The foreign body response studied in vitro

Introduction

To study the biocompatibility of a biomaterial in vitro as a model for in vivo cases, the response of the organism to a biomaterial in vivo must first be known. When a biomaterial gets implanted into the human body a foreign body response will occur. This response involves different phases over time, with first protein adsorption, second acute inflammation, third chronic inflammation, fourth giant cell formation and at last the forming of a fibrous capsule.

When a biomaterial gets implanted the first interaction will be a blood/material interaction with protein adsorption to the surface of the biomaterial. These proteins will form a provisional matrix that is essential for the further steps of the foreign body reaction, as the monocytes/macrophages and polymorphonuclear leukocytes (PMNs) can only bind with their receptors to the adsorbed proteins, the cells can't directly bind to the material.[1]The continuous protein adsorption and desorption is described by the Vroman effect.[2]Proteins with high mobility like albumin are initially being adsorbed to the surface of the biomaterial followed by proteins with less mobility that will replace the initial proteins. Proteins like fibrinogen, high molecular weight kininogen (HMWK), fibronectin and vitronectin are proteins with higher affinity to the surface of the biomaterial. The provisional matrix releases several bioactive agents that further control the next phases of wound healing.[3]

The tissue damage done by the insertion of the material is the main reason for an acute inflammation and infiltration of PMN's. Multiple molecules are being released after membrane destruction called alarmins that can be recognised by toll-like receptors on the PMN's that start the innate immune response.[4] Activated platelets, endothelial cells and the complement system also release chemoattractant which attracts PMN's and macrophages. Frustrated phagocytosis of the leukocytes and oxygenic burst makes a highly inflammatory milieu which attracts more PMN's[5]. This phase is described as the acute inflammation.

The chronic inflammation phase is mainly led by monocytes/ macrophages that are attracted by several cytokines and chemokines in the implantation site. These chemokines and cytokines have chemoattractant properties that lead the monocytes/macrophages to wound site. After arrival they adhere to the fibronectin, vitronectin, complement fragments and fibrinogen in the provisional matrix, the binding leads to activation of the monocytes. The activation can lead to two types of macrophages being M1 and M2 macrophages. M1 macrophages are pro-inflammatory macrophages that will try to phagocytose small particles from a biodegradable biomaterial to phagocytose the biomaterial and it will release reactive oxygen species and lysozymes. M2 macrophages are activated by interleukin-4 and interleukin-13 from mast cells and produce interleukin-10 and transforming growth factor-B and they induce an anti-inflammatory response.[6]M1 macrophages are the most important cells in the chronic inflammation phase and M2 cells are present later in the wound healing phase. M2 macrophages secrete cytokines that attract lymphocytes and cytokines and growth factors that activate fibroblasts, regeneration of the tissue and formation of a capsule.

When the macrophages can't phagocytose the material (frustrated phagocytosis) , macrophages will fuse together into a foreign body giant cell (FBGC) . FBGC's are large cells that consist of dozens of nuclei and can be up to several hundred µm large. Il-4 and Il-13 are the main interleukins produced by T-lymphocytes and mast cells that induce the fusion of macrophages to FBGC. because the phenotype switch from M1 to M2 macrophages is also induced by IL-4 and IL-13, it is believed that FBGC are a result of fusion of the M2 phenotype macrophages. Formation of the FBGC is seen as undesired in the foreign body reaction. FBGC secrete ROS and lysosomes that have an increased biodegradation effect on the biodegradable biomaterial. [1] Biomaterials designed to function as a non-biodegradable material in the body could fail under formation of FBGC and biodegradable designed materials could degrade quicker giving an undesired result.

Chronic inflammation and the presence of foreign body giant cells could eventually lead to the formation of a fibrous capsule around the implanted biomaterial. Mainly M2 macrophages but also other immune cells, keratinocytes, fibroblasts, endothelial cells, thrombocytes and adipocytes produce pro-fibrotic growth factors and pro-angiogenic growth factors like PDGF, VEGF and TGF-B. [7],[8].These molecules attract fibroblasts and endothelial cells. On the surface of the materials these cells will secrete fibres of collagen and other proteins to create a granulation tissue. Granulation tissue is a vascularized connective tissue that exist out of microscopic small blood vessels formed out of endothelial cells that branched off from already existing blood vessels, fibroblasts that secrete collagen and macrophages. the granulation tissue will later change into connective tissue surrounding the material or a fibrous capsule.[9] When a fibrous capsule is formed, Collagen 3 will be replaced by collagen 1 and fibroblasts that will differentiate into myofibroblasts under the influence of TGF-B. myofibroblasts will reform the capsule leading to mechanical stress. the fibrous capsule can eventually lead to failure of the implant where undesired mechanical properties of the material or undesired interaction with the material and the surrounding tissue can be a problem.

