Society For Biomaterials

Review Article

The pathology of the foreign body reaction against biomaterials

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Received 27 June 2016; revised 13 October 2016; accepted 1 November 2016
Published online 25 November 2016 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jbm.a.35958

Abstract: The healing process after implantation of biomaterials involves the interaction of many contributing factors. Besides their *in vivo* functionality, biomaterials also require characteristics that allow their integration into the designated tissue without eliciting an overshooting foreign body reaction (FBR). The targeted design of biomaterials with these features, thus, needs understanding of the molecular mechanisms of the FBR. Much effort has been put into research on the interaction of engineered materials and the host tissue. This elucidated many aspects of the five FBR phases, that is protein adsorption, acute inflammation, chronic inflammation, foreign body giant cell formation, and fibrous capsule formation. However, in practice, it is still difficult to predict the response against a newly designed biomaterial purely based on the knowledge of its physical–chemical surface features. This insufficient knowledge leads to a high number of factors potentially influencing the FBR, which have to be analyzed in complex animal experiments including appropriate data-based sample sizes. This review is focused on the current knowledge on the general mechanisms of the FBR against biomaterials and the influence of biomaterial surface topography and chemical and physical features on the quality and quantity of the reaction. © 2016 Wiley Periodicals, Inc. J Biomed Mater Res Part A: 105A: 927–940, 2017.

Key Words: foreign body reaction, biomaterials, biocompatibility, macrophages, foreign body giant cells, fibrosis

How to cite this article: Klopfleisch R, Jung F. 2017. The pathology of the foreign body reaction against biomaterials. J Biomed Mater Res Part A 2017:105A:927–940.

INTRODUCTION

Detection and elimination of intruding infectious agents is the main task of the mammalian immune system. These potential threads to the well-being of the organism are initially recognized by the innate immune system. It detects nonself molecular surfaces or patterns and induces an immune reaction that eliminates the agent or the infected cell. Elimination is mainly based on the phagocytosis and phagolysosomal digestion of the intruder into nondangerous, reusable, or excretable subunits. These mechanisms works usually well with bacterial, viral, and protozoal organisms or cells infected with them. However, quick elimination by phagocytosis fails when phagolysosomal-resistant mycobacteria or large metazoan organisms or foreign bodies are the target. In these cases, macrophages, giant cells accumulate around the infected tissue or ate the surface of the foreign body and a fibrous capsule is formed to isolate and prevent the outspread to other body regions. Most of the knowledge on the mechanisms of granuloma formation, which is an aggregate of macrophages transformed into epithelium-like cells and giant cells, surrounded by a collar of lymphocytes and plasma cells.[1]

Recently, biomaterial science has, however, tremendously contributed to the progress in the understanding of the nature of foreign body reaction (FBR). A biomaterial is defined as a substance that has been engineered to take a form, which is used to direct the course of any therapeutic or diagnostic procedure by interactions with the living organism.[2] Biomaterial engineering, therefore, aims at materials that integrate well into the designated tissue without eliciting a FBR. Therefore, biomaterial science put much effort in the understanding of the molecular interaction between the surface of engineered materials and the host response. The current concept of the FBR against biomaterials divides it into five phases: (i) protein adsorption, (ii) acute inflammation, (iii) chronic inflammation, (iv) foreign body giant cell formation, and (v) fibrosis or fibrous capsule formation.[2,3] Many general mechanisms of the host response against nonself, nonliving materials have been elucidated. It is, however, obvious that the specific response to a transplanted

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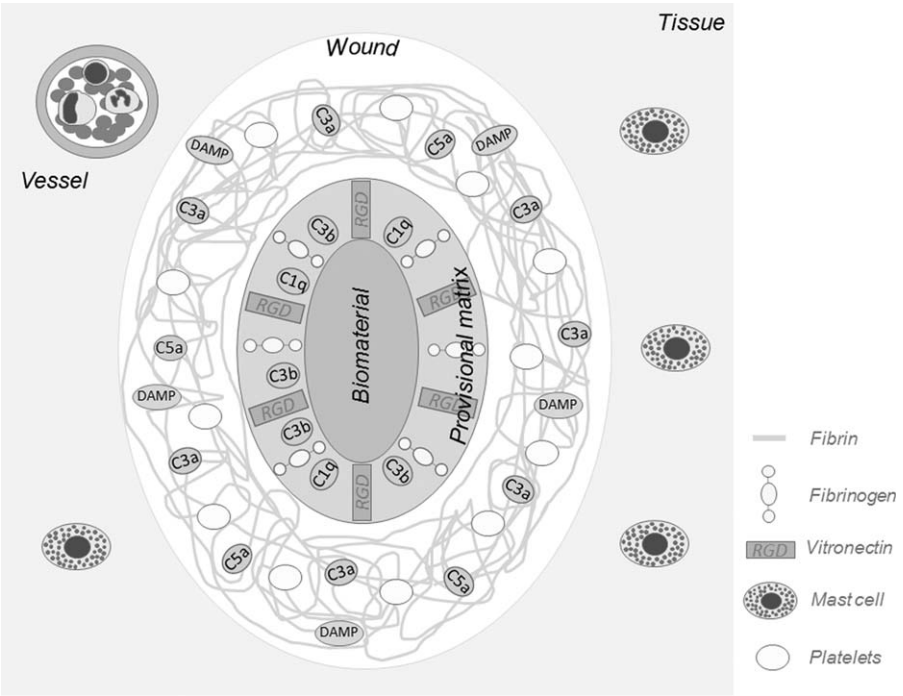

FIGURE 1. Phase 1 of the foreign body reaction—formation of a provisional matrix around implanted biomaterials.

biomaterial very much depends on its physical and chemical characteristics especially of its surface. One of the major current goals of biomaterial research is therefore to understand, predict and intentionally influence the reaction to a biomaterial. This review gives a summary on the current state of knowledge on the general mechanisms of FBR against biomaterials and puts a focus on how the topography as well as chemical and physical features of biomaterial surfaces influence the quality and quantity of the reaction, which occurs along a continuum from which some discrete intervals are described as typical phases.

