Bruna Corradetti *Editor*

The Immune Response to Implanted Materials and Devices

The Impact of the Immune System on the Success of an Implant

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Foreword

In the powerfully emerging world of smart, or functional materials, I cannot imagine a class with greater potential impact on healthcare and societal benefits than biomaterials with an ability to modulate inflammatory response—precisely the subject focus of this exceptionally timely monograph edited by Dr. Bruna Corradetti.

All materials for use in healthcare elicit an inflammatory response, bar none; but exactly as inflammation can be a fundamental step in a healing process, or a formidable foe, if frustrated into a chronic manifestation, this biological response to a material interface can be essentially helpful, or profoundly detrimental. Materials technology, and our understanding of the many facets of inflammation, has finally reached a point of sufficient maturity and convergence, to make it possible, for biomaterials to be designed so as to elicit a beneficial, or at least a functionally neutral response from the biology with which they contact.

The downstream vision from this exciting vantage point potentially portends transformational breakthroughs in multiple domains of healthcare, ranging from lifelong orthopedic implants, to indwelling molecular sensors, brain-machine interfaces, regenerative biomaterial-cell combinations for applications in pancreatic and hepatic medicine, central and peripheral nervous system repair, T-cell transplantation and novel therapeutic systems. They comprise both, drug-delivery implants and systemic administration constructs, with the ability to preferentially concentrate at inflammatory sites, sense their biological surrounding, and respond accordingly to optimize therapeutic benefit and minimize adverse effects.

I express my enthusiastic support for Dr. Corradetti's efforts in realizing this extraordinary collection of contribution from world-leading experts, to place the convergence of inflammatory modulation and biomaterials on a firmer footing, for decades of scientific work in this nascent era. It has been an honor to serve in an

editorial advisory capacity for this volume, and a great added privilege to be able to do so in concert with two exceptionally distinguished scientists as Dr. Anthony Atala and Ali Khademhosseini. My gratitude goes to them and to the authors for their outstanding contributions.

With all of this, I wish you all happy readings and a pathway of rewarding research, enhanced by the contents of this important monograph.

Sincerely,
Dr. Mauro Ferrari

Preface

This textbook is intended to be a resource for biomaterial scientists and biomedical engineers, in both industry and academia, interested in the development of smart strategies able to exploit the self-healing properties of the body and achieve functional tissue restoration. Nowadays, many textbooks and journals discuss the broad spectra of material properties that can be customized for any specific applications but only few of them characterize in detail the host response, as the driving factor in determining the success of an implant.

Thanks to the perspectives offered by experts in the field of regenerative medicine, tissue engineering, surgery, immunology, nanomedicine, and transplantation, this textbook will guide the readers throughout the fascinating cascade of events activated in the body following the implant of biomaterials and devices. In Chap. 1 Dr. Badylak provides an overview of the host response to various categories of biomaterials for regenerative medicine applications, from a host-centric and a biomaterial-centric perspective. In Chap. 2 Dr. Anderson discusses the humoral and cellular events occurring at the implant site immediately following implantation. In Chap. 3, Dr. Giachelli presents the current understanding of macrophages, their functions in physiological processes and dysfunction in response to the foreign body, as well as approaches to guide them towards resolution of the foreign body-elicited inflammatory response. Dr. Dobrovolskaia proposes in Chap. 4 regulatory challenges, translational considerations, and literature case studies pertinent to the immunological safety of nanotechnology-based devices. Dr. Sant and Dr. Goldsmith provide a discussion about the effects of natural vs. synthetic biomaterials, as well as the role of the biomechanical environment on tissue fibrosis, in Chaps. 5 and 9, respectively. Highlights about the role of the biomechanical and physicochemical properties in osteo-immunomodulation and the effect of surface topographical modification on the cellular and molecular mechanisms associated with osseointegration are reported in Chaps. 6 and 8, by Dr. Xiao and Dr. Ivanovski. In Chap. 7, Dr. Li describes challenges and opportunities in targeting key elements of the innate immune system in favor of transplant survival. In Chap. 10, Dr. Sabek reviews possible solutions for the challenges encountered in the pancreatic islet transplantation field, while in Chap. 11 Dr. Tacke discusses current strategies to target macrophages

in liver diseases and cancer. Novel concepts of T-cell immunomodulation for their clinical translation are presented by Dr. Hildebrandt in Chap. 12 to allow the transfer of the knowledge gained to implanted materials and devices.

