Host reactions to biomaterials

- All implants interact to some extent with the tissue environment in which they are placed.

<table>
<thead>
<tr>
<th>Biomaterial–Tissue Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Effect of the implant on the host</td>
</tr>
<tr>
<td>1. Local</td>
</tr>
<tr>
<td>a. Blood–material interactions</td>
</tr>
<tr>
<td>Protein absorption</td>
</tr>
<tr>
<td>Coagulation</td>
</tr>
<tr>
<td>Fibrinolysis</td>
</tr>
<tr>
<td>Platelet adhesion, activation, release</td>
</tr>
<tr>
<td>Complement activation</td>
</tr>
<tr>
<td>Leukocyte adhesion/activation</td>
</tr>
<tr>
<td>Hemolysis</td>
</tr>
<tr>
<td>b. Toxicity</td>
</tr>
<tr>
<td>c. Modification of normal healing</td>
</tr>
<tr>
<td>Encapsulation</td>
</tr>
<tr>
<td>Foreign body reaction</td>
</tr>
<tr>
<td>Pannus formation</td>
</tr>
<tr>
<td>d. Infection</td>
</tr>
<tr>
<td>e. Tumorigenesis</td>
</tr>
<tr>
<td>2. Systemic and remote</td>
</tr>
<tr>
<td>a. Embolization</td>
</tr>
<tr>
<td>Thrombus</td>
</tr>
<tr>
<td>Biomaterial</td>
</tr>
<tr>
<td>b. Hypersensitivity</td>
</tr>
<tr>
<td>c. Elevation of implant elements in blood</td>
</tr>
<tr>
<td>d. Lymphatic particle transport</td>
</tr>
<tr>
<td>B. Effect of the host on the implant</td>
</tr>
<tr>
<td>1. Physical–mechanical effects</td>
</tr>
<tr>
<td>a. Abrasive wear</td>
</tr>
<tr>
<td>b. Fatigue</td>
</tr>
<tr>
<td>c. Stress-corrosion cracking</td>
</tr>
<tr>
<td>d. Corrosion</td>
</tr>
<tr>
<td>e. Degeneration and dissolution</td>
</tr>
<tr>
<td>2. Biological effects</td>
</tr>
<tr>
<td>a. Absorption of substances from tissues</td>
</tr>
<tr>
<td>b. Enzymatic degradation</td>
</tr>
<tr>
<td>c. Calcification</td>
</tr>
</tbody>
</table>
Host reactions to biomaterials

- Complications are largely based on biomaterial-tissue interactions that include both:
  - effects of the implant on the host tissue and
  - effects of the host on the implant.
    - Inflammation
    - Foreign body reaction (FBR)
    - Immunological response
    - Systemic toxicity
    - Blood-surface interactions
    - Thrombosis
    - Device-related infections
    - Tumorigenesis
Host reactions to biomaterials

- Placing a biomaterial in the in vivo environment involves: injection, insertion, or surgical implantation, all of which injure the tissues or organs involved.

- The body responds to reestablish homeostasis.

- The degree to which the homeostatic mechanisms are perturbed determine the biocompatibility of a biomaterial.

- The host reaction can be:
  - Tissue-dependent,
  - Organ-dependent and
  - Species-dependent
The immune system has evolved to protect us from pathogens. Some, such as viruses, infect individual cells; others, including many bacteria, divide extracellularly within tissues or the body cavities.

The cells which mediate immunity include lymphocytes and phagocytes. Lymphocytes recognize antigens on pathogens. Phagocytes internalize pathogens and degrade them.

An immune response consists of two phases. In the first phase, antigen activates specific lymphocytes that recognize it; in the effector phase, these lymphocytes coordinate an immune response that eliminates the source of the antigens.

Specificity and memory are two essential features of adaptive immune responses. The immune system mounts a more effective response on second and subsequent encounters with a particular antigen.
Immunology-Basics

- Lymphocytes have specialized functions. B cells make antibodies; cytotoxic T cells kill virally infected cells; helper T cells coordinate the immune response by direct cell–cell interactions and the release of cytokines, which help B cells to make antibody.

