

HSCs play an important role in stem cell transplantation in patients with blood diseases [202]. The important factor of its regenerative potential is the BM microenvironment [202]. In recent years, it has been found that changes in HSCs in the bone marrow microenvironment can often be adjusted with biological materials [203]. As mentioned earlier, bone biomaterials play an important role in bone microenvironment by providing matrix for cell adhesion, proliferation and differentiation, and by regulating cell activity and function. Another concern is that the directional differentiation of stem cells is induced for artificial biotransformation through the interaction between bone biomaterials and stem cells. Novel bone biomaterials have emerged, including biodegradable bioactive ceramics, polymers, and metals with good biocompatibility [204].

Studies have shown that the different chemical composition, surface characteristics, and morphology of bone biomaterials may promote the proliferation of HSCs *in vitro*, so that HSCs can differentiate into mature blood cells or serve as a drug testing platform [205]. For instance, A.C. Wilkinson, et al. found that polyvinyl alcohol (PVA) was identified as a substitute for serum albumin in culturing HSCs. Under the action of PVA, 100 ng/ml Thrombopoietin and 10 ng/ml stem cell factor, mouse CD34, LSK, and HSC were amplified *in vitro* and maintained function-activity [206]. Similarly, for CD34⁺ hematopoietic stem and progenitor cell (HSPCs) derived from human cord blood, PVA can replace serum albumin [207]. However, compared to mouse HSCs, human CD34⁺, CD38⁻, CD90⁺, CD49f⁺, and HSCs are not sensitive to the hydrolysis state of PVA. Sambit Sahoo et al. developed a bio-hybrid fiber scaffold system by coating bioactive bFGF-releasing ultra-fine PLGA fibers on a mechanically strong, slow-degrading degummed knitted microfiber wire scaffold, which stimulated the proliferation of mesenchymal progenitor cells (MPCs) [208].

The introduction of biomolecules on the surface of biomaterials is the most commonly used biofunctionalization technology for cell culture [209]. Nanofibers (NFs) have been widely used in the past 20 years, due to their ability to mimic the ECM structure of many body tissues (such as bone marrow) [210]. To overcome the disadvantages of poor mechanical properties and poor processability of natural nanofibers, chemical surface treatment was performed on the surface of polymer NFS, and functional groups were introduced on the surface. K.-N. Chua, C. et al. reported that human CD34⁺ HSPCs cultured on grids of aminated polyethersulfone NFs exhibited stronger adhesion and larger HSPCs progenitor cell expansion and maintenance capacity than HSPCs cultured on unmodified, hydroxylated or carboxylated NFs grids or aminated membranes. This study shows that even simple surface chemistry can affect HSPC in the microenvironment [211].

The three-dimensional (3D) structure of biological materials can simulate microenvironment of bone hematopoietic system. Hydrogel is notable representative of biomaterials [212]. The properties of hydrogels can be adjusted according to the characteristics of the microenvironment, which makes them advantageous for certain applications or analytical methods [213]. In the field of *in vivo* and *in vitro* research based on biological materials, the use of hydrogel incorporation systems is extensive and diverse. The raw materials used to make 3D structured hydrogels can be natural ECM (such as fibrin, sodium alginate, chitosan, collagen, pullulan,

Table 1.1 Application of biomaterials in bone marrow hematopoietic system.

Biomaterials	Characteristic	Main functional group
Polyvinyl alcohol (PVA)	Replace serum albumin	–OH; C=C
PLGA microfiber wire scaffold	ECM-like biomimetic architecture	–COOH; –OH
Polyethersulfone nanofibers	Adhesion	–SO ²⁻
Natural hydrogels (fibrin, chitosan, collagen)	3D structure; supporting paracrine (large pores) or autocrine (small pores) signaling	–OH; –COOH; –NH ₂
Artificial hydrogel (polyethylene glycol, polyurethane)		