PHASE 1: FORMATION OF A PROVISIONAL MATRIX AT THE BIOMATERIAL SURFACE

The implantation of a biomaterial into the body includes injury and blood material interactions. Within seconds, proteins of the blood plasma—with high affinity to surfaces[2]—adsorb to the biomaterial to form a very sparse provisional (protein) matrix of 2–5 nm (Fig. 1).[4] This matrix finally develops into a fibrin-dominated thrombus[5] with region specific differences. Since all involved cells interact with the provisional matrix rather than the foreign body surface, its composition is assumed to be of major relevance for all subsequent events during the FBR *in vivo*.[6]

The composition of the early provisional matrix and the final thrombus depends on several features including the physico-chemical properties of the biomaterial surface and the blood plasma composition. The early phase of the protein adsorption is usually described by the Vroman effect.[7] This effect is characterized by a continuous adsorption and desorption of proteins. While high mobility proteins like albumin are adsorbed first, they are increasingly replaced by less motile proteins with higher affinity for the specific surface like fibrinogen, high molecular weight kininogen (HMWK), fibronectin, and vitronectin.[8–10] The Vroman effect is most prominent on hydrophilic surfaces where proteins are less tightly bound than on hydrophobic surfaces.[11] The final composition is, however, dependent on the serum protein concentration and the surface characteristics[9] fibrinogen and albumin usually adsorb to polymers in relative quantities equal to those in the serum while vitronectin seems to have a higher affinity and accumulates over time in the provisional matrix.[12,13] The amount of adsorbed vitronectin, and also fibronectin, on the biomaterial surface is of major importance for monocyte adhesion and giant cell formation via their integrin-mediated interaction with these proteins.[14,15] McNally In addition, the provisional matrix contains and releases several other chemoattractants, cytokines, and growth factors of diverse nature, which influence the FBR by modulating attraction and activity macrophages and other immune cells. Anderson et al., therefore describe the provisional matrix as "a naturally derived, biodegradable sustained release system in which bioactive agents are released to control subsequent phases of wound healing."[3]

The final matrix around a foreign material is mainly composed of fibrin and, thus, constitutes a fibrin clot. There are several hypotheses how fibrinogen is converted to fibrin on the surface of a transplanted biomaterial. First, the intrinsic coagulation system is initiated by biomaterial surface-promoted autocatalytic activation of FXII on negatively charged, anionic surfaces.[10,16,17] Recent findings however challenge the negative charged surface paradigm of FXII activation and propose a complex protein-adsorption-competition effect in the fluid phase on the biomaterial

TABLE I. Examples of Biomaterial Features with Influence on Protein Adsorption and Complement Activation

Biomaterial Feature	Influence on FBR	References
Poly(ethylene glycol) (PEG)/chain density ↑	Protein adsorption ↓	30,31
Poly(2-hydroxyethyl methacrylate), PHEMA	Protein adsorption ↓	3
Oligoethylene glycol	Protein adsorption ↓	32,33
Poly-(carboxybetaine acrylamide) (poly(CBAA))	Protein adsorption ↓	34
Poly(acrylamide)	Protein adsorption ↓	35
Peptoids	Protein adsorption ↓	36
Poly(carboxybetaine methacrylate) (PCBMA)	Protein adsorption ↓	37
Carboxybetaine-containing polymer brushes	Protein adsorption ↓	38
Hydrophobic surfaces including —CH3 groups	Albumin/Fibrinogen binding ↑, conformational changes in fibrinogen ↑	39,40
Negatively charged carboxyl/sulfate groups, sialic acid, heparin	Alternative pathway of complement activation ↑	9
Hydrophobic surfaces	Complement activation ↑	28
Nucleophiles like hydroxyl/amino groups, polyacrylonitrile	Alternative pathway of complement activation ↑	9
Surface roughness	Protein adsorption ↑	41–43
Wettability (hydrophobia vs. hydrophilia)	Protein adsorption ↓↑	8
Surfaces with extreme wettability	Protein adsorption ↓	44
Surface charge	Protein adsorption ↓↑	36,37,41

surface as the cause of FXII activation.[18] Contact activation of FXII alone is, however, not sufficient to induce a sufficient thrombus formation on biomaterials.[19] Platelet adhesion and activation by FXII-activated thrombin seems to be a necessary amplifier to induce fibrin deposition.[19–21] Thrombin then cleaves fibrinogen to fibrin, which leads to the typical fibrillary mesh-like fibrin coat on the surface of transplanted biomaterials. However, not all of the fibrinogen spontaneously attached to the initial provisional matrix is transformed into fibrin. The nontransformed fibrinogen seems to undergo an adhesion-mediated conformational change associated with the display of functional epitopes[22] that can interact with mainly α-integrins on platelet membranes leading to platelet adhesion, activation, and subsequent aggregation of further platelets.[3,23,24] In addition, adherent fibrinogen and von Willebrandt factor are also a potential adhesion matrix for macrophages.[25] The complement system is another system of major importance to the fate of biomaterials in the organism. Complement activation and the subsequent boost of the immune reaction and the plasmatic coagulation are also involved in the failure of implanted biomaterials.[26] The activation of the classical complement system pathway is thought to be induced by unspecifically bound immunoglobulins (IgG) in the provisional matrix, which bind the C1 subunits and activate the C3 convertase.[10,27] However, a direct binding of C1q to the biomaterial surface has also been proposed. Several surface characteristics of biomaterials like carboxyl, sulfate, hydroxyl, and amino groups seem to bind C3b and activate the alternative pathway. Here, bound C3b activates the C3 convertase, which induces a positive amplification loop and finally activates the downstream C5 convertase.[10,26,28,29] However, other biomaterials without the mentioned surface characteristics also seem to induce complement activation, which indicates that the process of complement activation is not fully understood yet.[10] Activation of the complement system results in the generation of high amounts of C3a and C5a, which are strong chemoattractants for phagocytes and also stimulate the degranulation of mast cells and neutrophils. In contrast, the majority of C3b is present on the provisional matrix and acts as a ligand for leukocyte adhesion via integrin receptors.[29] Depending on the leukocyte subsets that become activated, an arsenal of cytokines is generated and released that will determine the consequences of the material-blood interaction. Activation of the complement system is a driving force in incompatibility reactions of differing severity, such as thrombotic complications, acute or chronic inflammation, as well as encapsulation with a possible subsequent loss of function of a device.[3,10]

Influence of biomaterial surface characteristics on protein adsorption

Protein adsorption is a very complex process that depends on numerous variables of the surface like wettability, topography, elasticity, chemical composition and charge but also on characteristics of the proteins like structure, isoelectric point and relative concentration in the plasma and protein-surface affinity (Table I). It requires dehydration of the protein and the surface, redistribution of charged groups in the interface and is often associated with conformational changes in the protein molecule.[9] Because of the complex interaction of these parameters in the respective setting, a safe prediction of the composition of the provisional matrix on a specific surface is not possible without empirical data up to now. However, numerous studies focused on the question how the composition of the provisional matrix can be influenced and found some general rules (reviewed in Refs. 9,15,23,29). So far, several materials have been described to have reduced protein adsorption, due to their inherent physicochemical properties like wettability, roughness/topography, elasticity, and surface charge (Table I).