It has been a particular privilege for me to collaborate with each of the authors participating in this project, and I feel grateful for their inspired work and for the time they devoted to make this volume possible. I wish to express my public gratitude to Dr. Anthony Atala, Dr. Ali Khademhosseini, and Dr. Mauro Ferrari for serving as Editorial Advisors for this book, for their constant support, outstanding suggestions, and visionary ideas. It has been an honor working with you.

My greatest hope is that this book will stimulate further discussions and investigations on the powerful role of the host response in regenerative processes allowing for the development of cutting-edge approaches able to exploit it and achieve functional tissue healing.

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Abbreviations

ADA	Adenosine deaminase
aGvHD	Acute graft vs. host disease
ALP	Alkaline phosphatase
AMR	Antibody-mediated rejection
APC	Antigen-presenting cells
AST	Arginine stimulation test
ATMP	Advanced therapy medicinal product
BMI	Body mass index
BMP	Bone morphogenetic protein
CaP	Calcium phosphate direct deposition
CARPA	Complement activation related pseudoallergy
CaSR	Calcium sensing receptor
CCL	CC chemokine ligand
CDP	Common DC progenitor
cGvHD	Chronic graft vs. host disease
CID	Chemical inducer of dimerization
cMoP	Common myeloid progenitor
CSF	Colony-stimulating factor
CSFR	Colony-stimulating factor receptor
CXCL	Chemokine (C-X-C motif) ligand
CXCR	Chemokine receptor
DAF	Decay accelerating factor
DAMP	Damage-associated molecular pattern
DC	Dendritic cell
DDA	Degree of deacetylation
DKK-1	Dickkopf-1
DPP	Dipeptidyl peptidase
ECad	Epithelial cadherin
ECM	Extracellular matrix
EDRF	Endothelial-derived relaxing factor
EGF	Epidermal growth factor

egf-α	Tumor necrosis factor
EPCs	Endothelial progenitor cells
ER	Endoplasmic reticulum
ETS	E26 transformation-specific
FACS	Fluorescence-activated cell sorting
FBC	Foreign body capsule
FBGCs	Foreign body giant cells
FBR	Foreign body reaction
FDA	Food and Drug Administration
FG	Fasting glucose
FGF	Fibroblast growth factor
FXIIA	Activated Hageman factor
GDSC	Glutaraldehyde cross-linked collagen
GlcN	D-Glucuronic and D-glucosamine
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GvHD	Graft vs. host disease
H1/H2	Histamine receptor
HA	Hyaluronic acid
HDSC	Hexamethylenediisocyanate
HETE	Hydroxyeicosatetranoic acid
HIF	Hypoxia-inducible factors
HLA	Human leukocyte antigen
HMGB	High-mobility group box chromosomal protein
HRG	Histidine-rich glycoprotein
HSA	Human serum albumin
HSC	Hepatic stellate cells
HSCT	Hematopoietic stem cell transplantation
HUVECs	Human umbilical vein endothelial cells
IAT	Islet auto-transplantation
IBMIR	Instant blood mediated immune reaction
ICOS	Inducible costimulatory
IDE	Investigational device exemption
IFG	Impaired fasting glucose tolerance
IFN	Interferon
IGF	Insulin growth factor
IgG	Immunoglobulin G
IL	Interleukin
IL-R	Interleukin receptor
ILC	Innate lymphoid cells
IND	Investigational new drug
iNOS	Inducible nitric oxide synthase
IVGTT	Intravenous injection of glucose tolerance test
KC	Kupffer cells
KIR	Killer cell immunoglobulin-like receptors
KLF	Kruppel-like factor

