Chapter 5
Host Response to Synthetic Versus Natural Biomaterials

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Abstract Biomaterials have gained tremendous attention in regenerative medicine and tissue engineering applications due to their ability to enhance functional tissue regeneration. After implantation of biomaterial-based device or drug carrier, it comes in contact with surrounding cells and consequently elicits confined and/or chronic inflammatory responses. The immune responses to biomaterials do not depend only on the method of implantation such as surgery and injection but also depend on source of biomaterials and their physicochemical properties such as molecular weight, chemical composition, mechanical properties and degradation rate. Therefore, it is necessary to thoroughly understand the biological responses to the implanted biomaterials. In this chapter, a brief discussion about different natural and synthetic biomaterials and their inflammatory responses is provided. Different strategies to minimize the immune response have also been discussed.

Keywords Natural biomaterial • Synthetic biomaterial • Biocompatibility • Immune response • Immunomodulation

5.1 Introduction

Over the past several decades, biomaterial-based implants or medical devices have largely changed the scope of modern medicine [1]. With a range of applications in tissue engineering, drug delivery, medical devices and biosensors, biomaterials have

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greatly improved the treatment for numerous patients with diseases such as cancer, diabetes, cardiovascular diseases, and tissue loss. In the USA alone, there are at least 13 million biomaterial-based implants in clinical setting annually [2].

Despite the encouraging progress achieved in the recent years in areas such as polymer science, cell biology, immunology and biotechnology, biocompatibility of biomaterials remains a pressing challenge [3]. All implanted biomaterials initiate host responses, which may lead to the limited in vivo functionality and longevity, and thereby adversely affect the intended applications of biomaterial-based implants [4]. On the other hand, host response to biomaterials is necessary and beneficial in removing cellular debris due to injury and deterring the progression of infection [5]. Indeed, preventing host response such as the infiltration of macrophages was shown to lead to more severe tissue damage and decreased tissue regeneration capacity [6]. However, the initial host response to the injury can also lead to secondary tissue damage. Historically, biomaterial-based devices were designed to be inert eliciting minimal host response. However, the definition of biomaterials has further evolved to be "substances to direct, by control of interactions with components of living systems, the course of any therapeutic or diagnostic procedure" [1]. Therefore, biomaterials with the capability to modulate host response have emerged as a new frontier for biomaterial research [7].

The key concepts, mechanisms, and processes of biomaterial-related host responses such as acute/chronic inflammation, foreign body reaction (FBR), innate and acquired immunity are thoroughly discussed in the previous chapters and therefore are not reiterated here. The goal of this chapter is to compare and summarize host responses to natural and synthetic biomaterials and we envision that such discussion will foster the rational design of next generation biomaterials with enhanced biocompatibility. Based on their sources, biomaterials can be generally classified into natural materials such as extracellular matrix (ECM) proteins, polysaccharides, and decellularized tissue matrices; and synthetic materials such as organic and inorganic polymers, metals, nanoparticles, and their derivatives [2, 8]. The scope of this chapter is mainly focused on natural and synthetic polymers. In general, natural and synthetic biomaterials are largely different in inducing host reactions following implantation, which involves a series of events including provisional matrix formation, acute and chronic inflammation, blood–material interactions, and granulation/fibrous capsule development [9].

This chapter begins with the description and summary of major commonly used natural and synthetic biomaterials followed by detailed discussion of the inflammatory and immune responses induced by them. Finally, lessons learnt from previous studies and valuable strategies to improve biomaterials biocompatibility are presented along with the approaches to endow biomaterials with the capability to modulate host responses.

5.2 Natural Biomaterials

Nature has provided us with a range of materials with remarkable functional properties. Naturally derived biomaterials can be classified into proteins, polysaccharides, and decellularized tissue matrices. Protein and polysaccharide-based biomaterials can

be processed by two major methods. First, proteins or polysaccharides can be extracted from living organisms by dissolving in solvents or enzymes and reconstituted into fibrils. Alternatively, these biomaterials can be prepared by removing other components in living organisms by solvents or enzymes [10]. Decellularized tissue matrices are obtained by removing cells from native tissues/organs. Multiple decellularization protocols including physical, chemical, and enzymatic approaches have been applied to enable the effective decellularization process. Overall, one of the greatest advantages of using natural materials is that they are derived from materials already present inside the living systems [10]. Natural materials do not usually pose the problems of toxicity potentially faced by a range of synthetic materials. Also, they are bioactive with specific protein binding sites and other biochemical signals that may assist in a range of cellular activities including cell attachment, cell–cell communication, and eventually tissue regeneration [11]. Therefore, the field of biomimicry (e.g., "mimicking nature") is growing rapidly [12]. However, natural materials may pose problems of immunogenicity and possible contamination. Another problem faced by natural biomaterials is their relative instability, which might result in the tendency for mechanical failure or premature decomposition. Indeed, the biodegradation and biomechanical features of natural biomaterials are difficult to control [13].