When using a model for the FBR in vitro, a selection can be made on promising biomaterials that should show the most favoured foreign body reaction in vivo, without having to test every material in animals. By making this selection the use of animal experiments can be significantly reduced.[10]

Making a valid and representative model of the FBR to a biomaterial in vitro is a difficult task, due to the complex interactions of proteins and cells and the different phases of the FBR. This review will focus for now on the initial processes involved in the FBR. protein adsorption to the biomaterial will be discussed as well as the attraction and activation of PMN's and macrophages.

Protein adsorption to the biomaterial

Adsorption of proteins to the biomaterial is the first response of the body to the biomaterial. As it is the first step in the foreign body response, it can have great implications to the further development of the foreign body response. Knowing what properties of the biomaterial leads to different configurations of protein adsorption is important, because it can determine which biomaterial with certain chemical properties should be used in practice. When a biomaterial gets implanted, the quantities of given protein adsorpted to the surface is strongly dependent on the chemical properties of the implanted biomaterial. Polymeric biomaterials have been found to attract different proteins in different amounts depending on the surface chemistry and topology.The interfacial free energy is one of these properties. A study by Dulinska-Molak et al[11], found a correlation between the interfacial free energy and the amount of protein adsorpted on the surface of polyurethanes.

Generally, there has been found that the amount of interfacial free energy at the blood plasma-biomaterial interface determines the amount of the initially adsorbed proteins to the surface of the material. In a study by Huang et al[12],the surface energy and competitive protein adsorption of fluorocarbon end-capped poly(carbonate) urethane (PCUF) has been compared to polystene (PS) using reflectometry interference spectrometry(RifS). The lower interfacial energy between PCUF and protein compared to PS and protein resulted in more albumin, less fibrinogen and less igG and is believed to be responsible for the better blood compatibility. A low interfacial free energy with blood have been found to reduce the adsorption of proteins.[13]

There is also a big difference between adsorption of blood plasma proteins between hydrophilic and hydrophobic surfaces of implanted polymeric biomaterials. Low interfacial free energy surfaces have been found to adsorb larger amounts of blood plasma proteins. There has also been found that proteins change in conformational structure from their native structure when they are adsorbed to the surface of the biomaterial. Tanaka et al[14]. have found that protein adsorbed on polyarcylaat surfaces changed the secondary structure of the protein and saw a change in α-helix and β-helix structure. Nonpolar hydrophobic surfaces have been found to give the adsorbed surface proteins a higher degree in unfolding. Nonpolar hydrophilic surfaces show the opposite and give the least amount of protein unfolding. This change in conformation of these protein could possibly play a large role in determining biocompatibility. [15]

There are also other factors that will change the adsorption of blood – plasma protein, these are the addition of functional groups to the polymer, the surface electricity charge of the polymer, the molecular weight of the polymer, topography and roughness of the material. The surface of a solid polymeric biomaterial can also be modified. The material can get coated which can be of intact biomolecules or a plasma coating. The material can also be modified by altering the topography with nanopore structures. treatments, plasma discharge and radiation grafting. All these factors have been found in research to have an impact on the adsorbed protein composition on the surface of the material. An example of this is added oxygen containing groups to the surface increasing the adsorption of proteins like vitronectin, fibronectin, collagen but decreasing the adsorption of Albumin[13],[16]