LPS	Lipopolysaccharide
LRR	Leucine-rich repeat motifs
LTB_4	Leukotriene B_4
LVAD	Left ventricular assist devices
M1	Classically activated macrophages or pro-inflammatory macrophages
M2	Alternatively activated macrophages or anti-inflammatory/pro-wound healing macrophages
MCP-1	Monocyte chemotactic protein 1
M-CSF	Macrophage colony-stimulating factor
MDP	Monocyte-macrophage DC progenitor
MDSC	Myeloid-derived suppressor cells
MHC	Major histocompatibility complex
MIP	Macrophage inflammatory protein
miR	microRNA
MMP	Matrix metalloprotease
modSLA	Sandblasted hydrophilic nano-rough surface
MoMF	Monocyte-derived macrophage(s)
MPS	Mononuclear phagocyte system
MSCs	Mesenchymal stromal cells
MSFM	Memphis serum-free media
MWCNT	Multi-walled carbon nanotubes
NBD-PE	1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine-N-(7-nitro-2-1,3-benzoxadiazol-4-yl)
NF-kB	Nuclear *factor* kappa
NGF	Neuronal growth factor
NK	Natural killer
NLR	NOD-like receptors
NO	Nitric oxide
OGTT	Oral glucose tolerance test
OPG	Osteoprotegerin
OSM	Oncostatin M
PAMAM	Polyamidoamine
PAMP	Pathogen-associated molecular patterns
PBMA	Poly(butylmethacrylate)
PCA	Procoagulant activity
PCBMA	Poly(carboxybetaine methacrylate)
PCL	Poly(ε-caprolactone)
PDGF	Platelet-derived growth factor
PDMS	Polydimethylsiloxane
PDO	Polydioxanone
PEG	Polyethylene glycol
PGA	Polyglycolide
PI/IRI	Proinsulin to immunoreactive insulin
PIBCA	Polyisobutyl
PIHCA	Polyisohexylcyanoacrylate

PLA	Polylactide
PLGA	Poly(lactic-co-glycolic acid)
PLGA-PLL	Poly(lactic-co-glycolic acid)-poly-L-lysine
PMB	Poly(2-methacryloyloxyethyl phosphorylcholine(MPC)-co-n-butylmethacrylate(BMA)s)
PMNs	Polymorphonuclear leukocytes
POPC	1-Palmitoyl-2-oleoyl phosphatidylcholine
PPAR	Peroxisome proliferator-activated receptor
PRR	Pattern recognition receptor
PTFE	Polytetrafluoroethylene
PU	Polyurethane
PVA	Polyvinyl alcohol
PVA-SPION	Poly(vinyl alcohol)-coated superparamagnetic iron oxide nanoparticles
QD	Quantum dots
RANKL	Receptor activator of nuclear factor kappa-B ligand
RBC	Red blood cells (erythrocytes)
RES	Reticuloendothelial system
RGD	Arginine-glycine-aspartic acid
RLR	RIG-like receptors
ROS	Reactive oxygen species
SIBS	Poly(styrene–isobutylene–styrene) copolymer
SLA/Sr	Sandblasted micro-rough surface containing strontium
SLA	Sandblasted micro-rough surface
SOST	Sclerostin
SRBC	Sheep red blood cells
STZ	Streptozotocin
T1DM	Type 1 diabetes mellitus
TAM	Tumor-associated macrophages
T-cells	Thymocytes
TGF	Transforming growth factor
TIMP	Tissue inhibitor of metalloprotease
TLR	Toll-like receptors
TNF	Tumor necrosis factor
t-PA	Tissue-type plasminogen activator
T-regs	T-regulatory cells
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor
VFH	Vinylidene fluoride-hexafluoropropylene copolymer
Zr-SLA & Zr-modSLA	Zirconium alloy SLA and modSLA surfaces

Chapter 1
Host Response to Implanted Materials and Devices: An Overview

Michelle E. Scarritt, Ricardo Londono, and Stephen F. Badylak

Abstract The host response to implanted materials and devices is influenced not only by the design of the material itself, but also by the local and systemic environment of the host. Much of the early response follows the well-described cascade of events of wound healing from hemostasis to scar formation. An implanted material can positively or negatively modulate this cascade of events, culminating in a constructive remodeling response, a persistent inflammatory response, a foreign body response with encapsulation, or an adaptive immune response. An overview of these events, as well as the influence of biologic versus synthetic materials, is discussed in this chapter.

Keywords Host response • Immune response • Hemostasis • Scar • Leukocyte • Macrophage • Constructive remodeling • Extracellular matrix

1.1 Introduction

The host response to an implanted biomaterial is determined by factors related to both the material itself and the host into which the material is placed. The long-term functional outcome, that is, the ability of the material to perform its intended function, is ultimately determined by the host response.

The evolution of and advances in biomaterials during the past 30–40 years, including the raw materials, device configuration, and manufacturing methods, have focused upon material properties such as degradability, pore size, surface functionality, and mechanical properties, among others. With the exception of studies related to the foreign body reaction (FBR) to nondegradable (e.g., permanent) implants, relatively little attention has been given to the host innate and acquired immune response elicited by these materials following implantation. The present chapter provides an overview of the host response to various categories of biomaterials from both a host-centric and a biomaterials-centric perspective.