cellulose, silk fibroin, etc.) or synthetic polymers (such as PEG, polyurethane, poly(lactic-co-glycolic acid), and PCL) [214]. However, when preparing hydrogels, natural sources and synthetic compounds are often used to prepare hydrogels together, which have improved physical and chemical properties. The research team of A.E. Gilchrist, S. successfully fabricated hydrogels with different pore sizes, supporting paracrine (large pores) or autocrine (small pores) signaling, and obtained cell behavior data. The results showed that when cultured alone, murine BM-derived lineage⁻ Sca1⁺ c-Kit⁺ (LSK) HSPCs proliferated significantly in the paracrine signal supporting gelma matrix, but when HSPC and MSCs were co-cultured in the autocrine signal support gel, the expansion rate was much higher [215]. RUWAN D.et al. also described the successful cultivation of HMSCs in a three-dimensional collagen matrix under mechanical strain. In addition to providing a 3D structure, the hydrogels were also allowed to be tuned to have functionalization, mechanical properties, and degradability to improve compatibility with the human environment [216]. T. Bai et al. reported that a zwitterionic hydrogel with peptide chain cleavage sites was used to amplify HSPC derived from human cord blood and bone marrow and cultured for several generations. In immunocompromised mice, the number of long-term HSCs can be increased by 73 times and can be reconstituted for at least 24 weeks [205] (Table 1.1).

Part of the application of the above-mentioned materials for BM microenvironment is at the cellular level, and we are still facing great challenges. Often the application of biomaterials *in vitro* and *in vivo* will make a big difference, due to the complex and changeable environment in the body that is difficult to control.

1.3.3 Biomaterials and Bone Immune System

In addition to the main site of hematopoiesis, BM also contains lymphoid progenitor cells and mature immune cells (B cells, neutrophils, macrophages, and T cells) [217]. The immune system has the functions of immune surveillance, defense, and regulation. Immune cells exist in the bone microenvironment and interact with

bone to perform the functions of the “bone immune system” in concert [218]. The key role of the bone immune system in bone microenvironment against foreign bodies and pathogens has long been familiar to researchers [219]. With the clear understanding of this new research field of bone immunology, the reciprocal regulation between immune cells and bone morphogenetic cells has been studied in greater depth, and the two systems are thought to be tightly linked through various cytokines, signaling molecules, transcription factors, and receptors [164].

In the clinical treatment of bone defects, biomaterials show a significant therapeutic role, when bone microenvironment changes [220]. However, the host immune response determines the fate of implants *in vivo*, whether they are formed in new bone, wrapped in fibrous tissue, or used for drug delivery for decrease of autoimmune response in the bone microenvironment [221]. The traditional biomaterial design includes the manufacture of inert biomaterials that can stimulate osteogenesis; however, *in vivo* and *in vitro* often fail to achieve consistent evaluation results. This has led to the evolution of biomaterials for implants with bone immunomodulatory properties [222]. These orthopedic biomaterials are endowed with good bone immunomodulatory properties that can trigger the desired immune response for proper bone regeneration process [176]. Under these circumstances, to regulate the crosstalk with immune cells (macrophages, neutrophils), various methods have been adopted such as changing chemical/structural characteristics or adding biologically active molecules.

An ideal biomaterial should be able to stimulate good crosstalk between immune cells and cells of the skeletal system at different stages of bone healing. In this case, to be able to design biological materials that control the polarization of macrophages and the positive crosstalk with bone-forming cells, it is often through changing the chemical/topographic characteristics or adding biologically active molecules [223]. As mentioned earlier, the interaction between the surface of the biomaterial and the protein adsorption layer is critical for the emergence of an immune response to the implantable biomaterial. In this regard, existing studies confirmed that changing different surface chemical properties, hydrophilicity, surface charge or functional groups, can affect the response of immune cells [164]. Hydrophobicity or hydrophilicity of biomaterials is the key factor affecting protein adsorption. The hydrophilicity of biomaterials has a non-negligible relationship with protein layer adsorption, fibrin formation and clot formation [224]. Strongly hydrophilic biomaterials have inherent immunogenicity. Kakizawa et al. prepared monodisperse silica nanoparticles that showed different hydrophobic poly (amino acid) surface modification and reported that the secretion of IL-1 β and IFN- γ is related to the hydrophobicity of poly(amino acids) [225]. In addition, their research also showed that strong hydrophilic biomaterials can promote the process of bone regeneration. Li et al. discovered lower hydrophilicity of Ti surfaces can induce the secretion of a variety of pro-inflammatory cytokines (TNF) compared to heparin/fibronectin functionalized titanium surface- α , MCP-1, and IL-1 β) [226]. The addition of hydrophilic molecules such as PEG and polyoxyethylene (PEO) to carriers and tissue engineering structures as surface modifiers for implants to improve their hydrophilicity and reduce protein adsorption [227]. Future strategies can use

changes in surface chemistry to regulate immune response to achieve natural healing response to injury. Immune response is also closely related to the surface charge of implanted biomaterials [228]. Therefore, the following functional groups, such as amino ($-\text{NH}_2$), hydroxyl ($-\text{OH}$), carboxyl ($-\text{COOH}$), are usually investigated, and *in vivo* applications have found that the amino and hydroxyl groups can induce immune cell infiltration and form a complex surrounding the thick fibrous capsule of the implant [229].

