Chapter 2
Soft Tissue Response

J.M. Anderson

2.1 Introduction

Soft tissue responses to biomaterials for medical devices are generally viewed from the inflammation and wound healing perspectives and are usually considered as parts of the tissue or cellular host responses to injury. Placement of a biomaterial or medical device in the soft tissue environment involves injection, insertion, or surgical implantation, all of which injure the tissues or organs involved. Early host responses are dynamic and change with time (Table 2.1). It is important to consider this time variable in determining the host response or biocompatibility of a material.

2.2 Types of Response

Four general types of response may occur following the implantation of a biomaterial. These are a minimal response, a chemically induced response, a physically induced response, and cellular/tissue necrosis [1].

A minimal response is generally called fibrous encapsulation and the implant is encapsulated within fibrous tissue containing mainly collagen with a few fibroblasts. At the tissue/implant interface, a one to two cell layer of macrophages and foreign body giant cells is present which constitutes the foreign body reaction.

J.M. Anderson (✉)
Department of Pathology Case Western Reserve University, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106–2622, USA

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Table 2.1 Sequence of Local Events Following Implantation

Injury
Acute Inflammation
Chronic Inflammation
Granulation Tissue
Foreign Body Reaction
Fibrosis

Chemically induced responses may range from an acute, mild inflammatory response to a chronic, severe inflammatory response. These responses may be the result of leaching of biomaterial additives or degradation products.

Physically induced responses are usually the result of the size, shape, porosity, and other geometric factors of the biomaterial or device. The form and topography of the surface of the biomaterial may determine the composition of the foreign body reaction. With biocompatible materials, the composition of the foreign body reaction and the implant site may be controlled by the surface properties of the biomaterial, the form of the implant, and the relationship between the surface area of the biomaterial and the volume of the implant. High surface to volume implants such as fabrics, porous materials, or particulate, will have higher ratios of macrophages and foreign body giant cells at the implant site than will smooth-surface implants, which will have fibrosis as a significant component of the implant site [2–5]. These three general types of responses are generally found with biocompatible materials.

The fourth type of response, i.e., cellular necrosis, is a toxic reaction which leads to cell death. It is generally taken as a sign of the incompatibility of a material and is generally the response to highly toxic additives, residual monomer, or degradation products released from the biomaterial [6]. The similarity between chemically induced responses leading to chronic, severe inflammatory responses and cellular/tissue necrosis should be considered in determining the biocompatibility of a biomaterial.

Mechanical factors and edge effects may modify the response to a biomaterial. Implant motion or micromotion can lead to variations in the fibrous capsule thickness and the composition of the fibrous capsule and the interfacial foreign body reaction. Edges and sharp changes in surface features may lead to a variation in fibrous capsule thickness and the presence of variable concentrations of chronic inflammatory cells, i.e., monocytes and lymphocytes.

Immune and neoplastic responses are specialized responses which are rarely seen with biomaterials and medical devices. Immune responses are generally created by the phagocytosis of particulate by macrophages which biochemically process the material and communicate with lymphocytes to produce the immune response. The metal sensitivity response is a well-known immune response to metallic corrosion products. Neoplastic, i.e., tumor formation, responses are generally considered to be an example of solid state tumorigenesis. Solid state tumorigen-

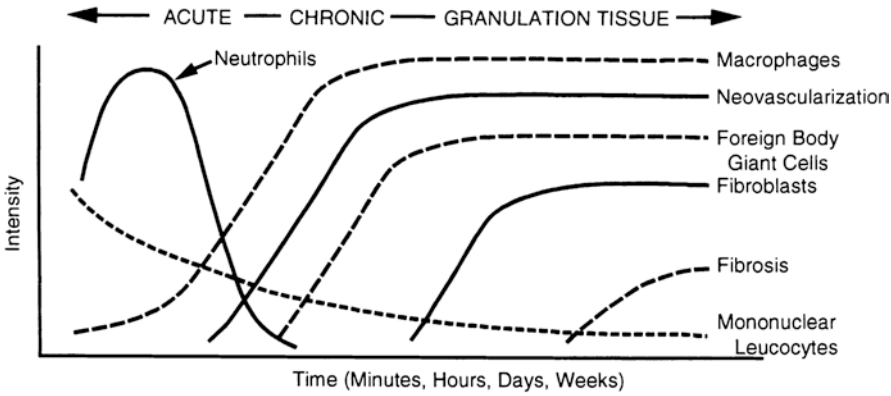

Fig. 2.1 The temporal variation in the acute inflammatory response, chronic inflammatory response, granulation tissue development, and foreign body reaction to implanted biomaterials. The intensity and time variables are dependent upon the extent of injury created in the implantation and the size, shape, topography, and chemical and physical properties of the biomaterial.

esis is generally linked to the extent or degree of fibrous capsule formation and the potential for solid state tumorigenesis is reduced with increasing foreign body reaction.