With regard to host responses to natural biomaterials, although they are considered to have remarkable biocompatibility, natural biomaterials are also immunogenic [14]. The immunogenicity issue is especially serious in the case of xenogeneic materials, where antigens such as DNA, α-Gal epitopes (Galα1-3Galβ1-(3)4GlcNAc-R), and damage-associated molecular pattern (DAMP) molecules are presented [14]. Moreover, the manufacturing methods involved in the decellularized tissue matrices also determine host response to them [14, 15]. Incomplete decellularization process may result in a residual α-Gal epitopes or DNA and may lead to ECM rejection or acute immune responses [16]. Besides, the host response to biomaterials is also device-specific, which means that in addition to the source of the biomaterial, the intended clinical application and the site of implantation may also affect the severity of the host response. In this section, we give an account for different natural polymers and their immunogenic responses. We also discuss how the chemical composition, mechanical properties, surface chemistry and degradation time of different polymers affect the immune responses as summarized in Table 5.1.

5.2.1 Collagen

Collagen is the most abundant type of protein found in connective tissues [17]. So far, at least 29 subtypes of collagen have been identified [18]. All of them have the common triple helical structure with repeated $[Gly\text{-}X\text{-}Y]_n$ sequence, where X and Y are frequently proline and hydroxyproline, respectively [19, 20]. Among these different collagens, type I collagen has been most widely studied. The triple helical structure of collagen and its fibers are often packed into highly organized fibrillar structure, which provide tensile strength and structural integrity to various types of tissues and organs [21]. Collagen is relatively stiffer than other elastic proteins such

Table 5.1 Natural versus synthetic materials: chemical composition, mechanical properties, surface chemistry, degradation time and immune responses of different polymers

Biomaterials	Young's modulus (GPa)	Tensile strength (MPa)	Degradation time	Predominant host response	Cytokine production
Natural					
Collagen	Uncrosslinked: 0.046–1.8 Crosslinked: 0.383–0.766 [21]	Uncrosslinked: 0.91–7.2 Crosslinked: 46.8–68.8 [21]	>1 month [173]	Pro- and anti-inflammatory	IFN-γ, IL-13 [41]
Gelatin	3 [174]	20 [175]	Based on their water content [176]	Pro-inflammatory	TNF-α, IL-12, IL-6 [177]
Chitosan	0.007 [178]	2.43 [178]	<1 month [179]	Pro- and anti-inflammatory	IFN-γ, IL-2, TNFα, IL-10 [57, 58]
Hyaluronan	$(0.07–0.09) \times 10^{-3}$ [180]	0.011–0.013 [180]	Around 1 week [181]	Pro-inflammatory	TNF-α, IL-1β, IL-6 [74]
Heparin	NA	NA	NA	Anti-inflammatory	IL-10 [80]
Alginate	$(0.01–0.05) \times 10^{-3}$ [182]	0.005–0.04 [182]	Controlled by molecular weight [183]	Pro-inflammatory	TNF-α, GM-CSF, IL-12, IL-6, IL-1 [87]
Silk	10–22.6[184]	300–1100 [184]	10–24 weeks [185]	Pro-inflammatory	IFN-γ, IL-2, TNF-α, IL-1β[100, 102]
Synthetic					
PGA	6–7 [186]	60–99.7 [186]	6–12 months [187]	Pro-inflammatory	IL-1β, IL-6, GM-CSF, TNF-α[188]
PLA	0.35–3.5 [186]	21–60 [186]	12–24 months [189]	Pro- and anti-inflammatory	IL-6, IL-12/23, IL-10 [114]
PLGA	1.0–4.34 [186]	41.4–55.2 [186]	<2 months [190]	Pro- and anti-inflammatory	TNF-α, IL-6, TGF-β1 [191, 192]
PCL	0.21–0.44 [186]	20.7–42 [186]	>24 months [193]	Pro-inflammatory	TNF-α, IL-1β IL-6 [194, 195]
PTFE	0.39–2.25 [196]	10–45 [196]	Nondegradable	Pro-inflammatory	TNF-α, IL-1β IL-6 [133, 197]

as elastin, but it is an elastic material with a high resilience of nearly 90 %, and is capable of reversible deformation [22]. Biologically, collagen serves as a natural substrate for cellular activities, which makes collagen an excellent material for tissue engineering applications. Currently, there have been several FDA (Food and Drug Administration) approved collagen-containing products that have entered into the market for treating exuding diabetic ulcers, spinal dural repair, and regeneration of bone graft substitute [23, 24]. Moreover, collagen has also been explored in cardiovascular, musculoskeletal, and neuronal tissue engineering [25–28].