The sequence of protein adsorption to the biomaterial to the adhesion of cells contains a few steps. After implantation of a biomaterial in the body, proteins in the body fluid start to immediately adsorb to the surface of the material and there is competition between the different proteins in the body fluid for adsorbing to the surface. The largest percentage of mass from all proteins in the body fluid comes from the albumin (Ab) and immunoglobulin (IgG). Extracellular matrix (ECM) proteins are relatively less abundant in comparison with Ab and IgG. The ECM proteins in the layer of adsorbed proteins contain amino acid sequences that integrins on the membrane of the cell can bind with. Most of the known integrins bind to the arginine-glycine-asparagine (RGD) sequence, but there are also a few other integrins that bind to other integrin-binding sequence motifs. These sequence motifs are present on the initially adsorbed proteins like fibronectin and vitronectin. The conformation of the ECM proteins within the protein layer and the orientation of the RGD sequence has a strong influence on the ability for cells to surface of materials. Unfolded proteins on a superhydrophobic surface can have RGD sequence sites that are not well accessible by cells reducing the number of cells adhered to the surface[16].The interface of these binding sites from the ECM to the integrin and from the integrin to cell has great influence on the activation of the cell in terms of proliferation, survival, and gene expression. The protein structure of the protein layer with its ECM proteins are dependent on the surface morphology of the biomaterial. In vitro tests can determine which morphological structure of the biomaterial can lead to the desired initial protein – cell

interactions. [17] Chandler-Temple et al[18], used a series of surface-modified expanded poly(tetrafluorethylene) membranes to test for varying levels of macrophage inflammatory response. Adsorbed proteins were identified with surface-matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI-Tof-MS) and related to the response of the RAW 264.7 macrophages. Results showed evidence for a correlation between the cell response and the composition of proteins adsorbed on the surface caused by modification of the surface chemistry. Lamers et al[19], evaluated the macrophage response on nano grooved silicon wafers in vitro with RAW264.7 macrophages and in vivo with mice by looking at the production of cytokines of the macrophages. Results showed that the cytokine production was controlled by the nanogrooves on the surface of the material.

Upon adsorption of proteins, there are also cascade systems that get activated, being the complement system and coagulation system. These cascade systems get activated upon binding of several proteins that can start the cascade systems. The start of these cascade systems is also dependent on the conformational changes of the protein when adsorbed to the surface of the biomaterial. C1q, mannose-binding leptin (MBL) and Properdin are recognition proteins of the complement system. High molecular weight kininogen and FXII are recognition proteins of the coagulation system that start with contact activation on the biomaterial. TF and FVII are recognition particles of the coagulation system released from damaged tissue created from the implantation of the biomaterial.[20]

The coagulation system gets activated through two ways which are the intrinsic and the extrinsic pathway. The intrinsic pathway is initiated by adsorption of FXII on the biomaterial surface which upon adsorption changes to the activated form FXIIa. FXIIa interacts with other coagulation factors to create FXa. The extrinsic pathway is initiated by TF released from damaged tissue. TF interacts with other coagulation factors to also create FXa, this is where the intrinsic and extrinsic pathway merges. FXa activates thrombin further down the cascade. Thrombin activates platelets which release mediators of the coagulation cascade which forms more thrombin, this creates an amplifying effect. Thrombin also cleavages fibrinogen to fibrin. Fibrin proteins form strands making the mesh around the surface of the biomaterial. Besides the activation from thrombin, platelets also get activated from binding to fibronectin adsorbed to the surface of the biomaterial.[21]

C1q is the recognition protein of the complement system that is associated with complement activation from implanted biomaterials. C1q bind to adsorbed immunoglobins like IgG which initiates the complement cascade.[22] Inflammation is the main consequence of complement activation coming from the C3a and C5a proteins which will activate PMN's, monocytes and the platelet activation. The conformational changes of adsorbed surface protein allow for C3b and its degradation product iC3b fragments to bind to the protein and enhance the complement cascade via the alternative pathway. The C3b fragments would usually induce the process op opsonization where it binds to a pathogen. C3b fragments have receptors that can activate macrophages to phagocyte the bound particle, this is not possible for large biomaterials which could lead to frustrated phagocytosis and form foreign body giant cells.[20] The complement system also has inhibitory proteins that downregulate the complement activation. The properties of the surface affect the interaction of the inhibitory proteins thus influencing the complement cascade system. Factor H and C1q inhibitor are such complement inhibitors. [22]

In summary, the composition and structure of the adsorbed protein layer is dependent on the chemical surface properties of the biomaterial. The interfacial free energy and the hydrophobicity / hydrophilicity of the material are very important values which can be changed with a range of

different techniques. The initially bound protein in their turn determine the form and expression of the cascade systems.