2.3 Inflammation

Inflammation is defined as the reaction of vascularized living tissue to local injury (Table 2.1) [7, 8]. The size, shape, and intended application of a biomaterial or medical device determine the implantation procedure which in turn determines the extent or degree of initial injury. The size, shape, and chemical and physical properties of the biomaterial may be responsible for variations in the intensity and time duration of the inflammatory and wound healing processes. Figure 2.1 illustrates the temporal sequence of inflammation and wound healing. The inflammatory response is a series of complex reactions involving various types of cells whose implant site concentrations (densities), activities and functions are controlled by various endogenous and autogenous mediators [9]. The predominant cell type present in the inflammatory response varies with the age of the injury, i.e., the time since the implant was inserted. Neutrophils, which are the characteristic cell type of acute inflammation, predominate during the first several days following implantation and are replaced by monocytes as the predominant cell type. Acute inflammation is of relatively short duration, lasting from minutes to days, depending on the extent of injury. The main characteristics of acute inflammation are the exudation of fluid and plasma proteins (edema) and the immigration of leukocytes (predominantly

neutrophils). Following localization of leukocytes at the implant site, phagocytosis and the release of enzymes, reactive oxygen intermediates (ROI), and other agents occur following activation of neutrophils and macrophages. Agents released from activated leukocytes, hydrogen ions (acid), enzymes, ROIs and others, may effect the biodegradation of biomaterials [10, 11]. The major role of the neutrophils in acute inflammation is to phagocytose and destroy microorganisms and foreign material.

Acute inflammation is of relatively short duration, lasting from minutes to days, and is dependent on the extent of injury. As the acute inflammatory response subsides, monocytes and lymphocytes predominate in the implant site and are the characteristic cells of chronic inflammation [7, 8]. Monocytes, migrating from the blood, in the acute and chronic inflammatory responses differentiate into macrophages within the tissue in the implant site. These macrophages will fuse or coalesce into foreign body giant cells (Figure2.1). Macrophages and foreign body giant cells are prominent at the tissue/implant interface, even with biocompatible materials. In Figure 2.1, the intensity and time variables are dependent upon the extent of injury created in the implantation and the size, shape, topography, and chemical and physical properties of the biomaterial.

In the phagocytosis process, recognition and attachment of neutrophils and monocytes/macrophages are expedited when the biomaterial is coated by naturally occurring blood serum factors called opsonins. The two major opsonins are IgG and the complement-activated fragment C3b. Both of these plasma-derived proteins are known to adsorb to biomaterials and neutrophils and macrophages have corresponding cell membrane receptors for these opsonization proteins. These receptors may also play a role in the activation of the attached neutrophils, monocytes, macrophages, or foreign body giant cells. Small particles, of the order of 5 μm in largest dimension, may undergo the phagocytosis or engulfment process by neutrophils, monocytes/macrophages, or specialized cells in the reticuloendothelial system (liver, spleen, etc.). Medical devices with surface areas of biomaterial many times greater than the size of the cell may stimulate frustrated phagocytosis. Frustrated phagocytosis does not involve engulfment of the biomaterial but rather the extracellular release of leukocyte products in an attempt to degrade or destroy the biomaterial [12]. Macrophages and foreign body giant cells adherent to the surface of the biomaterial may undergo frustrated phagocytosis with the release of hydrogen ion (acid) enzymes, ROIs, and others. Little is known regarding the extent or time period of frustrated phagocytosis and its dependence on the chemical and physical properties of the biomaterial.

The cells and components of vascularized connective tissue (Table 2.2) are involved in the inflammatory and wound healing responses. Thus, injury to soft tissues involves the specific types of cells which constitute the organ or tissue as well as the cells and components of vascularized connective tissue. Vascularized connective tissue can be viewed as the general network which holds together specific cell types in unique three-dimensional patterns to constitute organs or tissues.

While it is convenient to consider blood-material interactions separately from tissue-material interactions, it must be emphasized that blood-material interactions

Table 2.2 Cells and Components of Vascularized Connective Tissue

Intravascular (blood) cells	Blood plasma proteins
Erythrocytes (RBC)	Coagulative Proteins
Neutrophils	Complement Proteins
Monocytes	Albumin
Eosinophils	Fibrinogen
Lymphocytes	Gamma-Globulins
Basophils	Others
Platelets	Extracellular matrix components
Connective tissue cells	Collagens
Mast Cells	Elastin
Fibroblasts	Proteoglycans
Macrophages	Fibronectin
Lymphocytes	Laminin

and the inflammatory response are intimately linked and, in fact, early responses to injury involve mainly blood and blood vessels. Therefore, both cellular and humoral elements, i.e., plasma proteins, etc., are considered as cells and components of vascularized connective tissue.