In general, the epitopes presented in the telopeptide regions of tropocollagen molecule are responsible for immune response [29, 30]. The immunogenic response of collagen depends upon the helical part conformation as well as the amino acid sequence of the polymerized collagen fibril [31–33]. Collagen is one of the primary initiators of the coagulation cascade and often used for attracting fibroblasts in vivo during wound healing [34]. The high thrombogenicity of collagen has led to its application as hemostatic agent. There are several collagen-based products that have already entered the market or undergoing clinical trials for surgical sealants or hemostat application [35]. The in vivo response of collagen was studied by implanting collagen sponge in rats for up to 8 weeks [36]. Scar tissue was developed within 1 week after implantation with signs of slight inflammation. Subsequently, fibrous tissue was observed at two weeks after implantation. At the same time, the collagen sponge was found to be completely degraded. Four weeks after implantation, previously observed fibrous layer had thickened to form wave-like scar tissue. The same scar tissue further matured in the following two weeks. Eventually, this wave-like scar tissue then began to be resolved after 8 weeks [36].

The mechanical property of collagen significantly decreases during extraction, scaffold fabrication, and sterilization steps [37–39]. Therefore, extra chemical crosslinking is necessary to regain the mechanical property and stability of collagen for tissue engineering application. The incorporation of such external crosslinking agents may impart cytotoxicity and host immune response to collagen [40–42]. Ye et al. [41] investigated the inflammatory response of two differently cross-linked dermal sheep collagen disks (hexamethylenediisocyanate, HDSC or glutaraldehyde cross-linked collagen, GDSC) in mice. It was observed that GDSC showed higher neutrophil infiltration at day 2 and 21 with release of high levels of interferon-gamma (IFN-γ), a cytokine related to pro-inflammatory response whereas HDSC showed little neutrophil infiltration at day 2. It was also found that GDSC completely degraded after 28 days but HDSC remained intact. HDSC increased the level of interleukin-13 (IL-13), anti-inflammatory cytokine. Therefore, it should be noted that the inflammatory response depends not only on the biomaterial type but also on their compositions.

5.2.2 Gelatin

Gelatin is a mixture of proteins produced from hydrolysis of collagen obtained from the connective tissues [43]. Structurally, gelatin molecules contain repeating sequences of glycine–proline/hydroxyproline–proline/hydroxyproline triplets,

which then form the triple helical structure of gelatin [8]. It has good ability to form gels because the helical regions in the gelatin protein chains are able to immobilize water [17]. Gelatin possesses better biocompatibility than its precursor collagen with lower risk of host rejection or infection [2, 44]. Therefore, gelatin has been frequently used in biomedical application as wound dressing, adhesive, or absorbent pad for surgical use as well as tissue engineering scaffolds [8].

5.2.3 Chitosan

Chitosan is a cationic polysaccharide composed of D-glucosamine and *N*-acetyl-D-glucosamine repeating units. It is obtained by alkaline hydrolysis of chitin which is the second most abundant natural biopolymer derived from exoskeletons of shrimps, fungal cell wall, and insects [45–48].

In 1970, chitosan was discovered to facilitate the wound healing process and after that, it has been broadly used in biomedical applications from sutures and wound dressing material to drug/gene delivery and tissue engineering [47, 49–53]. Vande Vord et al. [54] implanted porous tubular chitosan scaffold in mice intraperitoneally. The dramatic infiltration of neutrophils was observed at the implant site after 1 week indicating chemotactic effect of chitosan on immune cells. Other groups have also reported similar chemotactic effect of chitosan to neutrophils [55].

The percent of cationic amine groups in chitosan varies with the degree of deacetylation (DDA) of chitin during alkaline hydrolysis and as a result, the immune response of chitosan depends on its DDA, molecular weight, ionic charge and solubility. Chitosan exhibited hemostatic effect and complement activation [56]. Previous reports suggest that chitosan has dual immune response, i.e., it shows both pro- and anti-inflammatory responses. Low molecular weight chitosan (3 kDa) was found to have more pro-inflammatory response through stimulation of tumor necrosis factor alpha (TNF-α), IL-6, and IFN-γ secretion compared to that of high molecular weight (50 kDa) chitosan [57]. In another study, Oliveira et al. [58] reported downregulation of TNF-α and upregulation of anti-inflammatory cytokine levels (IL-10 and tumor growth factor-beta1, TGF-β1) in macrophage cells with high molecular weight chitosan. However, the same chitosan showed opposite effects in dendritic cells, i.e., increased secretion of pro-inflammatory cytokines (TNF-α and IL-1β) and decreased IL-10 secretion, suggesting that the immune response can be highly dependent on the cell types.

Due to presence of strong hydrogen bonding in chitosan, it is not soluble in water at physiological pH. It is only soluble in acidic environment as its pKa value is 6.5 [59, 60]. Therefore, solubility of chitosan is another important parameter for macrophage activation. Chen et al. [61] prepared water soluble chitosan through incorporation of hydroxypropyl group in its structure and studied its effect on the macrophages. Water-soluble chitosan decreased the production of pro-inflammatory cytokines IL-6 and TNF-α when monocyte-derived macrophages were stimulated with dust mite allergen *Dermatophagoides farina*. In another study, Bajaj et al.

reported that zwitterionic chitosan derivative showed increased solubility in wide pH range [62]. They did not observe any abnormal change in cytokine levels of unstimulated macrophages in presence of unmodified chitosan and zwitterionic chitosan. However, the cytokine levels (TNF-α and IL-6) were significantly decreased by zwitterionic chitosan compared to unmodified chitosan in macrophages stimulated by lipopolysaccharide (LPS) [62].

