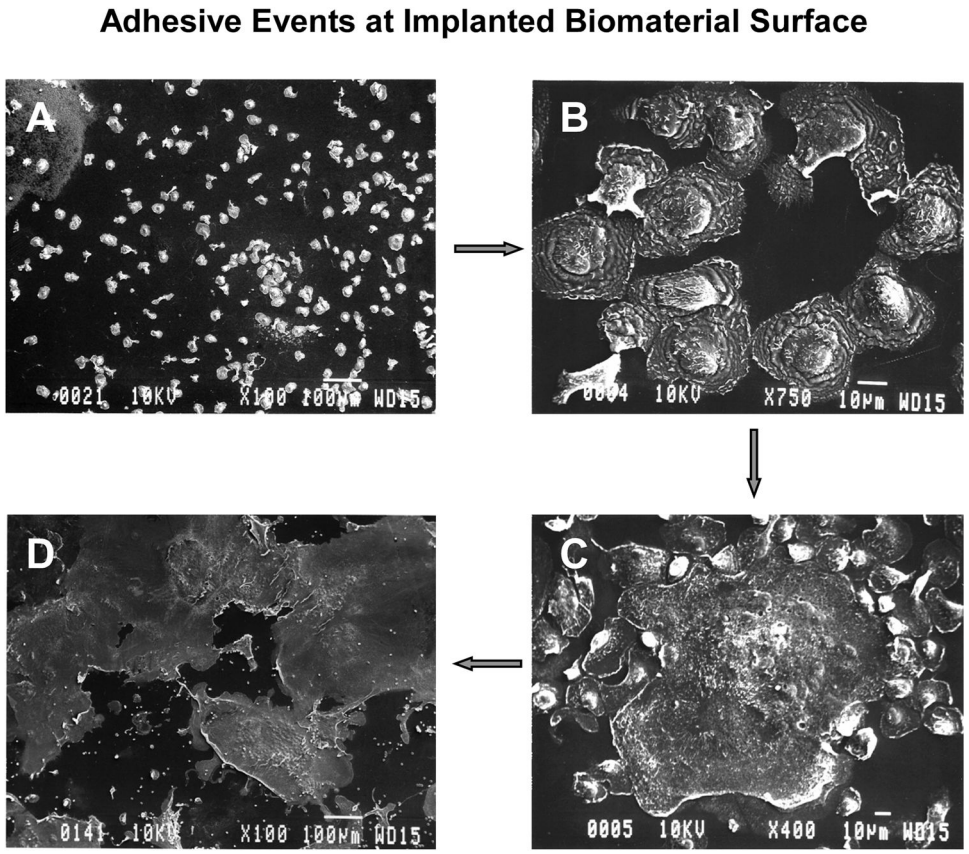

Figure 3.

Scanning electron microscopy images of an Elasthane 80A Polyurethane surface from an *in vivo* cage study showing the morphological progression of the foreign body reaction. The sequence of events at the Polyurethane surface includes (A) monocyte adhesion (0 days), (B) monocyte-to-macrophage development (3 days), (C) ongoing macrophage-macrophage fusion (7 days), and (D) foreign body giant cells (14 days).

Table 1

Molecular Mediators Involved in Macrophage Fusion[a]

	FBGC		Osteoclasts	
	in vitro	**in vivo**	**in vitro**	**in vivo**
Soluble Mediators				
IL-4 [58]	X	X		
IL-13 [60]	X			
MCP-1 [24,146]	X	X	X	
α tocopherol [65]	X			
Plasma fibronectin [73]		X		
Osteopontin [70]	X	X		
Receptors				
Mannose Receptor [60,61]	X			
β1 and β2 Integrins [30]	X			
SIRPα [147]			X	
CD44 [148]			X	
CD47 [149]			X	X
DC-STAMP [68]	X	X	X	X
Tetraspanins [150]		X	X	X
Signal Transductors				
Diacylglycerol kinase [65]	X			
Rac 1 [64]	X	X		
V-type ATPase [63,151]	X			X
iPLA2 [63]	X			

[a] Adapted from Themis Kyriakides, unpublished work

Table 2

A Comparison of Alternatively Activated and Classically Activated Macrophages

Parameter	Classical[a]	Alternative[a]		Biomaterial Effects (Day 3/Day 10)			
	LPS & IFN-γ	IL-4 & IL-13	IL-10	Hydrophobic	Hydrophilic & Neutral	Hydrophilic & Anionic	& Cationic
Cytokines							
IL-1	↑	↓	↓	↑/↓	↑/↓	↑/↓	↑/↓
IL-6	↑	↓	↓	↑/↓	↑/↓	↑/↓	↑/↓
IL-10	↓	↑		↑/↑	↑/↑	↑/↑	↑/↑
IL-12	↑	↓		↔	↔	↔	
TNF	↑	↓	↓	ND	ND	ND	ND
Chemokines							
IL-8	↑		↓	↑/↓	↑/↓	↑/↓	↑/↓
MIP-1β	↑	↓	↓	↓/↓	↓/↓	↑/↓	↓/↓
MDC	↓	↑		↑/↑	↑/↑	↔/↑	/↑
TARC	↓	↑		↔	↔	↔	
Mig	↑	↓	↓	↔	↔	↔	
RANTES	↑	↓	↓	↑/↑	↑/↑	↑/↑	↑/↑
IP-10	↑	↓	↓	↔	↔	↔	
ENA-78	↑			↑/↔	↑/↔	↔	
MCP-1	↑			↑/↑	↑/↑	↑/↑	↑/↑
MIP-1α	↑	↓	↓	ND	ND	ND	ND
Eotaxin	↑			↔	↔	↔	
Eotaxin-2	↓	↑		↑/↑	↑/↑	↔/↑	/↑
GRO	↑			↔	↔	↔	
MMP/TIMP							
MMP-9		↓		↑/↑	↑/↑	↑/↑	↑/↑
TIMP-1			↑	↑/↑	↑↑/↑	↑/↑	↑/↑
TIMP-2				↑/↑	↑/↑	↑/↑	↑/↑

Bold: measured by ELISA and cytokine array; otherwise: only by cytokine array; "↑"/"↓": level of production increased or decreased.

[a] Adapted from references: [122,124–126,152–157]