2.4 Wound Healing and Fibrosis

The wound healing response is initiated by the action of monocytes and macrophages, followed by proliferation of fibroblasts and vascular endothelial cells, i.e., capillaries, at the implant site. The proliferation of fibroblasts and the formation of capillaries constitute granulation tissue. Modified fibroblasts, i.e., myofibroblasts, which have contractile properties which assist in wound site closure are transiently present in granulation tissue. As fibroblasts predominate over macrophages in the healing response, collagens and other extracellular matrix molecules are deposited in the implant site. The extent of the wound healing response is generally dependent on the extent or degree of injury or defect created by the implantation procedure. Wound healing progresses by primary union (or first intention) if the healing is clean such as a surgical incision in which the wound edges have been approximated by surgical sutures, clips, or staples. Healing under these conditions occurs with a minimal loss of tissue. Wound healing by secondary union (or secondary intention) occurs when there is a large tissue defect that must be filled or there has been an extensive loss of cells and tissue. In wound healing by second intention, regeneration of specific organ or tissue cells cannot completely reconstitute the original architecture and more granulation tissue is formed resulting in larger areas of fibrosis or scar formation. Thus, the surgical procedure to create the implant site may influence the extent or degree of the wound healing response.

The end-stage healing response to biomaterials and medical devices is generally fibrous encapsulation by collagenous fibrous tissue. This has been previously described as the minimal response. In the minimal response, the tissue/implant interface has a layer of macrophages and foreign body giant cells, i.e., foreign body reaction, on the surface of the biomaterial and this is surrounded or encapsulated by a fibrous capsule which is composed of collagen, proteoglycans, and other extracellular matrix molecules. Fibroblasts may be present in the fibrous capsule.

2.5 Repair of Implant Sites

Repair of implant sites involves two distinct processes: regeneration, which is the replacement of injured tissue by parenchymal cells of the same type, or replacement by fibrous connective tissue that forms a capsule [7]. These processes are generally controlled by either (i) the proliferative capacity of the cells in the tissue or organ receiving the implant and the extent of injury as it relates to tissue destruction or (ii) persistence of the tissue framework of the implant site. The regenerative capacity of cells permits their classification into three groups: labile, stable (or expanding), and permanent (or static) cells. Labile cells continue to proliferate throughout life, stable cells retain this capacity but do not normally replicate, and permanent cells cannot reproduce themselves after birth of the host.

Perfect repair, with restitution of normal structure, theoretically occurs only in tissues consisting of stable and labile cells, whereas all injuries to soft tissues composed of permanent cells may give rise to fibrosis and fibrous capsule formation with very little restitution of the normal tissue or organ structure. Tissues composed of permanent cells (e.g., nerve cells, skeletal muscle cells, and cardiac muscle cells) most commonly undergo an organization of the inflammatory exudate, leading to fibrosis. Tissues composed of stable cells (e.g., parenchymal cells of the liver, kidney, and pancreas), mesenchymal cells (e.g., fibroblasts, smooth muscle cells, osteoblasts, and chondroblasts), and vascular endothelial and labile cells (e.g., epithelial cells and lymphoid and hematopoietic cells) may also follow this pathway to fibrosis or may undergo resolution of the inflammatory exudate, leading to restitution of the normal tissue structure. The condition of the underlying framework or supporting stroma of the parenchymal cells following an injury plays an important role in the restoration of normal tissue structure. Retention of the framework may lead to restitution of the normal tissue structure, whereas destruction of the framework most commonly leads to fibrosis. It is important to consider the species-dependent nature of the regenerative capacity of cells. For example, cells from the same organ or tissue but from different species may exhibit different regenerative capacities and/or connective tissue repair. An example of species differences in cell proliferation and regeneration is the endothelialization process, proliferation of endothelial cells, on the luminal surface of vascular grafts which does not occur in humans but does occur in other mammals including other primates.

Following injury, cells may undergo adaptations of growth and differentiation. Important cellular adaptations are atrophy (decrease in cell size or function), hypertrophy (increase in cell size), hyperplasia (increase in cell number), and metaplasia (change in cell type). Hyperplasia of smooth muscle cells at blood vessel/vascular graft anastomoses may lead to failure of the graft by stenosis or occlusion, i.e., narrowing of the lumen, and thrombosis. Other adaptations include a change in which cells stop producing one family of proteins and start producing another (phenotypic change) or begin a marked overproduction of protein. This may be the case in cells producing various types of collagens and extracellular matrix proteins in chronic inflammation and fibrosis. Causes of atrophy may include decreased workload (e.g., stress-shielding by implants), as well as diminished blood supply and inadequate nutrition (e.g., fibrous capsules surrounding implants).