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The immediate events following implantation include the adsorption of plasma proteins on the surface of the implant followed by all biologic processes associated with acute inflammation. These processes include the innate immune response to the biomaterial itself, and the response to the unavoidable tissue injury associated with the surgical procedure. Simultaneously, activation of the initial steps of the adaptive immune system occurs with downstream sequelae that either positively or negatively affects implant integration. An overview of the continuum of events associated with the innate and adaptive immune response is depicted in Figs. 1.1 and 1.2.

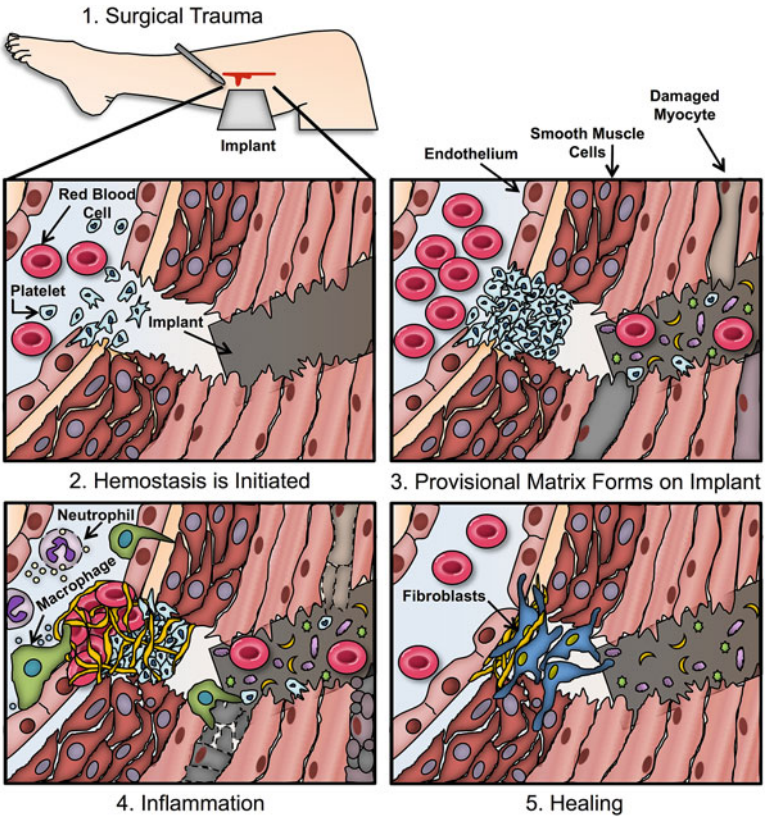

Fig. 1.1 Continuum of events following implantation of a material or device. (1) The surgical procedure inevitably damages the tissue at the implantation site. (2) Vascular damage initiates the coagulation cascade leading to the formation of a platelet-fibrin-red blood cell clot. Vascular damage also facilitates blood-implant interaction. (3) Proteins from the blood and interstitial fluid dynamically adsorb to the implant (Vroman effect). (4) A mileu of cytokines and chemokines are released by activated cells at the implant/injury site. Neutrophils, followed by monocytes and macrophages, are recruited to clear debris. Persistence of leukocytes/macrophages leads to chronic inflammation. (5) Healing is initiated and includes formation of granulation tissue, angiogenesis, and remodeling

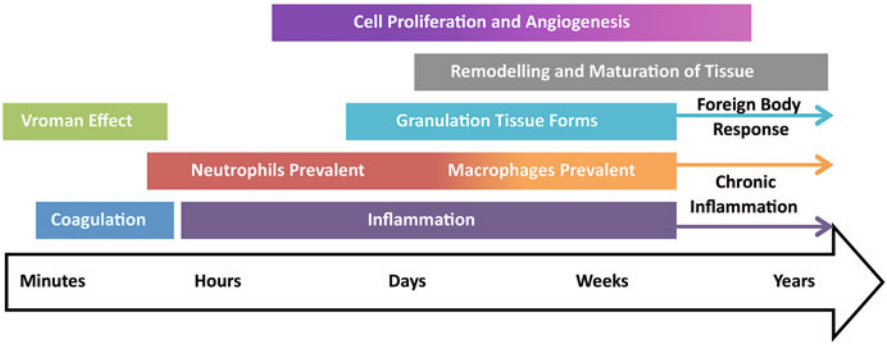

Fig. 1.2 Timeline of the host response following implantation of a material or device. The events that encompass the host reaction to an implant can be grouped according to broad response times. The Vroman effect and coagulation cascade occur within minutes of surgery, while immune cells infiltrate within hours and can persist for years after implantation

1.2 Innate Immune Response to Implanted Materials

Tissue injury following surgical implantation of any biomaterial is associated with well-described processes that include hemostasis, inflammation, and the formation of scar tissue.