5.2.4 Hyaluronan

Hyaluronan, also called hyaluronic acid (HA), is a linear polysaccharide consisting of repeating units of D-glucuronic acid and *N*-acetyl glucosamine. It is found mainly in ECM of connective and epithelial tissues. Due to its anionic nature and high structural homology across species, it is almost nontoxic, non-antigenic, and non-immunogenic [63, 64]. FDA has approved HA for various eye surgeries including retinal detachment, corneal transplantation and cataract removal [65]. Apart from these, HA has also been used as lubricant gels for various joint disorders, lip fillers, wound healing, drug/protein delivery, and tissue engineering applications [66–70].

Due to protein binding capability of HA, it shows inflammatory responses through binding with cell surface receptors, particularly CD44 and Toll-like receptors (TLR) 2 and 4 of inflammatory cells, although the extent of inflammation depends on molecular weight of HA [71–73]. It is reported that low molecular weight HA shows pro-inflammatory response through upregulation of TNF-α and IL-12β whereas anti-inflammatory response was obtained by high molecular weight HA which increased IL-10 levels [74]. Kajahn et al. studied the effect of sulfate functionalization and degree of substitution of HA on macrophage activation. Sulfated HA-derivative with higher degree of substitution showed anti-inflammatory effect compared to non-functionalized HA and low substituted HA-derivative [75].

5.2.5 Heparin

Heparin is a naturally occurring linear glycosaminoglycan that consists of repeating units of D-glucuronic and D-glucosamine (GlcN) linked with 1, 4 linkage. Heparin possesses highest negative charge among the known biomolecules due to presence of high contents of sulfonic and carboxylic acid groups in its chemical structure [76]. It is generally obtained from porcine mucosal tissues having molecular weights ranged from 5 to 40 kDa.

Heparin is mainly used as an anticoagulant of blood. It is also used for pain relief, anti-inflammatory, anticancer, angiogenesis regulation, and inhibitor of complement activation [77]. Heparin and its derivatives mainly show anti-inflammatory response [78] although it is suggested that it may show either pro- or anti-inflammatory activity. An anti-inflammatory response (inhibition of TNF-α) was observed for low molecular weight heparin in a porcine sepsis model [79].

In another study, heparin showed dose-dependent anti-inflammatory response (reducing the pro-inflammatory cytokines TNF-α, IL-6, IL-8, and IL-1β) in LPS-stimulated THP-1 cells and primary monocytes. However, in the presence of LPS binding protein, heparin showed pro-inflammatory effect [80].

5.2.6 Alginate

Alginate, obtained from brown seaweed, is a naturally occurring anionic polymer consisting of mannuronic acid and guluronic acid units in an irregular block-wise pattern. Due to its low toxicity, easy accessibility and good gelation property in presence of divalent cations such as Ca^{2+}, alginate has been extensively studied and used for many biomedical applications such as drug/protein delivery, tissue engineering, cell/micro-organism immobilization as well as food applications [48, 81–86].

Sodium alginate showed pro-inflammatory response in macrophage cells (RAW264.7) through nuclear factor-kappaB (NF-kB) pathway and produced IL-1β, IL-6, IL-12, and TNF-α in time and dose-dependent manner [87]. Thomas et al. [88] studied the inflammatory response of four different commercialized alginate dressings, Kaltostat® (Convatec), Tegagen HG® (3M Healthcare), Comfeel: Seasorb filler® (Coloplast), and Sorbsan® (Braun). Among all the dressings, Kaltostat® showed more pro-inflammatory response through increasing TNF-α cytokine.

The repeating units, mannuronic acid (M) and guluronic acid (G) in alginate exists in irregular block pattern with varying proportions of MM, GG, and MG blocks [89]. Iwamoto et al. [90] synthesized different alginate oligomers (saturated and unsaturated) consisting only M or G and mixed MG repeating units and studied the effect of alginate structure on inflammatory response in macrophages. The unsaturated alginate oligomers exhibited pro-inflammatory response (increased TNF-α level) in RAW264.7 cells while saturated oligomers produced low TNF-α level. Among the unsaturated oligomers, G8 (eight repeating units of G) and M7 (seven repeating units of M) showed potent pro-inflammatory response inducing secretion of TNF-α along with IL-1α, IL-1β, and IL-6.