Polymorphonuclear leukocytes in the acute inflammation phase

After the protein adsorption, the acute inflammation begins. The acute inflammation is characterized by the presence of PMN's. PMN's get attracted by mediators released due to damage of the tissue, but also from mediators from the adsorbed protein layer and the cascade systems that get activated from the start of the protein adsorption. The PMN's that are active at the site of the implantation are leukocytes that for the most part is seen as neutrophils. Eosinophils and basophils make up a much smaller part with eosinophils taking up around 10% and basophils 1%. Out of all PMN's, neutrophils are the cells that interact and influence the FBR the most so the focus will on these cells.

Local circulating PMN's first get attracted to the implantation site. The PMN's get attracted from the activated C3a and C5a factors of the complement system and from mediators of the activated platelets. Another mediator is histamine from degranulated mast cells. Arriving at the implantation site, the PMN's bind with their integrin receptors in the cell membrane to the RGD sequence of proteins adsorbed to the surface of the material. [21]

Alarmins from damaged tissue bind to pathogen recognition receptors (PRR) on the PMN's. there are alarmins that are secreted by damaged cells such as heat shock protein (HSP), High mobility group box 1 (HMGB1), ATP and uric acid. Alarmins can also be created by the cleavage of ECM proteins, this is done by proteolytic enzymes released from the damaged tissue. The binding of these alarmins to PMN's activates the secretion of reactive oxygen species (ROS) and the release of proteolytic enzymes. These ROS and proteolytic enzymes can induce the degradation of degradable polymeric materials and they also damage the surrounding tissue increasing the period of the acute inflammation. PMN's will also start producing IL-8, this interleukin effects other PMN's recruiting them to the acute inflammation site. The extensive ROS release in reaction to the biomaterial causes the ROS reserves of PMN's to deplete reducing the ability of killing microbes. This can contribute to a major bacterial infection of the implantation site in case bacteria are present at this site. [23] [24]

Neutrophils phagocytise microorganisms or parts of organisms, but the capacity and process of phagocytosing biomaterial particles is not well understood. Another function of the neutrophil is the release of neutrophil extracellular traps (NETs). Neutrophils can make NETs in two ways, either by releasing mitochondrial DNA or by a form of cell death called NETosis. NETosis is the more common way of creating NET. Chromatin with DNA and histones is released and will form dense fiber like structures, this fiber structure can trap microbes and neutralize them. The use of NET against biomaterial has also been studied and so far we have seen neutrophils create NET against a wide range of biomaterials, but the triggers for it occurrence and the influences it possesses on the FBR has yet to be studied. [23] [24]

Neutrophils also produce monocyte chemotactic protein 1 (MCP-1) and macrophage inflammatory protein 1β (MIP-1β). These cytokines attract monocytes and macrophages to but also dendritic cells (DC) and lymphocytes. These cytokines also function as a suppressor for the influx of new neutrophils, making way for an increased influx of macrophages and monocytes. [21]

PMN's have a relatively short lifespan in comparison with macrophages and will quickly go in apoptosis. One of the main reasons thought for the short lifespan of neutrophils is the damage done

to surrounding tissue from the proteolytic enzymes and ROS. Proinflammatory cytokines will change the lifespan of PMN's to be longer and after phagocytosis of microbes, the neutrophils will quickly go in apoptosis. [25]

Monocytes/macrophages in the acute and possibly chronic inflammation phase

The monocytes and macrophages are the driving cell that define the chronic inflammation phase. Monocytes arrive at the inflammation site and can bind to proteins of the provisional matrix such as collagen, fibronectin, laminin, fibrinogen and vitronectin via β1,β2 and β3 integrins.[26] These activated monocytes can differentiate into different phenotypes of macrophages. Classically activated are called M1 macrophages and alternatively activated are called M2 macrophages.M1 macrophages are pro inflammatory macrophages, these macrophages will phagocytose the wound debris, neutrophils that underwent apoptosis, bacteria and will try to phagocytose the biomaterial. M1 macrophages also secrete chemokines that maintain the inflammatory immune reaction by attracting more inflammatory cells. M2 macrophages can be divided in two phenotypes being tissue repair macrophages and regulatory macrophages. Tissue repair macrophages secrete anti-inflammatory mediators and growth factors.[21] [27]