Surface wettability, that is hydrophobicity or hydrophilicity is an important characteristic for protein adsorption on biomaterial surfaces.[9] Since hydrophilic surfaces more tightly bind water molecules, a stable water layer on a surface represents a barrier for surface-protein as well as cellular interactions on hydrophilic surfaces.[45,46] Hydrophobic surfaces, therefore, usually adsorb more proteins than hydrophilic, maybe due to a more easy replacement of water molecules from their surface.[47]

Other studies however showed that hydrophilic and hydrophobic surfaces can have a similar adsorption capacity.[36,37,39,41,48,49] Surface charge and protein conformation have been identified as additional factors that may be more relevant than wettability at least for some proteins on certain surfaces.[34] For instance, both fibrinogen and vitronectin have a higher affinity for positively or negatively charged hydrophobic surfaces as compared to uncharged hydrophobic surfaces.[36,37,41] To make matters more complicated, pH and small ions in the aqueous solution are also influencing the surface charge.[48] In addition, the alternative complement activation pathway seems to be more readily to activated surfaces containing negatively charged groups such as carboxyl and sulfate, sialic acid and bound heparin but may also be activated by other charge-independent mechanisms of factor H-binding.[10,32]

Surface topography, including general roughness, is another feature that often is associated with an increased protein adsorption, cell adhesion, and differentiation.[9,49–52] Besenbacheŕs group reported that nano-rough surfaces (surface features smaller than 100 nm) change protein conformations.[42] Proteins with dimensions of the same order as the surface are not conformationally altered, while proteins with dimensions much smaller or larger than the surface roughness are conformationally altered upon adsorption. These changes are hypothesized to be caused by roughness-mediated confined spaces that interfere with the wettability of the surface or may increase the surface energy to adsorb proteins.[43,53] For instance, parallel grooves on silicone substrates lead to a more even orientation of fibronectin, vitronectin, and dermal fibroblasts.[54] In addition, rough and hydrophobic surfaces are prone to the formation of stable gas nucleoli, even in the smallest micropores. Such entrapped air nuclei—not successfully removed from the surface—may also account for thrombogenicity.[43,48,52,55]

Shear stress and strain is elicited at the implant interface by body movements. Mechanical stress is a well-recognized stimulator of different cells. Griendling & FitzGerald reported that all cell types tested to date responded to shear stress.[56] At higher strain levels responses include the production of pro-inflammatory signals that recruit immune cells and can cause a FBR.[56–58] When the implant exhibits a higher elastic modulus than the surrounding tissue, movement of the tissue will result in stresses at the interface between the implant and tissue. This can lead to a pro-inflammatory signal, ending up in the formation of a fibrotic capsule, or what is often termed "poor biocompatibility" of the material.[59] Hilborn and Bjursten, therefore, proposed that biomaterial design should be focused on reducing unfavorable mechanical stresses around the implant by adapting the elastic modulus to the elasticity of the tissues.[59]

PHASE 2: ACUTE INFLAMMATION (MAST CELLS AND GRANULOCYTES)

Acute inflammation characterized by the infiltration of polymorphnuclear leukocytes (PMN) and mast cells is considered the second phase in the FBR against biomaterials (Fig. 2).[3] It is a short-lived, hours-to-few days-long, reaction that usually resolves within a week and can pass into chronic inflammation. Most of the currently used biomaterials like hydrogels and polymers are reported to be inert and nontoxic the presence of this acute reaction and even more the continuous chronic infiltration by macrophages at later time points is intriguing and not yet fully understood (reviewed in Ref. 30). Three mechanisms of leukocyte migration, adhesion, and activation in acute inflammation are currently considered:

1. Tissue damage during implantation.
2. Recognition and interaction with the provisional matrix.
3. Direct recognition of the biomaterial.

Tissue damage during the implantation process seems to be the main trigger for infiltration of the first PMN during acute inflammation. Diverse endogenous damage-associated molecular patterns (DAMP, syn. Alarmins) like ATP, uric acid, bioactive lipids, and heat shock proteins are freed after cell membrane disruption.[30] DAMP are then recognized by the PMN and mast cells and lead to migration toward the implantation site. Typical pattern recognition receptors (PRR) for these danger signals are Toll-like receptors (TLR), which are able to initiate the innate immune response.[29] In addition to DAMP, chemoattractants like coagulation factor VII, XI, von Willebrand factor (vWF), platelet factor 4 (PF4) or P-selectin are released by activated platelets, endothelial cells, and the complement system and attract PMN and later macrophages to the site of implantation.[19,31] In addition, the interaction of endothelial cells with leukocytes and the mechanisms of vascular permeability may also have an effect on the progress of the FBR.[33,35,38]

Upon arrival and adhesion of the PMN at the implantation site, PMN and neutrophils are activated and degranulate. Mast cell-derived histamine, IL-4, IL-13, and PMN-derived IL-8, MCP-1, and MIP1β are subsequently attracting more leukocytes including macrophages to establish the chronic inflammation phase.[39,40,44] In addition, frustrated phagocytosis of the neutrophils and oxygenic burst initiates a highly pro-inflammatory milieu and progressive tissue degeneration, which perpetuates and boosts the attraction of more PMN and initiates chronic inflammation.[60]

Implantation of the biomaterial in the surgical wound leads to the development of a provisional matrix.[3] There is convincing evidence that the proteins on and in the provisional matrix are recognized as a danger signal itself. For instance, fibronectin and vitronectin adsorbed to the surface are recognized by several α-integrins and TLR on leukocytes (reviewed in Ref. 29). Furthermore, biomaterial-adsorbed

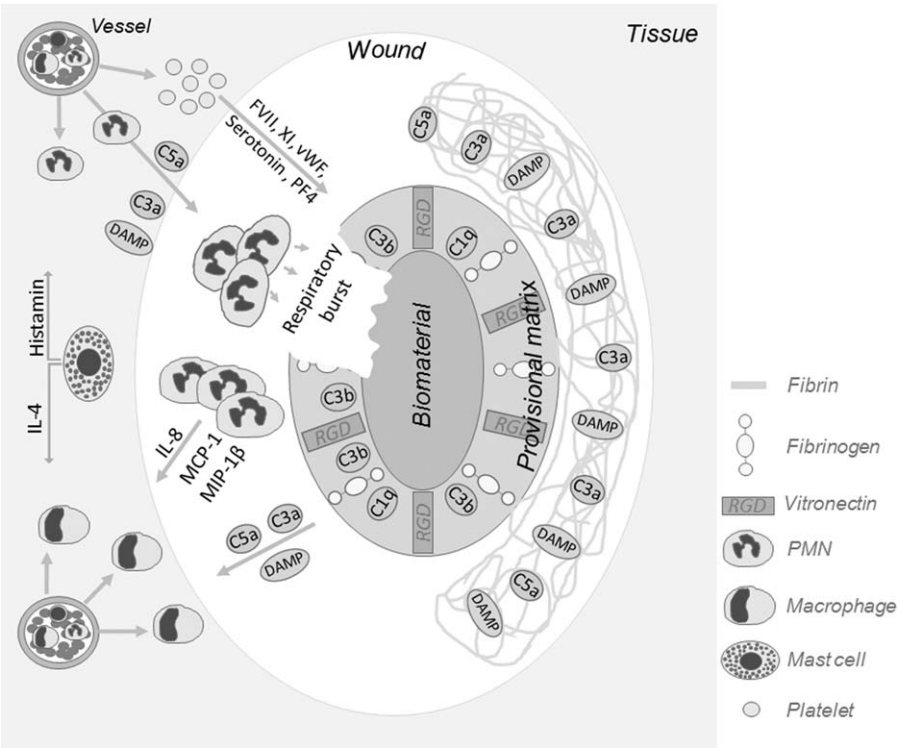

FIGURE 2. Phase 2 of the foreign body reaction—Acute inflammation with dominance of polymorphnuclear leukocytes (PMN, neutrophils), mast cell degranulation, and arrival of first monocytes/macrophages at the implantation site. FVII, XI: coagulation factor VII, XI, vWF: von Willebrand factor, PF4: platelet factor 4.