Hemostasis—the process of blood clotting—occurs rapidly following injury. Injury to endothelial cells exposes the underlying vascular basement membrane causing platelets to adhere, activate, and initiate the coagulation cascade [1, 2]. As a result, a fibrin-platelet clot forms to prevent or slow further hemorrhage.

The acute inflammatory response is initiated by cytokines and chemokines released from damaged cells [3]. Acute inflammation is marked by an influx of neutrophils followed within 24–48 h by mononuclear macrophages [4]. Activated neutrophils and macrophages have a phagocytic function that includes release of proteolytic enzymes which degrade cellular debris and the extracellular matrix (ECM). In addition to clearing cellular debris, these phagocytes engulf and destroy any bacteria and foreign substances and present antigen peptide fragments to thymocytes (T-cells). The acute inflammatory response normally subsides within 3–5 days. Persistence of polymorphonuclear leukocytes (e.g. neutrophils) is an indication of a chronic-active inflammatory response typically associated with infection or implant toxicity.

The formation of granulation tissue occurs in the later stages of the innate immune response and largely involves the proliferation of fibroblasts and endothelial cells. Fibroblasts create and remodel the extracellular matrix of the granulation tissue by synthesizing and secreting collagen, proteoglycans, and related molecules, while endothelial cells sprout and organize into new blood vessels to supply nutrients to, and remove waste from, the granulation tissue [5].

The presence of multinucleate giant cells at the interface with the implant is an indication of a FBR to the implanted material or device. Foreign body giant cells (FBGCs) form when monocytes and macrophages fuse in an attempt to engulf materials or debris greater than 50–100 μm in size [6]. In the later stages of granulation tissue formation,

activated fibroblasts may produce a fibrous capsule to surround the implant in an attempt to isolate it from the adjacent host tissue. This fibrous capsule will typically reach a steady state and remain as long as the implant is present.

1.3 Adaptive Immune Response to Implanted Materials

Macrophages and dendritic cells may initiate an adaptive immune response through antigen presentation. Dendritic cells may also be drawn to the implant site by recognition of foreign substances. The foreign constituent is typically a pathogen, in which case dendritic cells internalize, process, and present antigens to T-cells via major histocompatibility complex (MHC) molecules. However, particles, ions, or degradation products from implanted materials or devices may also be recognized as foreign by macrophages and dendritic cells [7, 8]. Implantation of a material from an allogeneic or xenogeneic source, especially one that contains cells or cell debris, can exacerbate the host response due to the presence of non-self, foreign epitopes, which also elicit a T-cell mediated response. When a T-cell recognizes an antigen bound by a dendritic cell or macrophage, the T-cell becomes activated.

Subsets of activated CD4+ T-cells, termed helper T-cells, secrete cytokines that regulate inflammation. These helper T-cells can be activated to display pro-inflammatory (Th1) or anti-inflammatory (Th2) secretory profiles [9]. A Th1-mediated immune response is commonly associated with a pro-inflammatory response to xenogenic materials, materials with cytotoxic degradation products, and/or nondegradable synthetic materials, while Th2 responses typically support greater tolerance of the implant [10, 11]. A Th2-like secretory response has been implicated in the gradual development of a FBR [12, 13]. Th2 cells also engage in cross-talk with macrophages and are associated with a regulatory/anti-inflammatory macrophage phenotype (often termed type 2 macrophages (M2), which are discussed in more detail below) [14, 15]. Implantation of a biologic scaffold material derived from porcine small intestinal submucosa (SIS matrix) elicited a Th2 cytokine expression profile, constructive remodeling, and eventual graft acceptance in a mouse model of abdominal wall defect [16, 17]. Clinical implantation of SIS matrix similarly led to a Th2 cytokine secretory profile with no signs of rejection in follow-ups out to 2 years [11]. In a recent study, dendritic cell activation by adhesion to albumin/serum-coated tissue culture plates was associated with a Th2 secretory profile, whereas activation by adhesion to collagen and vitronectin corresponded to a Th1 profile [18]. Thus, this report suggests that the provisional matrix formed by protein adsorption to implanted materials may also influence the adaptive immune response.