- Antigens are molecules which are recognized by receptors on lymphocytes. B lymphocytes usually recognize intact antigen molecules, while T lymphocytes recognize antigen fragments on the surface of other cells.

- Clonal selection involves recognition of antigen by a particular lymphocyte; this leads to clonal expansion and differentiation to effector and memory cells.

- The immune system may break down. This can lead to immunodeficiency or hypersensitivity diseases or to autoimmune diseases.
The IS (immune system) acts to protect from the constant exposure to pathogenic agents:
- Bacteria
- Fungi
- Viruses
- Cancerous cells
- Parasites

The IS must recognize a multitude of structures and differentiate from "self".

The IS is a complex system/network of
- Proteins
- Cells and
- Distinct organs
Immunology-Basics

- The exterior defence of the body presents an effective barrier to most organisms.

- Very few infectious agents can penetrate intakt skin.

- Infections may occur via the gastrointestinal or urogenital tracts, nasopharynx and lung.

- Some can only infect the body if they enter the blood directly (malaria, hepatitis B, HIV).
Immunology-Basics

- Any immune response involves, firstly, recognition of the pathogen, and secondly, a reaction to eliminate it.

- The different types of immune response fall into two categories:
  - Innate (or non-adaptive) immune response (IR) and
  - Adaptive immune response

- In contrast to the innate IR the adaptive IR is:
  - Highly specific.
  - Improves the response with each successive exposure to the same agent (e.g. Life-long immunity after diphtheria-vaccination).
  - Is primarily produced by leucocytes.
Components of the immune system

<table>
<thead>
<tr>
<th>cell</th>
<th>lymphocytes</th>
<th>leucocytes</th>
<th>auxiliary cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B cell</td>
<td>T cell</td>
<td>tissue cells</td>
</tr>
<tr>
<td></td>
<td>large granular lymphocyte</td>
<td>mononuclear phagocyte</td>
<td>mast cell</td>
</tr>
<tr>
<td></td>
<td>phagocytes</td>
<td>neutrophil</td>
<td>basophil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>eosinophil</td>
<td>platelets</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>tyrosine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>interferons</td>
</tr>
</tbody>
</table>

**Fig. 1.4** The principal components of the immune system are shown, indicating which cells produce which soluble mediators. Complement is made primarily by the liver, although there is some synthesis by mononuclear phagocytes. Note that each cell produces and secretes only a particular set of cytokines or inflammatory mediators.
Hematopoiesis: all the cells in the blood develop from common precursor cells (pluripotent stem cells).
Immunology-Basics

- Phagocytes:
  - Mononuclear phagocytes:
    - Derived from the bone marrow.
    - Migrate into the tissues where they develop into tissue macrophages.
    - Engulf particles and infectious agents, internalize and destroy them.
    - Very effective in presenting antigens to T-lymphocytes.
  - Polymorphnuclear neutrophils:
    - Monocyte-lineage
    - Also called neutrophils or PMN
    - Majority of the blood leucocyte
    - Migrate into the tissue particularly at sites of inflammation.
    - Short-lived (engulf material, destroy it, and then die).
Immunology-Basics

- Lymphocytes occur as two major types which are responsible for specific recognition of antigens:
  - **B-cells**
    - Each B cells encode a surface receptor specific for a particular antigen.
    - After recognition of its specific antigen, the B-cell multiply and differentiate into a plasma cell, which produce large amounts of the receptor in a soluble form that can be secreted (antibody).
    - The antibodies are large glyko-proteins found in the blood and tissue fluids
  - **T-cells**
Immunology-Basics

- **T-cells**
  - Recognize antigens when they are presented by MHC molecules (major histocompatibility complex).
  - They do this via their TCR (T cell antigen receptor)
  - Influence other cells by:
    - Release of cytokines
    - Direct cell-cell interaction
Immunology-Basics

- **T-cells**: There are several types
  - **Type-1 T-helper cells** \((TH^1)\): interact with phagocytes and help them to destroy interacelluler pathogens.
  - **Type-2 T-helper cells** \((TH^2)\): interact with B-cells and help them to divide, differentiate and make antibody.
  - **Cytotoxic T-cells** \((Tc)\): is responsible for destroying host cells infected by viruses or other intracellular pathogens.
Immunology-Basics