In the process of natural degradation in the microenvironment when biodegradable biomaterials are implanted, the immune response will also be affected by surface changes and degradation products [230]. Furthermore, there are great differences in the structure of biomaterials, and some of them can further promote the process during initial degradation, leading to structural collapse and loss of original functions. After the bio-implantation, the blood in the injured blood vessel begins to interact rapidly with the biomaterial. The surface properties of biomaterials can exhibit differences in the amount and type of adsorbed proteins and further recruitment and adhesion of various cells. Implantable biomaterials are not only passive targets when confronted with the host immune system, but they also have a dramatic effect: the magnitude and type of the implant-mediated immune response can be modulated.

In addition to surface chemistry, the morphological features and porosity of biomaterials also affect the plasticity and function of immune cells [231]. The surface roughness of biological materials can also affect the interaction with immune cells, which is a characteristic of biological materials. In the study of Ali K. Refai et al. on the effect of titanium (Ti) surface morphology on the activation of macrophages and the secretion of pro-inflammatory cytokines and chemokines, four topography were used: topography produced by mechanical polishing, coarse sandblasting, acid etching, sandblasting, and acid etching (SLA) [232]. It was found that unstimulated macrophages increased their pro-inflammatory cytokine (TNF- α) secretion when adhered to rough surfaces. This *in vitro* study showed that surface morphology, especially SLA surface, regulates the expression of macrophage pro-inflammatory cytokines and chemokines in a time-dependent manner. Generally speaking, the roughness can be presented on a micro-scale, and there is evidence that the micro-patterned surface show a beneficial effect on the bone immune microenvironment, thereby increasing the success rate of implantation. For example, Hotchkiss et al. discovered that micro-roughness-modified Ti surface promotes phenotypic transformation of M2 macrophages with increased IL-4 and IL-10 cytokine production, while smooth Ti matrix promotes M1 polarization [233].

In recent years, nano-scale biomaterials have been extensively studied, because the surface depth of bone tissue is about 32 nm [234]. Biomaterials that can be surface-regulated at the nanoscale can directly affect important processes such as cell adhesion and proliferation. Chen et al. prepared a plasma-polymerized allylamine surface to modulate immune cell responses by immobilizing gold nanoparticles of different sizes (16–68 nm) [176, 235]. From the results obtained, the scale of the nanotopography can significantly modulate the immune microenvironment by altering the gene expression profiles of inflammatory cytokines.

Table 1.2 Summary of biomaterials that do not affect the immune system in the bone microenvironment.

Biomaterials				
Physical and chemical properties	Hydrophilicity	Ethanol amine	Polyoxyethylene (PEO)	Polyethylene glycol (PEG)
	Surfaces scaffold pore size and porosity	Polydioxanone	Gold nanoparticles	Plasma-polymerized allylamine

The porosity and pore size of biomaterials are considered to be another relevant surface feature in that because the penetration of oxygen and nutrients can affect the fate of macrophages [236]. The small pore size on the surface will destroy the diffusion of nutrients and oxygen, especially in the interior of the implant material, resulting in a local hypoxia microenvironment. The local hypoxic environment leads to the development of a local inflammatory response, leading to the formation of granulation tissue and complete blockage of the pores, creating a barrier between the surrounding bone cells and the implant. In addition, appropriate hypoxic environments can stimulate the release of angiogenic growth factors, which are local host tissues necessary for angiogenesis [237]. Therefore, biomaterials should exhibit suitable pore sizes to enable the creation of a moderately hypoxic environment, which not only prevents inflammation but also promotes angiogenesis. Garg et al. showed that increasing polydioxanone scaffold pore size and porosity enhanced M2 macrophage markers. The surface with larger pores down-regulates the production of iNOS compared with smaller pores, which promotes the transition to the M1 phenotype [238].

Based on these observations, the strategy of adjusting the immune response by adjusting the physical and chemical properties of biological materials can be considered a valuable method. These biological materials can be used in smart drug delivery carriers, and materials that are friendly to the immune system can be used in the treatment of bone diseases, which will also provide a sufficient reference for developing new drug delivery systems for bone-related diseases (Table 1.2).

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