In the initial inflammation phase of the FBR, the M1 macrophage phenotype will be present first. M1 macrophages are differentiated from monocytes under the presence of interferon-γ (INFγ) and tumor necrosis factor (TNF) or by lipopolysaccharide (LPS). INFγ is produced by natural killer cells (NK) from the innate immune response and T-helper (TH) cells from the adaptive immune response. TNF is produced by antigen presenting cells (APC). Antigen on an TLR starts the transcription of TNF. Later, in the chronic inflammation phase, the M2 macrophage phenotype gets activated. This phenotype becomes active under the presence of IL-4 and IL-13, these interleukins can be produced with the innate pathway from basophils, mast cells and granulocytes as well as the adaptive immune pathway from TH2 cells. The adaptive immune pathway is the main source for tissue repair macrophages activation. Activated tissue repair macrophages secrete ECM and activate fibroblasts promoting the wound healing process. Regulatory macrophages are created by both the innate and adaptive immune system by prostaglandins, glucocorticoids, apoptotic cells, and IL-10 from regulatory T cells. There is another signal needed for the regulatory phenotype to become active, this happens with the signal of a TLR-ligand. Regulatory macrophages are needed for downregulating the inflammation and are known for their upregulation of IL-10 and downregulation of IL12. IL-10 is an anti-inflammatory cytokine that inhibits the production of inflammatory cytokines.[27]

Pro-inflammatory macrophages will try to phagocytise parts of the biomaterial. The proteolytic enzymes and ROS secreted will help degrade the biomaterial and the macrophages will try to phagocytose the particles. Single cell macrophages are only capable in phagocytosing particles that are not bigger than 5µm. larger particles cannot be phagocytosed and will lead to frustrated phagocytosis and the macrophages will fuse into foreign body giant cells (FBGC). IL-4 and IL-13 are the cytokines that promote the fusion of macrophages. Vitronectin is a surface bound protein that not only binds monocytes but also supports the adhesion and fusion of macrophages. The binding to this protein and the interleukin signals leads to the macrophages making fusogenic molecules on the interfaces between fusing macrophages. FBGC are not just one type of macrophages fused together

but can be seen as a completely different cell type. FBGC produce and secrete IL-1α, IL-6,IL-8,TNF-α but later on in the FBR IL-10, TGFβ, PDGF and MCP-1 will also be produced.[26 21 9]

Long lasting chronic inflammation and FBGC formation can eventually lead to the creation of a fibrous capsule around the implant. TGFβ and PDGF produced by FBGC and M2 macrophages are pro-fibrotic and pro-angiogenic factors, these factors activate fibroblast and endothelial cells. Fibroblasts and endothelial cells migrate to the biomaterial and granulation tissue is formed by deposited collagen and other ECM proteins. The extensive deposition of collagen and ECM proteins creates a fibrotic capsule around the implant. Myofibroblasts differentiated from fibroblasts under the presence of TGFβ, can start to contract and could cause deformation and mechanical stress to the implant if the material is susceptible to this. Fibrotic encapsulation is almost never beneficial for the intended chemical or structural interaction the biomaterial should have with the surrounding tissue. [26 21 28]

Conclusions

The foreign body response of the host to a biomaterial is a important concept that needs to be well understood for allowing us to be able to create biomaterials that show the preferred and intended reaction with the tissue of the host to fulfil its function. In this review the initial protein adsorption, cascade systems, the PMN's and the macrophage/monocyte roles in the FBR were discussed are important factors of the foreign body response. The initial protein adsorption is an important factor, because it sets up for the following cells in the foreign body response. Trying to change the FBR to a biomaterial can be done by modifying the surface chemistry of the used biomaterial. Free interfacial surface energy and the hydrophobicity are important properties that determine the composition of the protein adhesion. There are different methods for changing the surface properties such as coating of the material, creating nanopore structures plasma discharge and radiation grafting. The attraction of PMN's is for a large part dependent on the adsorption of proteins of the cascade systems and macrophages have been found in research that cytokine production is influenced by the differences in surface chemistry. Controlling these important cell types in the foreign body reaction by changing the surface chemistry and protein adsorption are essential for a preferred host-biomaterial interaction.