- Cytotoxic cells:
  - recognize and destroy other cells that have become infected:
    - Tc cells (especially important)
    - NK cells (natural killer cell or LGL-large granular lymphocytes):
      - Recognize surface changes on a variety of tumor cells (loss of MHC molecules) and virally infected cells.
    - Eosinophils:
      - Engage and damage large extracellular parasites (e.g. Schistosomes: tropic worms).
Immunology-Basics

- **Auxiliary cells**: A number of cells mediate inflammation; attract leucocytes and release soluble mediators of immunity towards a site of infection.

  - **Basophils and mast cells**:
    - Contain granules filled with mediators that produce inflammation; they are released when the cells are triggered.
    - Mast cells lie close to blood vessels in all tissues.
    - Basophils are functionally similar but are mobile.

  - **Platelets**:
    - Can also release inflammatory mediators when activated during thrombogenesis or by antigen-antibody complexes.
Immunology-Basics

- A wide variety of soluble mediator molecules are involved in the development of immune response:
  
  - C-reactive protein:
    - bind the C-molecule of pneumococci thereby promoting their uptake by phagocytes.
  
  - Complement system
  
  - Cytokines
  
  - Antibodies
Complement system:
- System of about 20 serum proteins controlling inflammation.
- „Opsoninzation“ of microorganisms for uptake by phagocytes.
- Attraction of phagocytes to the site of infection (Chemotaxis).
- Increase of blood flow and permeability of capillaries to plasma molecules.
- Damage to plasma membrane on Gram-negative bacteria and enveloped viruses.
- Release of further inflammatory mediators from mast cells.
Immunology-Basics

- Cytokines: Glycoproteins signaling between lymphocytes, phagocytes and other cells of the body:
  - Interferons (IFNs):
    produced by virally infected cells (IFN-α, -β) or certain activated T-cells (IFN-γ).

IFNs induce a state of antiviral resistance in uninfected cells; are produced early in infection.
Cytokines (cont.):

- Interleukines (IL-1 to IL-22):
  - Large group of cytokines produced mainly by T-cells (some are also produced by other cells).
  - They have a variety of functions, but most of them are involved in directing other cells to divide or differentiate.

- Colony-stimulating factors (CSFs):
  - Involved in directing the division and differentiation of precursor cells. E.g. M-CSF promotes development of monocytes in bone marrow and macrophages in tissues.

- Chemokines:
  - Large group of chemotactic cytokines directing movement of cells around the body (e.g. from blood into the tissue).

- Other cytokines: TNF$\alpha$, TNF$\beta$, TGF$\beta$ having a variety of functions; mediating inflammation and cytotoxic reactions.
Chemotaxis:

Chemokines activate the circulating cells causing them to bind to the endothelium and initiating leukocyte migration across the endothelium.

In the tissue the attracted cell will migrate towards the site of infection by chemical attraction.
Antibody:
- Also called immunoglobulins (Ig).
- Group of serum molecules produced by B-cells.
- Each Ig can bind specifically to just one antigen via the F_{ab} portion.
- The F_{c} portion interacts with other elements of the immune system (phagocytes, complement molecules).
- Neutrophils, macrophages and other mononuclear phagocytes have F_{c} receptors on their surface.
Immunology-Basics

- Antigens:

Original term for any molecule that induce B-cells to produce a specific antibody (antibody generator).

Each antibody binds to restricted part of the antigen (called the „epitop“).

The antigen is the initiator and driving force for all adaptive immune response.
Immunology-Basics

- T cells also recognize antigens:

  but they recognize antigens originating from within cells that are presented at the surface of the host cell as small polypeptide fragments.

  The antigens are presented by MHC molecules (major histocompatibility complex).
Clonal selection:

Each lymphocyte (B- or T-cell) is genetically programmed to recognize only one particular antigen.

The antigens selects for and generates specific clones of its own antigen-binding cells.

The immune system generates antibodies (and T-cell receptors) that can recognize an enormous range of antigens; many will never be used.
Phagocytosis:

Phagocytic cells bind to bacteria/cells "opsonized" by complement factor C3b, antibody or antibody and C3b.