fibrinogen and HMWK undergo conformational changes that free αMβ2-integrin binding sites for PMN and macrophages.[36,61] The interaction of PMN and macrophages with the provisional matrix is described to constitute the major factor during inflammation.[2] The inflammatory response and capsule formation seem also to depend on the shape of the implant. Capsule thickness and inflammatory infiltration cells significantly decreased for scaffolds during days 7–28, while remaining unchanged for films produced from the same polymer.[62] In addition, experimental prevention of integrin binding of PMN and incubation of PMN with hydrophobic polymers in a protein-free setting is not completely abolishing acute inflammation.[63] It is therefore assumed that many biomaterials are less inert and nonimmunogenic than expected and are recognized directly by TLR or via identification of hydrophobic portions of biomolecules (see next paragraph).[64]

Taken together, acute inflammation, although short lived, is the first step in the events that leads to a FBR and eventually device failure. Its severity is usually dependent on the extent of the tissue injury during implantation. Cytokine mediators released by PMN in this phase often influence the character and degree of subsequent inflammatory cell recruitment and activation as well as the phenotypes of monocytes/macrophages during chronic inflammation. The direct mechanisms of this influence, meaning understanding how this acute inflammation can be modeled to achieve the desired outcome, are minimal. Especially mast cells may be of relevance in this phase due to their IL-4 and IL-13 release, while the quantity of infiltrating PMN may even be inversely correlated with the amount of the subsequent FBR.[6]

Influence of the biomaterial surface on acute inflammation

There is considerably less research on the influence of biomaterial properties on the acute phase of inflammation than on their influence on protein adsorption or macrophage behavior and fibrosis. Quality and quantity of protein adsorption, the amount of tissue damage during implantation and contamination of the implant clearly have a dominant influence on the development of the following inflammation including the acute phase. Most notably, the provisional matrix is assumed to impair direct contact between infiltrating early leukocytes and the biomaterial. However, as mentioned above, biomaterials in a protein-free setting may induce similar inflammation as protein-covered biofilms.[29,63,64] This observation indicates that biomaterial surfaces may be directly recognized by PMN and macrophages in the early phase of inflammation, for instance by recognition of hydrophobic micro- or nanoareas of the biomaterial by TLR or activation of scavenger receptors.[64]

TLR mostly recognize molecules in the provisional matrix. However, few studies found that cationic polymers like polyethyleneimine, polylysine, cationic dextran, and cationic gelatin are stimulating TLR4 directly.[65] Activation of TLR by identifying hydrophobic portions (hyppos) of biomaterials seems to be another mechanism of biomaterial

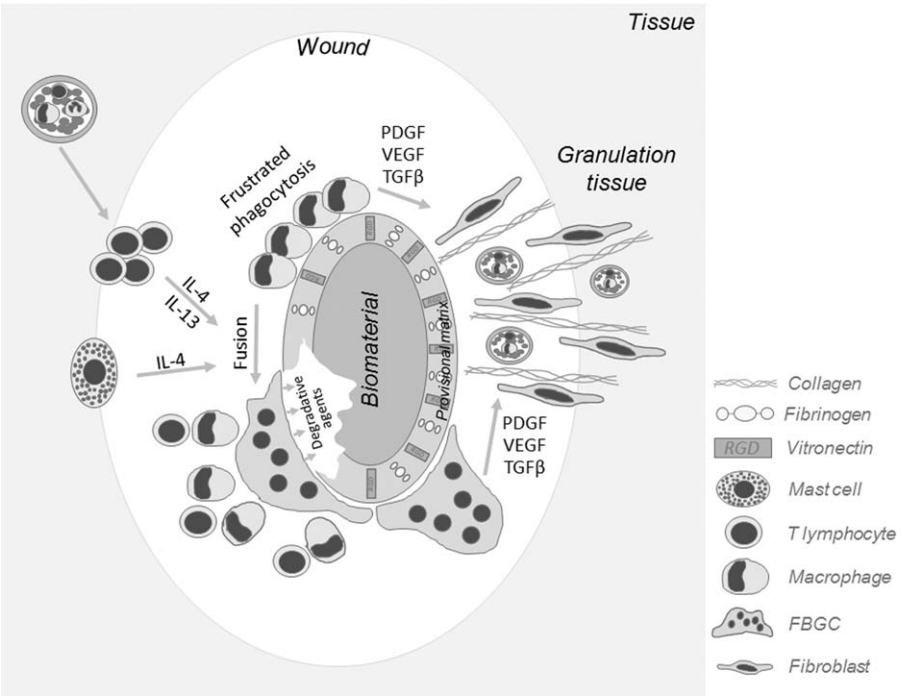

FIGURE 3. Phase 3 and 4 of the foreign body reaction—Chronic inflammation with dominance of lymphocytes and macrophages, which will fuse to foreign body giant cells (FBGC) after frustrated phagocytosis and under the influence of lymphocyte and mast cell-derived IL4 and IL13. In addition, macrophage and FBGC-derived growth factors induce the development of granulation tissue.

recognition.[66] TLR2 and TLR4 seem to bind and be activated by relatively unspecific hydrophobic interactions, which allow the detection of a wide range of substances like of alarmins attached to the biomaterial. However, few studies indicate that biomaterial structures, like hydrophobic polypropylene oxide, hydrophilic polyethylene oxide regions, oxidized alkane polymers and polystyrene directly activate TLR1,2,4,6 in a protein-free setting.[43,49,63,67,68] Hyppos may therefore be the cause of tissue damage- and provisional matrix-independent biomaterial-associated inflammation. Information on the direct influence of the surface topography like roughness on acute inflammation is not available.

PHASE 3: CHRONIC INFLAMMATION (MACROPHAGES, LYMPHOCYTES AND GIANT CELLS)

In biomaterial science, the term chronic inflammation usually describes a rather short period of 2–3 weeks (weeks 2–5 after implantation), which is characterized by the infiltration with lymphocytes and monocytes (Figs. 3 and 4) and does not include the formation of foreign body giant cells (FBGC) and a fibrous capsule at later time points.[69] This is in contrast to the common pathologic nomenclature, which uses chronic inflammation as the term for everything that is postacute. During the chronic phase, but also earlier and in parallel to neutrophil recruitment, circulating monocytes and lymphocytes respond to platelet-, PMN-, and mast cell-derived chemoattractants at the implantation site.[3]

Monocytes/macrophages are considered the central cells in the initiation, duration and outcome of the host response against implanted biomaterials.[64] They are attracted to the implantation site by complement factors, transforming growth factor (TGF-β), platelet-derived growth factor (PDGF), platelet Factor 4 (PF4), macrophage chemoattractant protein 1–4 (MCP-1,2,3,4), RANTES, macrophage inflammatory protein 1α (MIP-1α), and MIP-1β.[70,71] In addition, they are also directly recognizing biomaterials or biomaterial-associated proteins by TLR and scavenger receptors.[29]