5.2.7 Silk

Silk is a unique class of structural proteins obtained from silk producing glands of arthropods such as spiders, silkworms, scorpions, mites, and bees. Silk possesses bulky repetitive modular hydrophobic domains interrupted by small hydrophilic groups and having large molecular weight 200–350 kDa or more. The biomedical use of silk (silkworm silk) began with sutures in wound treatment [91]. Due to its exceptional biocompatibility, low immunogenicity, antibacterial activity, and controllable biodegradability, it has been widely used in biomedical field [92–96]. Silk fibers and films have been widely used for tissue engineering scaffold applications due to its high mechanical loads or tensile forces and slow degradation rate [97].

Native silk is composed of a core structural protein, fibroin which is surrounded by a glue-like protein, sericin [98]. It is thought that sericin is responsible for antigenicity of silk [99]. Panilaitis et al. [100] observed that whole silk fiber did not show any inflammatory response in RAW264.7 cells at short as well as long time periods. Interestingly, when macrophages were exposed to sericin recoated-fibers in presence of LPS, sericin synergistically released TNF. Meinel et al. [101] also observed similar inflammatory response with silk fiber. As the sericin of native silk is responsible for inflammatory response, when sericin was removed from the native silk fiber, the sericin-free silk fiber became non-inflammatory in vivo compared to native silk fiber [102]. However, the mechanical property of native silk fiber significantly decreased after removal of sericin because it is the binding component of silk. In some reports, silk-based scaffold showed some inflammatory responses and this may be caused due to remnant solvent in the scaffold during pre- or post-processing of the scaffold [103, 104].

5.2.8 Decellularized Tissue Matrices

Decellularized tissue matrices represent lipid-free, decellularized protein-based derivatives and purified protein extracts of previously living tissues or organs [15]. ECM plays an important role in the mechanical support, signal transduction, and nutrients/waste transportation. Decellularization is a multistep process to remove all cell components (which are the major antigens) from tissue/organ leaving the ECM intact. As a completely natural material, the ECM has been proposed to be immune-privileged and evade from a series of host reactions to foreign bodies [105]. However, host privileges such as the minimal FBR and improved implanted material performance has not been unequivocally demonstrated [15]. The host response to decellularized ECM-derived biologic materials involves both the innate and acquired immune response. A recent study examined the level of host response to five commercially available decellularized ECM-derived materials, including GraftJacket™ (human dermis), Restore™ (porcine small intestine submucosa), CuffPatch™ (porcine small intestine submucosa), TissueMend™ (fetal bovine skin), and Permacol™ (porcine dermis) [106]. It was shown that these five devices had large differences in terms of the acute and chronic host response and in their downstream tissue remodeling outcomes, respectively. The CuffPatch™ showed accumulation of dense collagenous tissue and a persistent FBR. The host response to TissueMend™ and Permacol™ showed low level of chronic inflammation and fibrous encapsulation. GraftJacket™, CuffPatch™, and Permacol™ induced the presence of multinucleated giant cells at implantation site, indicating the elevated FBR. This study showed that decellularized ECM-derived biologic scaffolds differ profoundly in inducing host response. Therefore, a more detailed investigation of the effect of various ECM constituents on the host immune response and tissue remodeling is needed.

5.3 Synthetic Biomaterials

In contrast to the natural biomaterials, synthetic biomaterials are easy and inexpensive to produce, have high batch-to-batch uniformity, and demonstrate more predictable and controllable physicochemical, mechanical, and degradation properties. Besides, synthetic materials also possess excellent processing characteristics, which can ensure their off-the-shelf availability. However, they also suffer from problems such as their "foreignness" to cells, eliciting inflammatory reactions, and their noncompliance or inability to integrate with host tissues [107]. The most popular synthetic biomaterials include polyesters such as polyglycolide (PGA), polylactide (PLA), polycaprolactone (PCL), polyurethane (PU), and polyhydroxybutyrate.

5.3.1 Polyglycolide or Polyglycolic Acid (PGA)

PGA is biodegradable, thermoplastic crystalline polyester with linear aliphatic structure. It is normally prepared by polycondensation or ring-opening polymerization using glycolic acid. Early successful study on PGA-based suture system encouraged the development of a wide range of biodegradable polymers as implants for different medical applications such as sutures and bone internal fixation device [35]. PGA has a fast degradation rate with acidic degradation products, which are thought to be responsible for the inflammatory reaction induced by PGA [108]. Meanwhile, PGA did not induce lymphocyte DNA synthesis. Therefore, PGA is immunologically inert. However, PGA induced major histocompatibility complex locus II antigen and IL-2R activation, showcasing its inflammatory response [109]. It has been shown that PGA initiates significant host reaction upon implantation in vivo. When synthetic PGA scaffolds seeded with somatic lung progenitor cells from mammalian lung tissue were implanted in immunocompetent mice, a serious cascades of FBR were observed that altered the integrity of the developing lung tissue [110]. However, there is no consensus on the immune effect of PGA to date. For example, tubular urethra made from PGA seeded with autologous muscle cells has been reported to survive for 6 years post-implantation in patients [111].