Engulfment by extending pseudopodia and formation of a phagosom.

Lysosomes release enzymes into the phagosome to digest the content.
Host reactions to biomaterials

● Inflammation:
  – Is a reaction of vascularized living tissue to local injury.
  – Serves to:
    • absorb,
    • neutralize,
    • dilute, or
    • wall off the injurious agent or process.
  – In addition, it induces a series of events to heal and reconstitute the implant site though replacement of the injured tissue by regeneration of native parenchymal cells, formation of fibroblastic scar tissue or a combination of these two processes.
Host reactions to biomaterials

- Immediately following injury there are changes in vascular flow and permeability.

- Fluids, proteins and blood cells escape from the vascular system into the injured tissue = „exudation“.

- Regardless of the tissue or organ into which a biomaterial is implanted, the initial inflammatory response is activated by injury to vascularized connective tissue.
Host reactions to biomaterials

- Blood and its components are involved in the initial inflammatory responses, blood clot formation and/or thrombosis also occur.

- Blood coagulation and thrombosis may be influenced by other mechanisms:
  - The extrinsic and intrinsic coagulation system
  - The complement system
  - The fibrinolytic system
  - The kinin-generating system
  - Platelets
Host reactions to biomaterials

- The predominant cell type present in the inflammatory response varies with the age of the injury.

  - Neutrophils predominate during the first several days.
    - Neutrophils are short-lived, disintegrate and disappear after 24-48h.
  - Than they are replaced by monocytes.
    - Following emigration from the vasculature, monocytes differentiate into macrophages (long-lived response; up to months).
Host reactions to biomaterials

- The size, shape, and chemical and physical properties of the biomaterial may be responsible for variations in the intensity and duration of the inflammatory or wound healing process.

- Biochemical mediators of inflammation are quickly inactivated, suggesting that their action is local.

- Lysosomal proteases and oxygen-derived radicals are also important in the degradation of biomaterials.
Host reactions to biomaterials

- Acute inflammation:
  - Is of relative short duration (minutes to days).
  - The main characteristics are:
    - Exudation of fluid and plasma proteins (edema)
    - Emigration of leucocytes (predominately neutrophils).
  - Leucocyte emigration is assisted by „adhesion molecules“ present on leucocytes and endothelial surfaces.
Host reactions to biomaterials

- The major role of neutrophils in acute inflammation is to phagocytose microrganisms and foreign material.

- The process of recognition and attachment is enhanced when the injurious material is coated by naturally occuring serum factors ("opsonins").
  - E.g.: IgG, C3b (also known to adsorb to biomaterials)

- Biomaterials are not generally phagocytosed by neutrophils or macrophages (most biomats are too big a "mouthfull" for the cells).

- But: instead "frustrated phagocytosis": release of leucocyte products occur in an attempt to degrade the biomaterial.
Host reactions to biomaterials

- Chronic inflammation:
  - Is histologically less uniform than acute inflammation.
  - Characterized by the presence of macrophages, monocytes, and lymphocytes, with the proliferation of blood vessels and connective tissue.
  - The chemical and physical properties of the biomaterial may lead to prolonged chronic inflammation.
  - Motion in the implant site by the biomaterial may also produce prolonged chronic inflammation.
Host reactions to biomaterials

- Monocytes and macrophages belong to the MPS (mononuclear phagocytosis system), also called RES (reticuloendothelial system)

- Consists of cells in the:
  - Bone marrow,
  - Peripheral blood, and
  - Specialized tissues