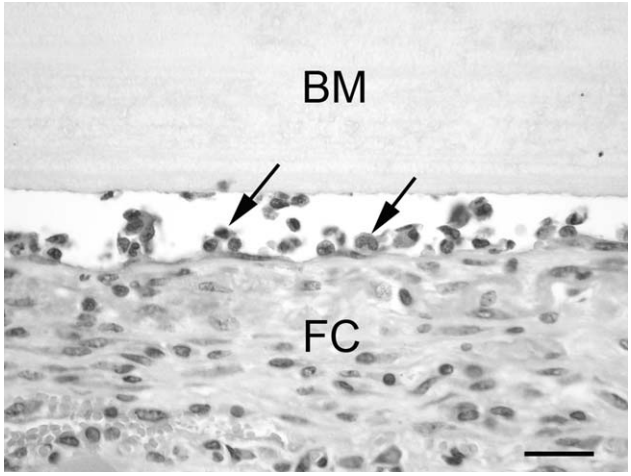

FIGURE 4. Phase 3 and 4 of the foreign body reaction—Poly(vinylidene fluoride-*co*-hexafluoropropene) (BM) 28 days after implantation into rat subcutis surrounded by macrophages (arrows) and a fibrous capsule (FC). HE-stain, Bar = 50 μm.

TABLE II. Biomaterial Features with Influence on Cell Adhesion and Quantity of Inflammation

Biomaterial Feature	Influence on FBR	References
Hydrophilic, anionic/nonionic (polyacrylamide/polyacrylic acid)	Macrophage adhesion ↓	66
Hydrophobic/hydrophilic, cationic surfaces	Macrophage adhesion ↑	66
Nickel	Inflammation ↑	83
Wear (debris) rate, corroding metals, magnesium	Inflammation ↑	83,84
Amino (—NH2) and hydroxyl (—OH groups	Inflammation ↑	77
—OH > —NH2 = —COOH > —CH3 surfaces	Infiltration and cell adhesion ↑	85,86
Uniform 30–40 μm pores	Macrophage infiltration ↑ Portion of M2 macrophages ↑	30,81,87,88
50 μm nanodots	Cell adhesion and density at maximum	82
Silica particle size <1000 μm	Inflammation ↑	80
Smaller PLGA microspheres	Macrophage influx ↑	89
Triangular > pentagon > circular shaped polymers	Inflammation ↑	90
Mismatch of stiffness of tissue and biomaterial	Inflammation ↑	80

PLGA, poly(lactic-*co*-glycolic acid).

After arrival, macrophages mainly adhere to fibrinogen, complement fragments, fibronectin, and vitronectin of the provisional matrix via β1-, β2-, and β3-integrin receptors.[41,72] This binding at the site of injury leads to activation of these monocytes. Several subtypes of activated macrophages can be differentiated (review in Liu et al.[73]). Classically activated, pro-inflammatory M1 macrophages are characterized by the synthesis of interleukin-1 (IL-1), IL-6, IL-8, and tumor necrosis factor α (TNF-α).[74–76] M1 boost inflammation and try to degrade the biomaterial by phagocytosis and by the release of ROS and lysosomal enzymes. As opposed to this, alternatively activated, anti-inflammatory M2 macrophages are induced by IL-4 and IL-13 from mast cells or TH2-lymphocytes.[45,53] M2 secrete the anti-inflammatory cytokines IL-10 and transforming growth factor-β (TGF-β) and induce tissue remodeling by matrix-metalloproteinases.[53,77] It is reported that the switch from M1 to M2 phenotype is associated with the fusion of macrophages into a foreign body giant cell (FBGC), which may be an attempt to increase their phagocytic functionality and avoid anoikis and apoptosis.[78,79] Recent studies, however, challenged the dichotomy of macrophage polarization and showed that there might be variable activation states in a continuum between M1 and M2.[30,80] This also seems to be the case in the FBR. Studies found that macrophages in the FBR have variable phenotypes with features of both, M1 and M2 polarization.[31] Nevertheless, other studies found a higher percentage of M2 at the implantation site to be associated with decreased scar tissue formation, tissue integration, and increased neovascularization.[39,40,60]

Lymphocytes are also found in the vicinity of implanted biomaterials during the chronic FBR phase. They are usually attracted by cytokines secreted by macrophages and FBGC at the implantation site, adherent to macrophages at the site and seem to participate in the inflammation process by the secretion of several cytokines.[6] The lymphocytes at the implantation site are mainly CD4+ T-lymphocytes and are mainly secreting IL4 and IL13, which are able to induce a M2 phenotype switch and FBGC formation. It has, therefore, been suggested that initial monocyte adhesion at biomaterials may be transient until lymphocytes are attracted, secrete cytokines and induce firm adherence and differentiation into macrophages and FBGC.[79,81] However, implantation of biomaterials into T-lymphocyte-deficient mice is also inducing a FBR similar to that of wild-type mice.[82] The role of lymphocytes in the FBR is therefore unclear at present.[64]

Taken together, independent from their phenotype, macrophages are the central cells for the fate of the implant during this phase of the FBR. They phagocytose the damaged tissue as well as degradation products of the implant and secrete cytokines and growth factors that facilitate inflammation and finally activate fibroblasts, tissue regeneration, and capsule formation. Lymphocytes are commonly present during the chronic phase of the FBR but their role is controversially discussed.

Influence of the biomaterial surface on chronic inflammation

There is a multitude of studies on the effects of biomaterial surface chemistry and topography on macrophage infiltration, adhesion, activation and the general quantity of inflammation on biomaterials (Table II). For instance, hydrophobic and cationic surfaces seem to promote macrophage adhesion over hydrophilic, anionic surfaces.[69] In addition, nickel, magnesium, corroding metals in general as well as hydroxyl and amino groups stimulate a more intense inflammation with higher numbers of infiltrating macrophages and lymphocytes (Table II).

Moreover, three-dimensional surface topography is also significantly influencing chronic inflammation. Biomaterials with pore sizes around 30–40 μm were associated with the highest number of infiltrating macrophages but also a higher portion of M2 macrophages and the highest vascularization and best healing success (Table II).[64,83] Similarly, 50 nm nanodots on an aluminum oxide based array increased IL-6 secretion, adhesion, density, and spread of macrophages as compared to flat surfaces or very large dots but their influence on the final outcome of the reaction, that is FBGC and capsule formation has not been elucidated.[84] Finally, a mismatch of a stiff material and a low tissue stiffness as well as sharper edges on triangular shaped biomaterials are increasing inflammation most probably due to higher mechanical irritation (Table II).[59]

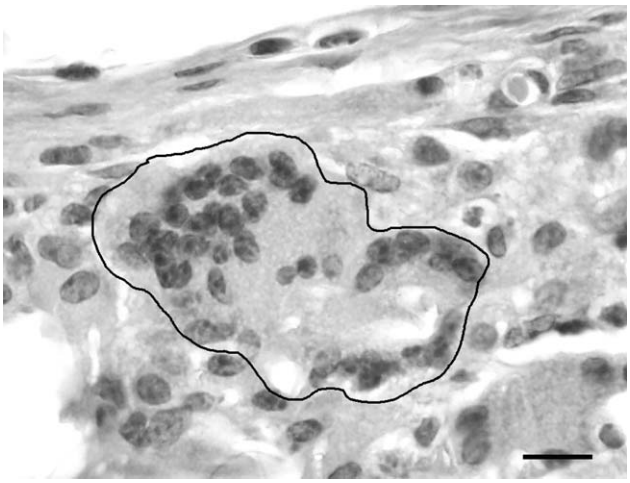

FIGURE 5. Phase 4 of the foreign body reaction—Foreign body giant cell formation (surrounded by a black line) is seen around poly(vinylidene fluoride-*co*-hexafluoropropene) (BM) 28 days after implantation into rat subcutis. HE-stain, Bar = 50 μm.