The immune response to PGA mainly occurs due to the degradation products through hydrolysis or enzymatic degradation [108]. A local inflammatory response has been reported after implantation of PGA-based sutures or orthopedic pins. Ceonzo et al. [112] studied the molecular mechanism of inflammation by PGA in vitro and in vivo. Both PGA and glycolic acid solution (degradation product of PGA) were injected intraperitoneally in genetically engineered mice and it was observed that glycolic acid was responsible for local inflammatory response.

5.3.2 Polylactic Acid (PLA)

PLA is biodegradable thermoplastic crystalline polyester with aliphatic chain. Unlike PGA, PLA has slow degradation rate and good strength and stiffness, which is suitable for load-bearing applications. Early study on PLA stent implanted in humans indicated its safe profile without inducing thrombosis and late stenosis for up to 6 months [113]. However, further study on PLA reported that PLA may induce inflammatory response when implanted in the body due to their acidic degradation products [114]. Tubular PLA constructs implanted beneath the skin of mice resulted in longer inflammatory reactions indicated by presence of epithelioid and giant cells [115]. The effect of phagocytosed PLA particle on macrophages was investigated in vivo. It was shown that upon phagocytosis of PLA particle, macrophage cell damage, cell death, and cell lysis were observed [116]. Like PGA, these host reactions have strongly limited their clinical applications.

5.3.3 Polycaprolactone (PCL)

PCL is also a biodegradable polyester. PCL has been approved by FDA for medical applications such as drug delivery devices and sutures. It has also been widely used as a material of choice for tissue engineered scaffold for a variety of tissues due to their elastic mechanical properties and slow degradation rate [117–122]. When PCL was implanted in the nervous system, microglia and astrocytes were found to be activated for up to 28 days post-implantation. However, 60 days post-implantation, no scar or FBR was observed around the scaffold [123].

5.3.4 Polyurethane (PU)

PUs share the common polymer backbone structure, which includes an aliphatic or aromatic units coming from the isocyanate monomers and a more complex moiety derived from polyether or polyester monomers. PU has been extensively investigated as a material of choice for long term cardiovascular medical devices, such as cardiac pacemakers and vascular grafts due to their moderate blood compatibility and mechanical properties [124]. However, they have been shown to elicit increase in the release of chemokines, cytokines, and growth factors in the in vivo models [125]. Subcutaneous implantation of lysine diisocyanate-based PUs in rats revealed that it did not aggravate capsule formation, accumulation of macrophages, or tissue necrosis [126].

5.3.5 *Polytetrafluoroethylene (PTFE)*

PTFE is another class of synthetic polymers consisting of tetrafluoroethylene repeating units in its chemical structure and commonly known as Teflon. Due to its inertness (insoluble in all common solvents), high thermal stability, and non-biodegradability, it has been used extensively in various commercial, industrial, and biomedical applications including large blood vessel repair material [127]. Apart from this, PTFE has also been used as a graft material such as in superficial femoral occlusion and left ventricular assist device. PTFE has been found to elicit mild to moderate inflammatory response in vivo. After implantation of expanded PTFE (ePTFE) in unilateral aorto-femoral bypass of dog, chronic inflammatory response was observed along with the presence of macrophages, myofibroblasts and deposition of complement C3 after 6 months of implantation [128].

5.4 Important Biomaterial Characteristics in the Host Response

Today, implanted systems are still facing the problem of host responses such as adverse blood–material interaction, inflammation, and immune reaction [129]. Minimizing the immune response to biomaterials may be achieved by the choice of materials that are intrinsically immune-inert [5]. Besides, it has been recognized that host response to polymers are closely associated with the physicochemical properties of material, which control the type, amount, conformation, and duration of proteins that could be adsorbed onto the polymer surface. Polymer chemistry can be actively utilized to widely tune the functional aspects of biomaterial matrices such as hydrophilicity, surface pore size, degradation rate, and degradation products. Tuning these physicochemical properties enable the alteration of protein adsorption, which consequently mediates the interactions with immune cells and their activation [5]. Specifically, the hydrophobicity of materials promotes protein adsorption and enhances monocyte adhesion because water on the surface of materials can be easily replaced by a hydrophobic surface of proteins [130]. On the contrary, hydrophilic polymer surfaces will easily allow water attachment and is not favorable for protein adsorption. With the reduced protein adsorption, material is shown to have decreased monocyte/macrophage adhesion and foreign body giant cell (FBGC) formation in vitro [131]. Hydrophilicity is not the only parameter that decides the extent of the host response to polymeric materials. As an example, it has been shown that hydrophilic but charged polymethacrylate can induce complement activation due to the electrostatic interaction between positively charged complement recognition protein C1q and negatively charged polymers [132]. When negatively charged polymethacrylate binds to blood plasma proteins including complement components or IgGs, complement activation and leukocyte response can be induced [132]. Biomaterial scaffolds, on the other hand, have multiple hierarchical structures ranging from molecular level where cross-linked or individual polymer chain form porous network