Local and system factors may play a role in the wound healing response to biomaterials or implants. Local factors include the site (tissue or organ) of implantation, the adequacy of blood supply, and the potential for infection. Systemic factors may include nutrition, hematologic and immunologic derangements, glucocortical steroids, and pre-existing diseases such as atherosclerosis, diabetes, and infection.

2.6 Summary

Inflammation, wound healing, foreign body response, and repair of implant sites are usually considered components of the general soft tissue response to biomaterials or medical devices. The extent or degree and temporal variations in these responses are dictated by the inherent biocompatibility characteristics of the biomaterial or medical device. Factors which may play a role in the soft tissue response include the size, shape, topography, and chemical and physical properties of the biomaterial. As the implantation procedure involves injury to vascularized connective tissue, blood responses and interactions may play a role in the general soft tissue response. The extent, degree or type of soft tissue response is generally considered to be tissue-specific, organ-specific, and species-specific. Thus, a given biomaterial may be considered to be biocompatible in one shape or form but not in another and in one tissue but not in another depending on the given application.

Additional Reading

Black, J. (1992) *Biological Performance of Materials - Fundamentals of Biocompatibility*, 2nd edn, Marcel Dekker, New York.

This volume is an excellent tutorial text for the engineer/biomaterial scientist/biologist/and others who have little or no knowledge in the area of biomaterials and medical devices. The text is divided into four parts: General considerations, material response: function and degradation of materials *in vivo*, host response:

biological effects of implants, and methods of test for biological performance. The fourth part, Methods of test for biological performance, is unique to biomaterials texts and provides the reader with *in vitro* and *in vivo* test models and methods as well as perspectives on the design, selection, standardization, and regulation of implant materials.

Cohen, I.K., Diegelmann, R.F. and Lindblad, W.J. (eds) (1992) *Wound Healing: Biochemical and Clinical Aspects*, W.B. Saunders Co., Philadelphia.

This is an edited volume containing 35 chapters. The volume addresses the following areas: Biological processes involved in wound healing (6 chapters), structural and regulatory components of wound healing (7 chapters), factors affecting tissue repair (7 chapters), repair of specific tissues (7 chapters), and clinical management of healing tissues (7 chapters). This is an excellent volume which provides an up-to-date and in-depth perspective of various aspects of wound healing. The references lists provided at the end of each chapter are extensive. The strength of the volume is its biological perspective and little is provided on biomaterials. The chapter by Frederick Grinnell on cell adhesion does offer a biomaterial perspective.

Gallin, J.A., Goldstein, I.M. and Snyderman, R. (eds) (1992) *Inflammation: Basic Principles and Clinical Correlates*, 2nd ed, Raven Press, New York.

This is an edited volume containing 58 chapters by individual authors. The volume is divided in the following areas: Soluble components of inflammation (10 chapters), cytokines (5 chapters), cellular components of inflammation (21 chapters), responses to inflammation (3 chapters), clinical correlates (13 chapters), and pharmacologic modulation of inflammation (4 chapters). Each chapter is a critical, in-depth review of the indicated subject and the references are extensive. This is an excellent volume for those wanting an in-depth overview of the inflammatory process and its components. No information is provided on biomaterial/inflammation interactions.

Greco, R.S. (ed.) (1994) *Implantation Biology: The Host Response and Biomedical Devices*, CRC Press, Boca Raton.

This is an edited volume containing 23 chapters. Three chapters deal with biomaterials in general, 6 chapters address specific blood and tissue interactions with biomaterials, 10 chapters address the use of biomaterials in specific surgical disciplines, and 3 chapters address tissue engineering and genetic manipulation of cells. The reference list for each chapter is extensive. This is an excellent overview of how biomaterials interact with the host and the specific use of biomaterials in indicated applications.

Harker, L.A., Ratner, B.D. and Didisheim, P. (eds) (1993) *Cardiovascular Biomaterials and Biocompatibility: A Guide to the Study of Blood-Tissue-Material Interactions, Cardiovascular Pathology*, **2** (3 Suppl), 1S–224S.

This is the third edition of a standard National Institutes of Health reference previously entitled *Guidelines for Blood-Material Interactions - Report of the National Heart, Lung, and blood Institute Working Group.* The volume contains 20 chapters and 3 appendices. The chapters address the following areas: Pathophysiologic mechanisms, materials and their physicochemical characterization, safety testing of materials and devices, and blood-vessel-material interactions.

The appendices are entitled: NIH Primary Reference Materials, International Standards for Biological Evaluation of Medical Devices, and Blood Analog Fluid for Medical Device Evaluation. This volume provides an in-depth perspective on cardiovascular materials and state-of-the-art information is provided regarding biomaterials. This is an excellent review, however, the editors limited the length and number of references for each chapter due to space considerations.

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