1.4 Macrophages and Constructive Remodeling

Macrophages respond to all implanted materials including synthetic materials such as metals, ceramics, and cements as well as naturally occurring materials such as collagen and ECM scaffolds [19]. Macrophages are critical to the fate of an implant.

As previously discussed, macrophages can initiate the adaptive immune response through antigen presentation; however, macrophages are also necessary for debris clearance, resolution of the pro-inflammatory response, and tissue regeneration via constructive remodeling. Constructive remodeling is the process by which implanted materials induce, facilitate, or otherwise support the replacement of injured tissues with new, site-appropriate functional tissue [20]. Constructive remodeling typically occurs when the early innate immune response shifts from a pro-inflammatory environment toward a non-inflammatory, regulatory environment. Similar to helper T-cells, macrophages can be activated toward a pro-inflammatory (M1-like) phenotype or a regulatory (M2-like) constructive phenotype. When activated, pro-inflammatory macrophages produce cytokines and chemokines, such as IL-1β, IL-6, TNFα, and iNOS, and can induce a Th1 inflammatory response. Regulatory macrophages, however, mediate Th2 responses [21]. An M2-like phenotype has been shown to be associated with mitigation of the pro-inflammatory state, constructive remodeling, and immunoregulation [22, 23]. In a study illustrating the importance of macrophages in constructive remodeling, depletion of macrophages from the peripheral blood in a rat model prevented efficient degradation of an implanted biomaterial and thereby inhibited the constructive remodeling response [24]. Considering the importance of macrophages in other processes such as tissue development [25, 26], tissue homeostasis [27, 28], and true tissue regeneration in species such as the axolotyl [29], the macrophage can easily be considered an orchestrator of the host response.

1.5 Host Response to Biologic Versus Synthetic Biomaterials

The clinical outcome of biomaterial-mediated strategies for tissue repair depends, in part, upon a number of biomaterial-related factors including mechanical properties, composition, surface topography, ability to resist infection, and degradability, among others [30, 31]. However, the ultimate determinant of clinical outcome is the host response to the biomaterial itself.

Although the initial phases of the biomaterial-mediated tissue repair process (e.g. iatrogenic injury during implantation, hemostasis, and activation of the innate immune system) are similar regardless of the identity and characteristics of the implanted material, the later phases and clinical outcome of the tissue repair process vary greatly depending on the biomaterial. Differences are likely to be observed as early as the protein adsorption phase, as materials with different surface topography, molecular structure and charge distribution adsorb unique profiles of proteins to their surface. In turn, differences observed in the later phases of the biomaterial-mediated tissue repair process are more obvious, and include the ability of some materials to modulate the innate immune response, recruit stem cells to the injury site, or, at a minimum, provide a compatible microenvironment for such cells, and promote constructive tissue remodeling.

Shortly after implantation, hemostasis and the Vroman effect result in a temporary fibrin-rich matrix that bridges the gap between the implanted material and the adjacent host tissue [5, 32–34]. In the case of degradable biomaterials, this temporary matrix

can serve as a bridge that facilitates cell migration and gradual infiltration into the biomaterial as the degradation process takes place. In the case of nondegradable materials, this temporary matrix serves as an interface between the biomaterial and the host.

As stated above, macrophages play a central role in the process of biomaterial-mediated tissue repair. Biomaterials, which tend to elicit a persistent M1 pro-inflammatory macrophage response, have been associated with clinical outcomes that include scar tissue formation, encapsulation, and seroma formation. In contrast, biomaterials associated with the presence of a predominantly M2 pro-remodeling macrophage phenotype after the M1 response promote clinical outcomes that include stem cell recruitment/proliferation and constructive tissue remodeling [23]. Hence, the macrophage response is an early predictor of the downstream outcome in the biomaterial-mediated tissue repair process. The biomaterial-related factors, which affect and modulate macrophage phenotype, have been the focus of recent studies, and likely will be central to the design of next generation biomaterials [30, 31].

1.5.1 Biologic Versus Synthetic Biomaterials

Synthetic biomaterials can typically be manufactured with great precision. Their mechanical properties can be finely tuned according to specific clinical applications, and their molecular composition can be reliably altered to match desired specifications. However, synthetic biomaterials—particularly nondegradable synthetic biomaterials—tend to produce a persistent pro-inflammatory response after implantation that includes the well-characterized foreign body reaction [35–41]. This inflammatory response usually reaches a steady state and eventually leads to a robust, organized fibrous tissue formation. In contrast, the properties of biomaterials derived from biologic sources are less amenable to fine tuning, modification, and precision manufacturing. Biomaterials derived from decellularized tissues, i.e., the extracellular matrix, vary in structure and composition depending upon the source tissue from which they are derived and the decellularization process used to produce these materials [42]. However, these materials have the ability to promote a pro-remodeling microenvironment including an M2 macrophage phenotype, and when used appropriately, can promote constructive remodeling [22, 43].