to microscopic level where the topographic features of the scaffold are presented. The pore size can create steric hindrance between proteins and the material surface. Materials with smaller pore size present limited surface area for protein binding. One the contrary, a surface with large pores can allow the binding of both large and small proteins within the pores at their corresponding protein configuration [129]. The small pore size was demonstrated to decrease capsule formation in vivo, irrespective of surface chemistry [133]. Additionally, PCL scaffolds with an aligned fiber topography was shown to have significantly reduced capsule formation compared to scaffolds with randomly aligned fibers [134]. The effect of the architecture of micro-structured biomaterials on determining response of macrophages has also been demonstrated [135]. Tuning surface chemistry by grafting or coating with polymer, proteins, or specific peptide sequences on polymer chains also alter protein adsorption and the host responses. As an example, poly(*N*-isopropylacrylamide) grafted poly(ethylene terephthalate) copolymer reduced protein adsorption and monocyte adhesion and resulted in reduced inflammatory cytokine levels after implantation [136]. Osteopontin coatings on a positively charged copolymer of 2-hydroxyethyl methacrylate and 2-aminoethyl methacrylate surfaces have reduced capsule thickness around the implant [137]. In addition, heparin coatings can be used to reduce coagulation and complement activation by binding to and activating antithrombin, which then inactivates thrombin and blocks blood clotting process. The coating with non-fouling polymers such as polyethylene glycol (PEG) can also minimize protein adsorption [138, 139].

5.5 Strategies to Overcome and Modulate the Host Responses

The immune response, if not controlled properly, has the potential to cause extensive secondary damage. Therefore, different strategies have been applied to reduce the unwanted host response to the implant. Moreover, many recent approaches have attempted to modulate the immune response to achieve the more effective regeneration outcome. This section summarizes the major strategies that have emerged over past few years.

5.5.1 Surface Modification

The host immune response can be reduced by chemical or physical modification of the material surface. The functional groups presented on the biomaterial surface can interact with protein molecules and consequently activate the immune cells. It is reported that the hydrophobic biomaterials such as vinylidene fluoride-hexafluoropropylene copolymer (VFH), poly(styrene–isobutylene–styrene) copolymer (SIBS), and poly(butylmethacrylate) (PBMA) show more interaction with the monocytes and result local immune response at the implant site [130]. The monocyte adhesion and

FBGC formation significantly reduced in case of hydrophilic (phosphorylcholine, BioLinx, polyacrylamide) and neutral biomaterial surface (sodium salt of polyacrylic acid) [130, 131]. However, hydrophilic and neutral biomaterials showed more pro-inflammatory response (release of IL-1β and IL-6) compared to hydrophobic surfaces although the inflammatory response was time dependent.

Change in surface topography and roughness is another strategy for immunomodulation [140, 141]. Higher cell infiltration and reduced fibrous capsule formation were obtained with aligned PCL nanofiber topography compared to randomly aligned PCL nanofibers [142]. Chen et al. [135] modulated the macrophage activation by imprinting parallel gratings (0.25–2 μm line width) on different biopolymers such as PLA, PCL, and PDMS. It was found that the density of macrophage cell attachment decreased on 2 μm gratings. In addition to this, larger grating line width (1 μm) induced more pro-inflammatory response (TNF-α) at 24 h, but the response decreased at 48 h. In another study, in vitro monocyte/macrophage stimulation was observed with variation of PTFE scaffold topography (different intra-nodal distances) [133]. Scaffold with larger intra-nodal distance (4.4 μm) showed 15-fold higher stimulation compared to nonporous scaffolds.

5.5.2 Surface Coatings

Apart from the surface chemistry or architecture, surface coating on biomaterial is another approach to mask the immune response of implant device. The immune response to implant device arises from nonspecific protein adsorption on the surface of implant device and results in leucocyte adhesion, called "biofouling." Therefore, surface coating of biomaterial may reduce such "biofouling" and can adversely affect immune response. Pre-adsorption of less inflammatory proteins (albumin) on polystyrene and PU surface was used previously due to its simple and straightforward approach [143, 144]. FBR was also decreased after coating of osteopontin on positively charged polymer surface [137]. The coating layer provides an interface between the implant surface and the tissue fluids, enabling different protein binding and downstream signaling in the immune cells, thereby possibly minimizing the induced tissue reactions [145]. Due to the lack of stability of such protein-based coating, non-fouling polymer (that prevents protein adsorption) coating has become alternative route for immunomodulation. PEG has been extensively applied as non-fouling polymer [146]. The non-fouling activity of PEG depends on its chain length or molecular weight, PEG chain density, and conformation [147–149]. Apart from PEG, PAAm, poly(*N*-isopropyl acrylamide), and poly(2-hydroxyethyl methacrylate) have also been used to prevent protein adsorption [150–152]. Hydrogel-type coatings have emerged as an interesting type and have been applied in a broad range of biomaterial devices [153, 154]. Hydrogel system can be made of materials from natural sources including ECM proteins (such as gelatin) [155], polysaccharides (such as alginate, chitosan), and synthetic polymers (such as poly(acrylamide)) [156].