(1) Anderson, J. M.; Mcnally, A. K. Biocompatibility of Implants : Lymphocyte / Macrophage Interactions. **2011**, 221–233. https://doi.org/10.1007/s00281-011-0244-1.

(2) Hirsh, S. L.; Mckenzie, D. R.; Nosworthy, N. J.; Denman, J. A.; Sezerman, O. U.; Bilek, M. M. M. Colloids and Surfaces B : Biointerfaces The Vroman Effect : Competitive Protein Exchange with Dynamic Multilayer Protein Aggregates. *Colloids Surfaces B Biointerfaces* **2013**, *103*, 395–404. https://doi.org/10.1016/j.colsurfb.2012.10.039.

(3) Gorbet, M. B.; Sefton, M. V. Biomaterial-Associated Thrombosis : Roles of Coagulation Factors , Complement , Platelets and Leukocytes. **2004**, *25*, 5681–5703. https://doi.org/10.1016/j.biomaterials.2004.01.023.

(4) Love, R. J.; Jones, K. S. Review Article The Recognition of Biomaterials : Pattern Recognition of Medical Polymers and Their Adsorbed Biomolecules. **2013**, 2740–2752. https://doi.org/10.1002/jbm.a.34577.

(5) Labow, R. S.; Meek, E.; Santerre, J. P. Neutrophil-Mediated Biodegradation of Medical Implant Materials. **2001**, *103* (May 2000), 95–103.

(6) Krzyszczyk, P.; Schloss, R.; Palmer, A.; Berthiaume, F. The Role of Macrophages in Acute and Chronic Wound Healing and Interventions to Promote Pro-Wound Healing Phenotypes. **2018**, *9* (May), 1–22. https://doi.org/10.3389/fphys.2018.00419.

(7) Xia, Z.; Triffitt, J. T. A Review on Macrophage Responses to Biomaterials. **2006**. https://doi.org/10.1088/1748-6041/1/1/R01.

(8) Koh, T. J.; Dipietro, L. A. Inflammation and Wound Healing : The Role of the Macrophage. **2020**, *13* (July 2011), 1–12. https://doi.org/10.1017/S1462399411001943.

(9) Anderson, J. M.; Rodriguez, A.; Chang, D. T. Foreign Body Reaction to Biomaterials. **2008**, *20*, 86–100. https://doi.org/10.1016/j.smim.2007.11.004.

(10) Jannasch, M.; Gaetzner, S.; Groeber, F.; Weigel, T.; Walles, H.; Schmitz, T.; Hansmann, J. Acta Biomaterialia An in Vitro Model Mimics the Contact of Biomaterials to Blood Components and the Reaction of Surrounding Soft Tissue. *Acta Biomater.* **2019**, *89*, 227–241. https://doi.org/10.1016/j.actbio.2019.03.029.

(11) Duli, I.; Lekka, M.; Kurzydłowski, K. J. Applied Surface Science Surface Properties of Polyurethane Composites for Biomedical Applications. **2013**, *270*, 553–560. https://doi.org/10.1016/j.apsusc.2013.01.085.

(12) Huang, Y.; Lü, X.; Qian, W.; Tang, Z.; Zhong, Y. Acta Biomaterialia Competitive Protein Adsorption on Biomaterial Surface Studied with Reflectometric Interference Spectroscopy. *Acta Biomater.* **2010**, *6* (6), 2083–2090. https://doi.org/10.1016/j.actbio.2009.12.035.

(13) Wang, Y.; Robertson, J. L.; Spillman, W. B.; Claus, R. O. Effects of the Chemical Structure and the Surface Properties of Polymeric Biomaterials on Their Biocompatibility. **2004**, *21* (8), 1362–1373.

(14) Tanaka, M.; Motomura, T.; Kawada, M.; Anzai, T.; Kasori, Y.; Shiroya, T.; Shimura, K.; Onishi, M.; Mochizuki, A. Blood Compatible Aspects of Poly (2-Methoxyethylacrylate) (PMEA) * Relationship between Protein Adsorption and Platelet Adhesion on PMEA Surface. **2000**, *21*, 1471–1481.