PHASE 4: FOREIGN BODY GIANT CELL (FBGC) FORMATION

Foreign body giant cell (FBGC) formation is considered the hallmark of the FBR, which separates it from typical chronic inflammation (Fig. 5). FBGC formation is the process of macrophage fusion, which leads to large, up to several hundred μm large, multinucleated giant cells with several to dozens of nuclei.[3,4] These cells are usually persistently present as long as the biomaterial is detected in the subcutaneous tissue.[87] The evolutionary advantage of FBGC is still not fully understood. FBGC are usually present if persistent and non-digestable microorganisms or foreign bodies are present. After failed/"frustrated phagocytosis" macrophages fuse into body giant cells seemingly to improve their effectiveness or in an attempt to avoid apoptosis.[88]

IL-4 and IL-13 have been identified as the most important environmental signals for "frustrated" macrophages to fuse.[34,36,37,47] T lymphocytes but also the permanently present but few mast cells have been identified as the sources of both interleukins. Adhesion to the biomaterial via β integrin receptors and the influence of IL-4 and IL-13 leads to the up-regulation of fusogenic molecules like mannose receptors DC-stamp, CD44, CD47, and E-cadherin at the fusion interfaces of both macrophage fusion partners.[3,89–93] The resulting FBGC are characterized by the expression of several membrane proteins including CD11, CD45, and CD31 and expression of receptors for IL-1 IL-2, IL-4, and IL-8 (reviewed in Ref. 3). Of note, IL-4 and IL-13 are considered the main factors involved in the phenotype switch to anti-inflammatory and pro-fibrotic M2. It has, therefore, been hypothesized that FBGC are derived from or closely related to M2 macrophage. In terms of cytokine synthesis, they secrete IL-1α; IL6, IL8, and TNF-α during the first month of the FBR, while at later time points IL-10 and transforming growth factor-β (TGF-β) but also MCP-1 are expressed. FBGC are, thus, not unequivocally attributable to one of the two main macrophage categories but may rather be a distinct cell type.[75,94]

FBGC formation at the biomaterial surface is considered to be undesired since in the long term they are the main source of bioreactive agents like reactive oxygen species (ROS), degradative enzymes and acids, which lead to biodegradation of the implanted material and, thus, device failure.[6,41] Depending on the chemical surface properties of the biomaterial, this leads to a variably fast degradation. For materials like resorbable sutures or hydrogels this degradation is desired.[66,95,96] For medical devices for which degradation is not desired, antioxidants are included in the material or at least its surface to moderate the oxidation.[49]

Influence of the biomaterial surface on foreign body giant cell formation

Macrophage fusion is not only dependent on the environmental signals and the presence of the fusiogenic molecules on their surface. The quantity and quality of the adsorbed proteins in the provisional matrix on the biomaterial (see paragraph on provisional matrix), the surface itself and topographic features also influence the severity of the FBR and FBGC formation. Of the abundant proteins of the provisional matrix with general influence on the FBR, adsorbed vitronectin, and to a lesser extent fibronectin seem to be most important but not essential for macrophages fusion (Table III).[3,97] There are few reports on the direct effects of the biomaterial surface on FBGC formation. Hydrophilic, anionic, and nonionic polyacrylamide/polyacrylic acid surfaces have decreased monocyte adhesion and FBGC formation compared to hydrophilic and hydrophobic, cationic surfaces.[69]

Surface topography has also been analyzed for its effect on macrophage fusion. Smooth, flat surfaces induce considerably more FBGC formation than rough surfaces.[6] The relevance of the size of spheres on FBGC is less consistent. Larger PLGA microspheres of ~30 μm have been found to

TABLE III. Biomaterial Features with Influence on Macrophage Fusion and General FBR

Biomaterial Feature	Influence on FBR	References
RGD-, vitronectin, chitosan-adsorbed surfaces	Macrophage fusion (IL-4-mediated) ↑	66
Hydrophilic, polyacrylamide (nonionic)/hydrophilic, polyacrylic acid (anionic)	Macrophage fusion ↓	66
Carboxylated/unmodified polystyrene	Macrophage fusion (IL-4-mediated) ↓	66
Larger (~30 μm) PLGA microspheres	Macrophage fusion ↑	89
Smooth, flat implants	FBR ↑	5
Larger spheres (1.5 mm, diverse materials)	FBR ↓	98

PLGA, poly(lactic-*co*-glycolic acid); FBR, foreign body reaction.

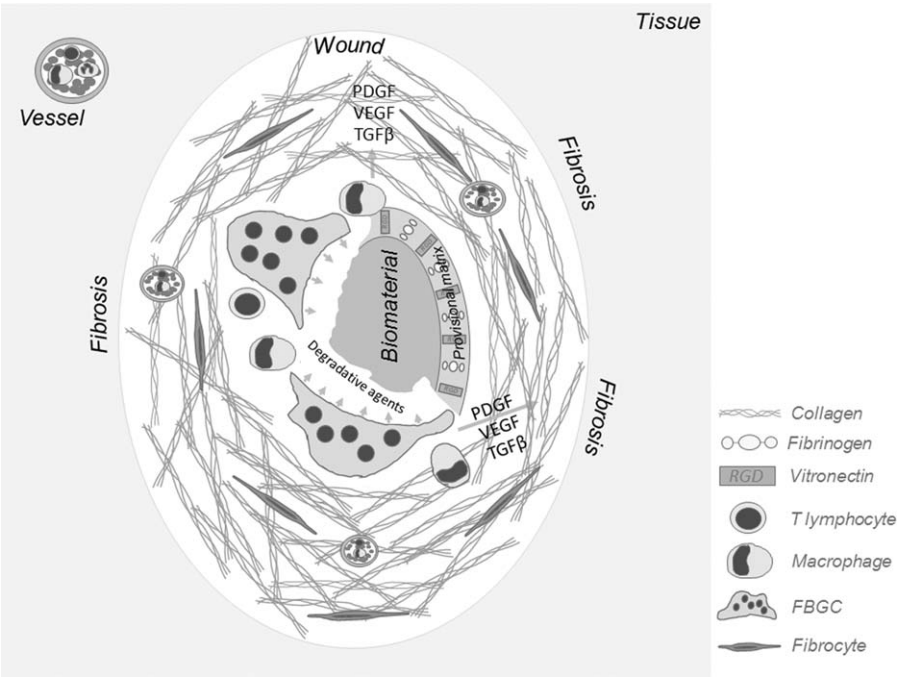

FIGURE 6. Phase 5 of the foreign body reaction—Fibrosis and capsule formation with few remaining macrophages, foreign body giant cells (FBGC), lymphocytes, and reduced number of vessels in the fibrotic scar tissue.