5.5.3 *Delivery of Bioactive Molecules*

Immunomodulation can also be controlled through systemic delivery of anti-inflammatory cytokines [5]. The flexible polymeric biomaterial structures enable the anti-inflammatory and immunomodulatory therapy by the incorporation of bioactive molecules such as cytokines, growth factors, and anti-inflammatory drugs [4, 5]. As soon as the payloads are released, the anti-inflammatory effects fade and inflammatory response will resume. Therefore, the beneficial effects of the immune response on regeneration may be retained using localized delivery systems along with biomaterial, which may not impact the entire immune system and have the potential to selectively recruit specific immune cells or create a local anti-inflammatory microenvironment.

Host response at the implant site can be controlled with the use of steroidal and nonsteroidal anti-inflammatory drugs. Glucocorticoids are potent suppressors of immune responses and have been used to inhibit the immune response by inhibiting the formation and secretion of inflammatory cytokines. Glucocorticoid treatment resulted in reduced inflammatory cells at the injury site by inhibiting inflammatory mediators, decreasing capillary permeability, and fibroblast proliferation [157]. Meanwhile, the inflammation and immune response were resolved by promoting anti-inflammatory cytokine secretion and inhibiting cellular (T helper 1, Th1) immunity in favor of humoral (Th2) immunity [158]. Biomaterial-based drug carrier such as microspheres, nanoparticles, hydrogels, microspheres-hydrogel composites have been designed to deliver drugs of interest to the implant site [159–162]. As an example, delivery of dexamethasone using PLGA microsphere-polyvinyl alcohol (PVA) hydrogel composite at the implantation site resulted in reduced implant-associated inflammatory reaction as indicated by the initial decreased levels of polymorphonuclear leukocytes and minimal macrophages and lymphocytes infiltration and fibrous capsule formation in the later stage [163]. However, an undesired effect of using dexamethasone as a therapeutic is its ability to reduce the secretion of vascular endothelial growth factor (VEGF) in the surrounding tissue, which down regulates angiogenesis and would potentially inhibit wound healing [4]. By the combination therapy of dexamethasone and VEGF delivery, this problem could potentially be overcome [159]. Similarly, delivery of nonsteroidal anti-inflammatory drugs has reduced IL-8 and polymorphonuclear leukocyte levels while not reducing significantly monocyte chemoattractant protein-1 and monocyte levels [164]. Coating of biomaterial surfaces with nitric oxide (NO)-releasing layer is another strategy suggested for long-term control of immune responses. Hetrick et al. applied NO releasing diazeniumdiolate-modified xerogel polymer coating on silicone elastomer implant, which resulted in reduced inflammatory cell recruitment and extent of inflammatory reaction at the implant site. This effect was sustained even after exhaustion of the payload release from the NO reservoir [165].

A range of signaling network of growth factors, including epidermal growth factor (EGF), fibroblast growth factor (FGF), VEGF, transforming growth factor beta (TGFβ), and platelet-derived growth factor (PDGF) control adhesion, migration,

proliferation, and differentiation of fibroblasts, keratinocytes, and endothelial cells during injury [166]. Biomaterials coated with or encapsulating these bioactive molecules are envisioned to have immunomodulatory effect.

Recently, biopolymer-based, microparticles or nanoparticles-based controlled delivery of immunomodulatory proteins have been studied as novel approaches [167, 168]. Rusanova et al. [169] encapsulated synthetic thrombin receptor (PAR1) agonist peptide into biodegradable PLGA microspheres and the controlled release of PAR1 from microsphere reduced the inflammatory response and resulted wound healing in ulcer rat model. Nucleic acid delivery has also been shown to effectively reduce the inflammatory response [170, 171]. Recently, Mirandi et al. reported the modulation of macrophage response to collagen based scaffold by the controlled delivery of cytokine IL-4 from PLGA-multistage silicone vector [172]. In the presence of IL-4, rat bone marrow derived macrophage showed overexpression of anti-inflammatory and M2 associated genes such as *Il10* both in vitro and in vivo.

5.6 Conclusions

In this chapter, we discuss various natural and synthetic biomaterials and how they affect the host immune responses. The nature of immune response, whether acute or chronic, depends on various factors such as implantation techniques, biomaterial source and their composition, molecular weight, surface property, mechanical properties, and degradation rate. The implanted device first comes in contact with blood plasma and ECM proteins. The adsorbed ECM proteins on the biomaterial surface attract the neutrophils and monocytes through cellular response and consequently result in the inflammatory response by macrophage. The immune response to biomaterials can be modulated through inhibition of protein adsorption on biomaterial surface by various techniques such as surface modification, surface coating and delivery of immune modulating agents. Therefore, the biomaterial-based implants should be engineered in such a way that the materials result in no or minimum immune response and unnecessary health risks to provide the best clinical outcomes for the patients.

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