BIOCOMPATIBILITY

Ability of biomaterials / prostheses / or medical devices to perform with an appropriate host response in a specific application.

The evaluation of biological responses on biomaterials / medical devices / prostheses to determine its performance as intended that present no significant harm to patients or users by evaluating conditions which simulates clinical use.
Tissue Responses to Biomaterials

1. Injury
2. Blood material interaction
3. Provisional matrix formation
4. Acute & chronic inflammations
5. Granulation tissues
6. Foreign body reaction
7. Fibrosis/fibrous capsule development
1. INJURY

Subsequent perturbation of homeostatic mechanisms that lead to cellular cascades of wound healing

Factors affecting injury response:
- Extent of injury
- Loss of basement membrane structures
- Blood-material interactions and provisional matrix formation
- Degree of cellular necrosis
- Extent of inflammatory response

Normal injury: Within 2 to 3 weeks following implantation
2. BLOOD MATERIAL INTERACTION

Inflammatory response (3 – 6 months) is activated by injury to vascularized connective tissues, followed by thrombus formation.

Fluid, proteins, and blood cells escape from the vascular system into the injured tissue in a process called **exudation**.

**Thrombus formation:**

- Activation of extrinsic and intrinsic coagulation systems
- Complement system
- Activation of fibrinolytic system
- Activation of kinin-generating system
- Platelet activation
2. BLOOD MATERIAL INTERACTION

Cells and components of vascularized connective tissues

<table>
<thead>
<tr>
<th>Intravascular (blood) cells</th>
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</thead>
<tbody>
<tr>
<td>Erythrocytes (RBC)</td>
</tr>
<tr>
<td>Neutrophils</td>
</tr>
<tr>
<td>Monocytes</td>
</tr>
<tr>
<td>Eosinophils</td>
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<tr>
<td>Lymphocytes</td>
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<tr>
<td>Basophils</td>
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<tr>
<td>Platelets</td>
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<table>
<thead>
<tr>
<th>Connective tissue cells</th>
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</thead>
<tbody>
<tr>
<td>Mast cells</td>
</tr>
<tr>
<td>Fibroblasts</td>
</tr>
<tr>
<td>Macrophages</td>
</tr>
<tr>
<td>Lymphocytes</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Extracellular matrix components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagens</td>
</tr>
<tr>
<td>Elastin</td>
</tr>
<tr>
<td>Proteoglycans</td>
</tr>
<tr>
<td>Fibronectin</td>
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<tr>
<td>Laminin</td>
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</tbody>
</table>

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

Ex: Neutrophils predominate during the first several days (24 – 48 hours) following injury and then are replaced by monocytes as the predominant cell type (days to weeks).

Following emigration from the vasculature, monocytes differentiate into macrophages (up to months).
3. PROVISIONAL MATRIX FORMATION

Provisional matrix is consists of:

- Fibrin (produced by activation of coagulative and thrombosis systems)
- Inflammatory products (released by complement system)
- Activated platelets
- Inflammatory cells
- Endothelial cells

Platelets activated during fibrin network formation, release platelet factor 4, platelet-derived growth factor (PDGF) and transforming growth factor (TGF), which contribute to fibroblast recruitment.

The complex 3D structure of fibrin network with attached adhesive proteins provides a medium for cell adhesion and migration.

- Implanted porous surfaces filled with fibrin exhibit new vessel growth within 4 days.

Components within or released from the provisional matrix: Initiate resolution, reorganisation and repair processes.
3. PROVISIONAL MATRIX FORMATION

Figure 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.
4. ACUTE INFLAMMATION

Relatively short duration (from minutes to days) depending on the extent of injury.

Main characteristics:

- Exudation of fluid and plasma proteins (edema)
- Emigration of leukocytes (predominantly neutrophils)

Histologically, acute inflammation presents as an abundance of neutrophils accumulated around venules within connective tissue.
4. ACUTE INFLAMMATION

Following localization of leukocytes at the injury (implant) site, phagocytosis and enzyme releases occur following activation of neutrophils and macrophages.

Phagocytosis: Injurious agent undergoes recognition and neutrophil attachment, engulfment, and killing or degradation.

Large biomaterials: Engulfment and degradation may or may not occur, depending on the properties and size of biomaterials.

- The process which does not involve engulfment of biomaterials will cause extracellular release of leukocyte products in an attempt to degrade the biomaterials.
4. CHRONIC INFLAMMATION

Chronic inflammation is less uniform histologically than acute inflammation.

Main sign: The presence of macrophages, monocytes, and lymphocytes, with the proliferation of blood vessels and connective tissue.

Persistent inflammatory stimuli lead to chronic inflammation.

Motion in the implant site by biomaterials may also produce chronic inflammation.

Lymphocytes and plasma cells are involved principally in immune reactions and are key mediators of antibody production and delayed hypersensitive responses.