induce more FBGC than smaller ~6 μm microspheres.[99] In contrast, spheres larger than 1.5 mm made of diverse materials including hydrogels, ceramics, metals, and plastics induced less fibrosis as compared to spheres of various smaller sizes.[100]

PHASE 5: FIBROUS CAPSULE FORMATION

Integration of the implanted biomaterial into the surrounding tissue with full regeneration after slow degradation of the implant is the desired outcome in most cases. However, establishment of a chronic inflammation and FBGC formation may finally lead to the formation of a fibrotic, collagenous capsule around the biomaterial (Figs. 6 and 7). Capsule formation is influenced by a variety of pro-fibrotic and -angiogenic growth factors like PDGF, VEGF, and TGF-β, which are secreted by M2 macrophages but also by several other cell types including other immune cells, keratinocytes, fibroblasts, endothelial cells, thrombocytes, and adipocytes.[78,98,101] Furthermore, proteolytic enzymes such as matrix metalloproteinases (MMP) secreted by macrophages and/or endothelial cells are also involved in the ECM remodeling around implanted biomaterials. For instance, inhibition of MMP-2 has been shown to decrease FBR against polyvinylidenfluoride meshes in mice.[102]

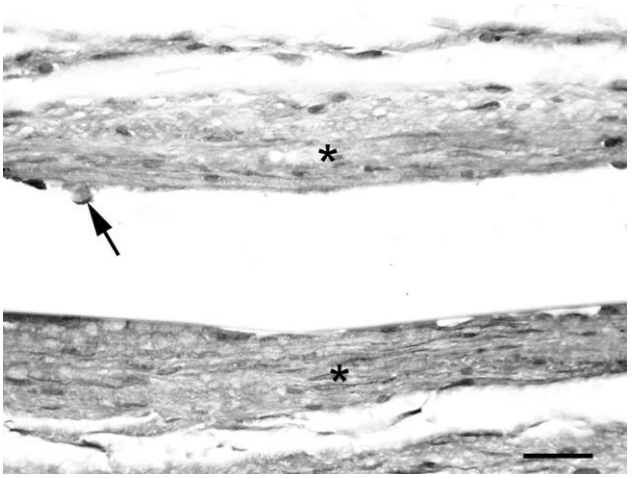

FIGURE 7. Phase 5 of the foreign body reaction—A fibrous capsule (*) surrounding implanted poly(*p*-dioxanone) (PPDO) 28 days after implantation. Only singe macrophages are detectable (arrow). Trichrome-stain, Bar = 50 μm.

Besides other effects, these factors activate and attract fibroblasts and endothelial cells to the surface of the biomaterial, which deposit collagen and other extracellular matrix proteins to form granulation tissue, which is composed of a loose net of collagen fibers, proliferating capillary sprouts, collagen secreting fibroblasts and phagocytosing macrophages.[103] This granulation tissue then matures into a less cellular and more collagenous, peripheral fibrous capsule, which can lead to mechanical impairment or failure of interaction of the biomaterial with the surrounding tissue.[30,31,104] This process is reflected in a gradual replacement of type III collagen by type I collagen. In addition, during capsule formation some of the fibroblasts differentiate into myofibroblasts under the influence of TGF-β, which can contract the capsule and thus lead to deformation, mechanical stress, and aesthetic problems.[30,39] In common wound healing, this process ends with the resolution phase, which is characterized by apoptosis and senescence of myo- and fibroblasts, regression of the neovasculature and

TABLE IV. Biomaterial Features with Influence on Vascularization, Fibrosis, and Encapsulation

Biomaterial Feature	Influence on FBR	References
Polyurethane > Polyurethane with silicone and polyethylene oxide	Encapsulation ↑	110
Amino (—NH2) and hydroxyl (—OH groups on hydrophilic surfaces	Fibrosis ↑	85
—COOH groups on hydrophobic surfaces	Fibrosis ↑	112
Poly(2-hydroxyethyl methacrylate), PHEMA	Encapsulation ↓	3
Poly-(carboxybetaine acrylamide) (poly(CBAA)	Encapsulation ↑	3
Gelatin hydrogels containing lysine diisocyanate ethyl ester	Encapsulation ↓	115
Surface cover of carboxymethylcellulose, hyaluronic acid, antiadhesive barrier solution, oxidized regenerated cellulose	Encapsulation delayed	113,114
Porosity/roughness of the surface ↑	Fibrosis ↓	53,77,80,83,110
4,4 μm intranodal distance in porous material	Encapsulation ↓	87
Uniform 30–40 μm pores	Encapsulation ↓	53,81
5 μm pores in polytetrafluoroethylene (PTFE) membranes	Vascularization ↑	90
Polypropylene fibers < 6 μm	Encapsulation ↓	116
Acute angels, rectangular > pentagonal > circular, increased height (perpendicular to skin)	Encapsulation ↑	80,89,90
2000 μm (thick) > 300 μm (thin) polyurethane	Encapsulation ↑	110
Spheres >1.5 mm in diameter	Fibrosis ↓	98

decrease in the collagen by a unique population of fibrinolytic macrophages.[105–107] During FBR, this resolution phase is, however, missing, most probably because of the persistence of the initiating agent, the biomaterial, and the continuing pro-inflammatory or pro-fibrotic stimulation of cells near the biomaterial.

So far, four general approaches are currently considered to reduce capsule formation or fibrosis, respectively: (1) physical, chemical and topographical biomaterial surface modification (see next paragraph), (2) alteration of the systemic immune reaction, and (3) alteration of the local immune reaction. DiEgidio et al. summarized that so far no study confirmed the efficiency of a systemic treatment to eliminate fibrous capsule formation. Only few studies found a mild decrease in capsule thickness, which was usually not considered sufficient to compensate for the induced systemic side effects.[104] Alternatively, local treatment by molecular coatings or the inclusion of modifying agents in the biomaterial or the local application of drugs into the implantation site seem to be more efficient.[108] Both approaches can influence inflammation and reduce capsule formation although complete capsule formation also has not been achieved. Usually, these locally released or administered steroids or TGF-β inhibitors have an initial impact on FBR and capsule formation. However, in most cases the long term kinetics have not been analyzed or a decline of the drug due to dilution and metabolization has been observed. In addition, these anti-inflammatory effects also impair wound healing and proper integration of the device into the tissue.[104] Recently, therapeutic interventions to increase the portion of M2 remodeling subtype macrophages in the lesion by targeting CCR1 and CCR2 on M1 inflammatory macrophages or the transfer of autologs M2 macrophages into the lesion have been proposed.[107,109]

Influence of the biomaterial surface properties on capsule formation and fibrosis