<table>
<thead>
<tr>
<th>TABLE 4</th>
<th>Tissues and Cells of MPS and RES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissues</td>
<td>Cells</td>
</tr>
<tr>
<td>Implant sites</td>
<td>Inflammatory macrophages</td>
</tr>
<tr>
<td>Liver</td>
<td>Kupffer cells</td>
</tr>
<tr>
<td>Lung</td>
<td>Alveolar macrophages</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>Histiocytes</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Macrophages</td>
</tr>
<tr>
<td>Spleen and lymph nodes</td>
<td>Fixed and free macrophages</td>
</tr>
<tr>
<td>Serous cavities</td>
<td>Pleural and peritoneal macrophages</td>
</tr>
<tr>
<td>Nervous system</td>
<td>Microglial cells</td>
</tr>
<tr>
<td>Bone</td>
<td>Osteoclasts</td>
</tr>
<tr>
<td>Skin</td>
<td>Langerhans’ cells</td>
</tr>
<tr>
<td>Lymphoid tissue</td>
<td>Dendritic cells</td>
</tr>
</tbody>
</table>
Host reactions to biomaterials

- These cells (MPS) may be responsible for systemic effects in organs and tissues secondary to the release of components or products from implants:
  - Corrosion products
  - Wear debris
  - Degradation products

- The macrophage produces a great number of biologically active products:
  - Neutral proteases
  - Chemotactic factors
  - Arachidon acid metabolites
  - Reactive oxygen metabolites
  - Complement components
  - Coagulation factors
  - Growth promoting factors
  - Cytokines
Host reactions to biomaterials

- Granulation tissue:
  - Within one day the healing response is initiated by the action of monocytes and macrophages.
  - Fibroblasts and vascular endothelial cells proliferate and begin to form granulation tissue (specialized type of tissue that is the hallmark of healing inflammation).
  - New small blood vessels are formed by budding or sprouting of preexisting vessels (neovascularization or angiogenesis).
  - Fibroblast proliferate, synthesize collagen and proteoglycans.
  - Some fibroblasts differentiate into smooth muscle tissue mediating wound contraction
Host reactions to biomaterials

- Foreign body reaction is composed of foreign body giant cells and the components of granulation tissue.

- Foreign body giant cells are formed by the fusion of monocytes and macrophages in an attempt to phagocytose material:

- The form and topography of the surface of the biomaterial determines the composition of the foreign body reaction.
Host reactions to biomaterials

- Flat and smooth surfaces (breast prostheses) have a foreign body reaction composed of a layer of macrophages one or two cells in thickness.
- Rel. rough surfaces (Teflon vascular prostheses): macrophages and foreign body giant cells at the surface.

- The foreign body reaction may persist at the tissue-implant interface for the lifetime of the implant.
- It is unknown if the foreign body reaction cells remain activated, releasing their lysosomal constitutes, or become quiescent.
- Generally, fibrosis (fibrous encapsulation) surrounds the biomaterial or implant with its interfacial foreign body reaction, isolating it from the local tissue environment.
Host reactions to biomaterials

- Fibrosis and fibrous encapsulation:
  - The end-step of healing response to biomaterials is generally fibrosis or fibrous encapsulation.
    - Exception: porous material inoculated with parenchymal cells or porous materials implanted into bone.
  - Repair of implant site can involve two distinct processes:
    - Regeneration: replacement of parenchymal tissue by parenchymal cells of the same type.
    - Replacement by connective tissue that constitutes the fibrous capsule.
Host reactions to biomaterials

- Tissues with static cells (little/no potential to reproduce after birth) give rise to fibrosis and fibrous capsule formation.
  - E.g.: nerve cells, skeletal and cardiac muscle cells

- Tissues consisting of cells with potential to reproduce may follow the pathway to fibrosis or may regenerate.
  - E.g.: parenchymal cells of liver, kidney, pancreas; mesenchymal cells (fibroblast); vascular endothelial cells; epithelial cells; lymphoid and hematopoietic cells.

- Regeneration capacity is species dependent.
  - Cells from the same organ/tissue but from different species may exhibit different regenerative capacities.
Host reactions to biomaterials

- Following injury many cells/tissues undergo adaption of growth and differentiation:
  - Atrophy (decrease in cell size and function)
  - Hypertrophy (increase in cell size)
  - Hyperplasia (increase in cell number)
  - Metaplasia (change in cell type)
  - Altered gene expression

- Local and systemic factors play a role in the wound healing response:
  - Local: tissue/organ of implantation, adequacy of blood supply, potential of infection
  - Systemic: nutrition, glucocortical steroids, preexisting disease (atherosclerosis, diabetes, infection,..)