Recent investigations attempt to combine the highly tunable and desirable properties of synthetic materials with the ability to promote a "friendlier" host response and immunomodulatory properties of biologic materials [44]. A thorough and long-term characterization of the host response to such hybrid materials has yet to be conducted (Fig. 1.3).

1.5.2 Extracellular Matrix as Biologic Scaffold

The ability of biomaterials derived from the extracellular matrix to promote constructive tissue remodeling can be attributed to both their structure and composition [42]. The ECM is a complex milieu of both structural and functional bioactive molecules. The ECM was once thought to serve the sole purpose of providing form, structural support,

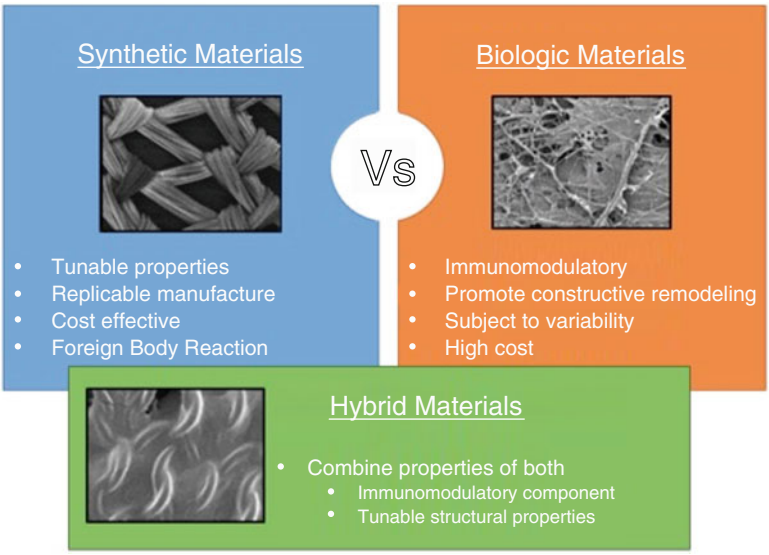

Fig. 1.3 Comparison of natural, synthetic, and hybrid biomaterials. Synthetic materials have highly tunable properties that can be adjusted with precision during manufacture depending on the intended applications. However, synthetic materials do not promote constructive tissue remodeling, and can produce foreign body response that leads to scarring and encapsulation. In contrast, biologic materials can promote constructive remodeling, but their mechanical properties and composition are subject to natural variability, and are less cost effective. Hybrid materials seek to combine the biocompatible properties of biologic materials, with the tunable mechanical properties of synthetic materials

and biomechanical properties to the different tissues. However, the ECM is now known to serve as a reservoir of information in the form of mechanical and biochemical cues that play key roles during development, homeostasis, and response to injury [45–47].

The ECM is secreted by the resident cells of each tissue and organ not only to provide structural support but also to facilitate communication between adjacent cells. In addition, the matrix itself engages in back and forth communication with the resident cells and each is responsive to the other. Hence, the extracellular matrix exists in a state of "dynamic reciprocity" with the local cells and the microenvironment [48].

The main components of the ECM include collagen, fibronectin, laminin, growth factors, cytokines, and glycosaminoglycans (Table 1.1). In addition, molecular fragments of these existing molecules, referred to as matricryptic peptides, in themselves possess biologic properties [46].

As the extracellular matrix undergoes structural and conformational alterations during degradation, exposure and/or release of these cryptic peptides into the microenvironment occurs (Table 1.2). The processes through which this is achieved include enzymatic cleavage, protein multimerization, adsorption of molecules to other ECM components, cell-mediated mechanical deformation, and ECM denaturation. Such properties as yet are not possible to design or manufacture in synthetic biomaterials. More importantly, since these processes are part of natural events, the host response when ECM materials are used as scaffold materials is markedly favorable.