(15) Latour, R. A. Biomaterials : Protein – Surface Interactions. **2005**, 1–15. https://doi.org/10.1081/E-EBBE-120041856.

(16) Bacakova, L.; Filova, E.; Parizek, M.; Ruml, T.; Svorcik, V. Modulation of Cell Adhesion , Proliferation and Differentiation on Materials Designed for Body Implants. *Biotechnol. Adv.* **2011**, *29* (6), 739–767. https://doi.org/10.1016/j.biotechadv.2011.06.004.

(17) Biomaterials, B. Materials Express. **2012**, *2* (1), 1–22. https://doi.org/10.1166/mex.2012.1053.

(18) Chandler-temple, A.; Kingshott, P.; Wentrup-byrne, E.; Cassady, A. I.; Grøndahl, L. Surface Chemistry of Grafted Expanded Poly (Tetrafluoroethylene) Membranes Modifies the in Vitro Proinflammatory Response in Macrophages. **2012**, 1047–1058. https://doi.org/10.1002/jbm.a.34408.

(19) Lamers, E.; Walboomers, X. F.; Domanski, M.; Prodanov, L.; Melis, J.; Luttge, R.; Winnubst, L.; Anderson, J. M.; Gardeniers, H. J. G. E.; Jansen, J. A. In Vitro and in Vivo Evaluation of the Inflammatory Response to Nanoscale Grooved Substrates. *Nanomedicine Nanotechnology, Biol. Med.* **2012**, *8* (3), 308–317. https://doi.org/10.1016/j.nano.2011.06.013.

(20) Ekdahl, K. N.; Lambris, J. D.; Elwing, H.; Ricklin, D.; Nilsson, P. H.; Teramura, Y.; Nicholls, I. A.; Nilsson, B. Innate Immunity Activation on Biomaterial Surfaces : A Mechanistic Model and Coping Strategies ☆. *Adv. Drug Deliv. Rev.* **2011**, *63* (12), 1042–1050. https://doi.org/10.1016/j.addr.2011.06.012.

(21) Franz, S.; Rammelt, S.; Scharnweber, D.; Simon, J. C. Biomaterials Immune Responses to Implants e A Review of the Implications for the Design of Immunomodulatory Biomaterials. *Biomaterials* **2020**, *32* (28), 6692–6709. https://doi.org/10.1016/j.biomaterials.2011.05.078.

(22) Gorbet, M.; Sperling, C.; Maitz, M. F.; Siedlecki, C. A.; Werner, C.; Sefton, M. V. Acta Biomaterialia The Blood Compatibility Challenge . Part 3 : Material Associated Activation of Blood Cascades and Cells. *Acta Biomater.* **2019**, *94*, 25–32. https://doi.org/10.1016/j.actbio.2019.06.020.

(23) Jhunjhunwala, S. Neutrophils at the Biological − Material Interface. **2018**. https://doi.org/10.1021/acsbiomaterials.6b00743.

(24) Selders, G. S.; Fetz, A. E.; Radic, M. Z.; Bowlin, G. L. An Overview of the Role of Neutrophils in Innate Immunity , Inflammation and Host-Biomaterial Integration. **2017**, 55–68. https://doi.org/10.1093/rb/rbw041.

(25) Kobayashi, S. D.; Voyich, J. M.; Burlak, C.; Deleo, F. R. Neutrophils in the Innate Immune Response. **2005**, 505–517.

(26) Klopfleisch, R.; Jung, F. Review Article The Pathology of the Foreign Body Reaction against Biomaterials. **2016**, No. v, 927–940. https://doi.org/10.1002/jbm.a.35958.

(27) Mosser, D. M.; Edwards, J. P. Exploring the Full Spectrum of Macrophage Activation. *Nat. Publ. Gr.* **2008**, *8* (12), 958–969. https://doi.org/10.1038/nri2448.

(28) Diegidio, P.; Friedman, H. I.; Gourdie, R. G.; Riley, A. E.; Yost, M. J.; Goodwin, R. L. Lessons Learned and the Road Ahead. **2014**, *73* (4), 451–460. https://doi.org/10.1097/SAP.0000000000000287.