The role of macrophages must be considered in the possible development of immune responses to synthetic biomaterials.
4. ACUTE & CHRONIC INFLAMMATION

ACUTE INFLAMMATION VERSUS CHRONIC INFLAMMATION

<table>
<thead>
<tr>
<th>ACUTE INFLAMMATION</th>
<th>CHRONIC INFLAMMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial short term response of the body to adverse stimuli.</td>
<td>Long term inflammatory reaction that lasts for months or years.</td>
</tr>
<tr>
<td>Not specific.</td>
<td>Specific, involves acquired immunity.</td>
</tr>
<tr>
<td>Response to physical and chemical damages, pathogen invasion, tissue necrosis, etc.</td>
<td>Response to prolonged irritation of chemicals, foreign particles, infection that cannot be overcome for a long time.</td>
</tr>
<tr>
<td>Involved immune cells: dendritic cells, Kupffer cells, histiocytes, resistant macrophages, mast cells.</td>
<td>Involved immune cells: macrophages, neutrophils, lymphocytes.</td>
</tr>
<tr>
<td>Response: (1) redness, (2) increased blood flow, and (3) edema.</td>
<td>Response: fibrosis and angiogenesis.</td>
</tr>
<tr>
<td>Cardinal signs: pain, heat, redness, and swelling.</td>
<td>No cardinal signs.</td>
</tr>
</tbody>
</table>
5. GRANULATION TISSUES

Granulation tissue:

- Pink, soft granular appearance on the surface of healing wounds
- May be seen as early as 3 to 5 days following implantation.

- **Fibroblast proliferation**
  - Active in synthesizing collagen and proteoglycans
  - Some fibroblasts may have features of smooth muscle cells (myofibroblasts) and responsible for wound contraction

- **Neovascularisation / Angiogenesis**
  - Proliferation of endothelial cells into capillary tubes and small blood vessels

- **Proteoglycans**

- **Collagen (Mostly Type I)**

- **Fibrous capsule**
5. GRANULATION TISSUES

Active granulation tissue has inflammatory cell infiltrate, newly formed blood vessels and young fibrous tissue in loose matrix.

Diagram showing stages of wound healing:
- Inflammation
- Granulation tissue
- Wound contraction
- Collagen accumulation and remodeling

Days: 0.1, 0.3, 1, 3, 10, 30, 100

Microscopic image of granulation tissue showing various cells.
6. FOREIGN BODY REACTION

Foreign body reaction is composed of foreign body giant cells and components of granulation tissue (macrophages, fibroblasts and capillaries) in varying amounts depending on the form and topography of implanted biomaterial.

- **FBR on normal breast silicone**
- **FBR on ruptured breast silicone**

Relatively flat and smooth surfaces (Ex: FBR on breast prostheses – One to two layers of macrophages and FBR).

Relatively rough surfaces (Ex: FBR on outer surfaces of expanded ePTFE vascular prostheses – Dense macrophages and foreign body giant cells at the surface).
6. FOREIGN BODY REACTION

Two factors that may play a role in multinucleated giant cell are:

- **Surface chemistry of biomaterials**
- **Protein adsorption capability**

Form and topography of biomaterial surfaces determines the composition of foreign body reaction:

- **High surface-to-volume implants** such as fabrics or porous materials will have higher ratios of macrophages and foreign body giant cells in the implant site

- **Smooth-surface implants** will have fibrosis as a significant component of the implant site.

Fibrosis (i.e. fibrous encapsulation) surrounds the biomaterial or implant with its interfacial foreign body reaction, isolating the implant and foreign body reaction from local tissue environment.

Some FBR may extend on implant beyond 20 years
6. FOREIGN BODY REACTION

Figure 2 In vivo transition from blood-borne monocyte to biomaterial adherent monocyte/macrophage to foreign body giant cell at the tissue/biomaterial interface. Little is known regarding the indicated biological responses that are considered to play important roles in the transition to foreign body giant cell development.
6. FOREIGN BODY REACTION

INJURY, IMPLANTATION

INFLAMMATORY CELL INFILTRATION
PMNs, Monocytes, Lymphocytes

EXUDATE/TISSUE

ACUTE INFLAMMATION
PMNs

CHRONIC INFLAMMATION
Monocytes
Lymphocytes

GRANULATION TISSUE
Fibroblast Proliferation and Migration
Capillary Formation

Th2: IL-4, IL-13

BIOMATERIAL

Monocyte Adhesion
Macrophage Differentiation
Macrophage Mannose Receptor Upregulation
Macrophage Fusion

FIBROUS CAPSULE FORMATION

FOREIGN BODY GIANT CELL FORMATION
7. FIBROSIS & FIBROUS ENCAPSULATION

Repair of implant sites involves two distinct processes:

- **Regeneration**: Replacement of injured tissue by parenchymal cells of the same type or by connective tissues that constitutes the fibrous capsule.
- **Extent of injury**: Relates to destruction or persistence of tissue framework of the implant site.

### Capacity of regenerative cells

**Permanent cells**
- Cannot reproduce themselves after birth
  - Nerve cells, skeletal muscle cells and cardiac muscle cells

**Stable cells**
- Retain capacity but do not normally replicate
  - Parenchymal cells of the liver, kidney and pancreas, mesenchymal cells such as fibroblasts, smooth muscle cells, osteoblasts and chondroblasts

**Labile cells**
- Proliferate throughout life
  - Epithelial cells and lymphoid and hematopoietic cells
5. FIBROSIS & FIBROUS ENCAPSULATION

Retention of framework: Lead to restitution of normal tissue structure
Destruction of framework: Lead 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.

Local and systemic 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, hematological and immunological derangements, glucocortical steroids, and preexisting diseases such as atherosclerosis, diabetes and infection.
TISSUE REACTION TO IMPLANTATION