Table 1.1 Main components of the extracellular matrix

Molecule	Composition	Notes	References
Collagen	Triple helix of peptide chains with sequence: Gly-Pro-X or Gly-X-Hyp where x can be a number of amino acids	Most abundant protein in the ECM	[54]
		More than 25 isoforms exist	[55]
		Type I collagen offers tensile strength to different tissues such as tendons and ligaments	[56]
		Type IV collagen has affinity for endothelial cells and is found in vascular structures	[57]
Fibronectin	Glycoprotein composed of two peptide chains joined together at the C terminal via sulfide bonds with protein-binding and cell-binding domains	Exists in both soluble and tissue isoforms	[55]
		Present in submucosal, basement membrane, and interstitial tissues	[58]
		Rich in domains that facilitate adhesion to multiple cell types via integrins	
Laminin	Laminin is a trimeric cross-linked polypeptide that exists in multiple configurations	Found in multiple tissues (particularly within the vasculature) within basement membranes acting as an adhesion molecule for different cell types and ECM	[59]
Glycosaminoglycans	Unbranched polysaccharides composed of repeating disaccharide units	Possesses the ability to retain water and bind to growth factors and cytokines sequestering them	[60]
Growth factors and cytokines	Small proteins (~5–20 kDa)	Growth factor and cytokine release from the ECM is a complex process that relies upon binding affinity, conformational changes, and degradation of the ECM during normal and pathologic processes	[61–63]
Matricryptic peptides	Molecular fragments of parent proteins	Structural and conformational changes in the ECM result in matricryptic peptide exposure, activation, and release into the microenvironment. These changes occur via enzymatic cleavage, protein multimerization, cell-mediated mechanical deformation, and ECM denaturation	[64–68]

Although the composition of the ECM has many common features across tissue types, differences do exist depending on the anatomic structure to which it belongs. For example, the extracellular matrix in tendons and ligaments needs to provide the necessary tensile strength to support and maintain the structure of the body, and hence, it is composed of mostly type I collagen [65]. Similarly, elastin is found in large amounts in compliant and elastic tissues such as the aorta [66]. Both type IV collagen and laminin are found in tissues with a basement membrane component such as urinary bladder and esophagus [67–69]. Therefore, although the molecular composition of the ECM is largely shared across tissues and species, the preferred source tissue from which each naturally occurring biomaterial is prepared for each clinical application has not been determined [20].

Table 1.2 Matricryptic peptides generated via ECM degradation

ECM parent molecule	Matricryptic peptide/site	Function	References
Collagen	C-terminal globular domain of collagen XVII (20 kd)	Angiogenesis inhibitor	[49]
	RGD fragment	Arteriolar vasoactivity	[50]
		Cell adhesion (αvβ3)	[51]
	(Pro-Pro/Hyp-Gly) collagen type I fragments	Cell migration	[52]
			[53]
	C-terminal telopeptide of collagen IIIα	Chemotaxis of progenitor cells	[46]
		Osteogenesis	[45]
	Peptide E1	Wound healing	[54]
	Peptide C2	Cell adhesion	[55]
Fibronectin	120-kd cell-binding domain	Cell migration	[56]
	40-kd gelatin-binding domain	Cell migration	[57]
	N- and C-terminal heparin binding fragments	Cell proliferation inhibition	[58]
	Type III repeat	Inflammatory pathway activation	[59]
	Fibronectin's III1 module	Cell growth and contractility	[60]
Laminin	RGD fragment	Cell adhesion	[61]
	alpha 5 beta 1 gamma1 fragment	Chemotaxis	[62]
		Inflammatory modulation	[63]
Elastin	VGVAPG sites	Cell migration	[64]

Tissue decellularization through which biomaterials composed of ECM are manufactured is typically a chemical, enzymatic, and mechanical process that aims to remove cellular material while preserving the structure and composition of the extracellular matrix. To date, several decellularization protocols have been developed, and the methods of tissue decellularization have been reviewed extensively [70, 71]. While biomaterials that have been properly decellularized have been shown to perform adequately in clinical applications, biomaterials that have been ineffectively decellularized tend to be associated with a persistent pro-inflammatory response and negative clinical outcomes [10, 43, 72]. Other factors that affect the host response to extracellular matrix-derived biomaterials include the age of the animal from which they are derived, post-processing modifications such as chemical crosslinking and solubilization, bacterial and endotoxin contamination, and methods of terminal sterilization [71, 73].

1.6 Host Response to Orthopedic Implants

Biomaterials used for orthopedic applications in the form of screws, plates, wires, rods, and external fixation devices include metals, plastics, and ceramics. Similar to biomaterials used in soft tissue and organ repair applications, the host response to the