There are numerous studies on the biocompatibility of biomaterials, which confirmed an influence of the surface properties on the late stage of the FBR, that is capsule formation and fibrosis (Table IV). Studies with confirmed influence of the biomaterial chemistry on capsule formation are rather rare. Polyurethane including silicone and polyethylene oxide moieties showed a decreased encapsulation when compared to pure polyurethane material.[110] Furthermore, gelatin-based hydrogels or hydrogels containing poly(carboxybetaine methacrylate) (PCBMA) induce only minimal fibrous reactions when compared to for instance poly-2-hydroxyethyl methacrylate (PHEMA) (Table IV). In addition, amino and hydroxyl groups on hydrophilic surfaces have been reported to induce the thickest capsules as compared to other groups.[111,112] In contrast, on hydrophobic surfaces, carboxyl groups seem to induce the thickest fibrous capsule.[113]

Another approach to reduce capsule formation is to cover the surface with anti-inflammatory materials.[104] Carboxymethylcellulose, hyaluronic acid (HA), antiadhesive barrier solution, and oxidized regenerated cellulose slow down the capsule formation but once the surface is degraded and metabolized, normal capsule formation is observed around the implant.[114,115]

The influence of surface topography and especially surface porosity on capsule formation has been most intensely studied. Numerous studies came to the conclusion that increased porosity is associated with better healing and decreased fibrosis and encapsulation (Table IV). Pores with intranodal distances of 4.4 μm and a general pore size of 30–40 μm diameter in diverse tissues or 5 μm in polytetrafluoroethylene (PTFE) membranes are associated with thinner fibrous capsules, higher vascularization, and better wound healing.[64,83,116,117] Furthermore, thin planar or circular shaped implants with wide angles and their implantation with their longer sides parallel to the skin and microspheres with a diameter larger than 1.5 mm or polyethylene fibers with diameters smaller than 6 μm induce less fibrous capsule formation (Table IV).

Besides the surface characteristics it is not really clear which role the chemical composition of the implant plays.

Andrade reported that, particularly for soft tissues, planar substrates of completely different chemical composition (polymers, ceramics, metals) elicited marked and composition-independent host foreign body responses.[118] All classes of materials induced a similar inflammatory reaction indicating that the material chemistry is of secondary importance.[59] Furthermore, if the factor material composition is the principal mechanism for the foreign body response, a more severe reaction would be expected with rough materials because the material's surface is much larger compared to a planar surface. The opposite has been shown. Changing from a planar surface to a microstructured surface for the same material reduced the foreign body response in experimental as well as clinical studies.[119–122]

OVERLAPPS OF FBR WITH THE COMMON WOUND HEALING

Until phase 3, the FBR has therefore many overlaps with the common wound healing process. Wound healing is also a well-orchestrated, highly efficient process that comprises the interaction of various cell types, soluble cyto- and chemokines, and an appropriate extracellular milieu during the wound healing cascade: inflammation, re-epithelialization, angiogenesis, granulation tissue formation, wound contraction, and lastly tissue regeneration.[85,86] Similar to the situation in the foreing body reaction, in the wounded area platelets adhere become activated and release growth factors and pro-inflammatory chemokines to recruit neutrophils and macrophages to the local wound site. These inflammatory cells phagocytose debris and bacteria and secrete mediators stimulating the chemotaxis of cell types necessary for the proliferative phase. During the proliferative phase, fibroblasts, endothelial and smooth muscle cells migrate through the wound, and proliferate to synthesize and deposit a provisional extracellular matrix (ECM) and to re-epithelialize the denuded surface, form new blood vessels, and contract the wound size. The ECM can directly bind to and also release certain growth factors (e.g., heparan sulfate binding to fibroblast growth factor-2), which may serve to sequester and protect growth factors from degradation, and/or enhance their activity. Also, indirect interactions occur which include binding of cells to the ECM via integrins, enabling cells to respond to growth factors (e.g., integrin binding is necessary for vascular endothelial growth factor-induced angiogenesis) and can induce growth factor expression (adherence of monocytes to ECM stimulates the synthesis of platelet-derived growth factor). Additionally, subcomponents of ECM molecules, can bind to cell surface receptors in the cytokine, chemokine, or growth factor families and stimulate cellular activities (e.g., tenascin-C and laminin bind to epidermal growth factor receptors, which enhances fibroblast migration). Growth factors such as transforming growth factor-beta also regulate the ECM by increasing the production of ECM components or enhancing synthesis of matrix degrading enzymes (Schultz, 2009). During the final stage, the newly formed granulation tissue is remodeled by the activity of matrix metalloproteinases (MMPs) balanced with tissue inhibitors of metalloproteinases (TIMPs), rearranging the loose, repaired tissue (Gurtner et al. 2008).

In the absence of a foreign body, wound healing is resolving and leads to full restitution of the damaged tissue or replacement by enduring scar tissue. The most prominent difference between common wound healing and an FBR is therefore the major influence of the surface of the foreign body on the adsorbed matrix with all consequences on the further progress of the inflammation and the chronic stimulus of the immune system by the foreign body, which is indigestible and stimulates macrophages to develop into FBGC. The research in both fields is therefore overlapping; however, especially the late phase of the FBR needs special attention and is not covered by the progress in the understanding of the mechanisms of wound healing in general.

CONCLUSION AND OUTLOOK

The successful regeneration of dysfunctional or missing tissue depends on the processes appearing in the interface between the implanted biomaterial and its surrounding tissue. Basic understanding of the mechanisms eliciting these processes is still limited but has started to evolve. However, we are far away from the point to orchestrate the interaction of the individual processes described to reach the appropriate milieu for the optimal regeneration of functional tissue. Because of their surface properties (e.g., microstructure or topography, ability to absorb plasma proteins, their degradability, mechanical properties, and overall porosity) biomaterials can directly influence the adhesion, activation, and differentiation processes and, thus, the following foreign body response. Additionally, the tissue response might be influenced by many other factors like implant design, implant localization, state of the host bed, surgical technique, and mechanical loading.

This complex and interrelated scenario makes it difficult to understand the complete foreign body response. Besides the vast knowledge gained through molecular biology methods, statistical principles are also of central importance in order to evaluate the importance of various influencing factors. In a first step, the study design has to be thoroughly planned. This includes the selection of an appropriate model that has to describe the processes, which should be evaluated with all influencing factors. In case important factors are missing, the interpretation of the results cannot be in accordance with the processes how they are *in vivo*. Another big challenge represents the appropriate sample size for a safe interpretation of the results. As an example for the comparative assessment of influencing factors a multivariate regression analysis can be carried out. For such an analysis, at least 10 experiments per influencing factor are needed. As the foreign body response is dominated by a lot of different influencing factors very high sample sizes result. In case of 10 different influencing factors, which seems to be a minimum in the complex process of FBR, 100 animals have to be included per time point. Not taken into account in this rough estimation is the variability of further concomitant

factors as well as of the individuals included in the study according to the probabilistic nature of biology.

This simple analysis shows why it is so difficult to understand the foreign body response and where the shortcomings are. This can only be overcome by joint efforts of the scientific community; single labs cannot shoulder this task. Good examples how such shortcomings can be overcome are epidemiologic studies with stringent study design performed in several countries or even continents. Performing such multicenter studies allows the inclusion of a sufficient number of animals/patients to achieve for a safe and validated assessment of the underlying material-induced processes.

This is the way we should precede and—in our opinion—the only possibility to understand the interaction and especially the weight of the different influencing factors, which are discussed to play a role in the foreign body response.

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