Host reactions to biomaterials

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

Biomaterial–Tissue Interactions

A. Effect of the implant on the host
   1. Local
      a. Blood–material interactions
         Protein absorption
         Coagulation
         Fibrinolysis
         Platelet adhesion, activation, release
         Complement activation
         Leukocyte adhesion/activation
         Hemolysis
      b. Toxicity
      c. Modification of normal healing
         Encapsulation
         Foreign body reaction
         Pannus formation
      d. Infection
      e. Tumorigenesis
   2. Systemic and remote
      a. Embolization
         Thrombus
         Biomaterial
      b. Hypersensitivity
      c. Elevation of implant elements in blood
      d. Lymphatic particle transport

B. Effect of the host on the implant
   1. Physical–mechanical effects
      a. Abrasive wear
      b. Fatigue
      c. Stress-corrosion cracking
      d. Corrosion
      e. Degeneration and dissolution
   2. Biological effects
      a. Absorption of substances from tissues
      b. Enzymatic degradation
      c. Calcification

Courtesy R. Zenz

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

Courtesy R. Zenz

Immunology-Basics

- **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.

Courtesy R. Zenz

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.

Courtesy R. Zenz

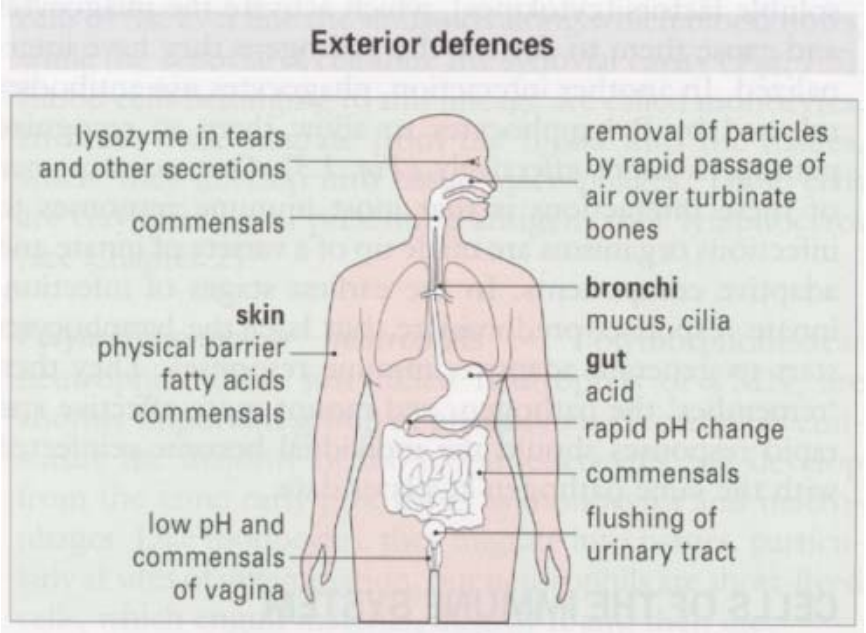
Immunology-Basics

- 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.

Immunology-Basics

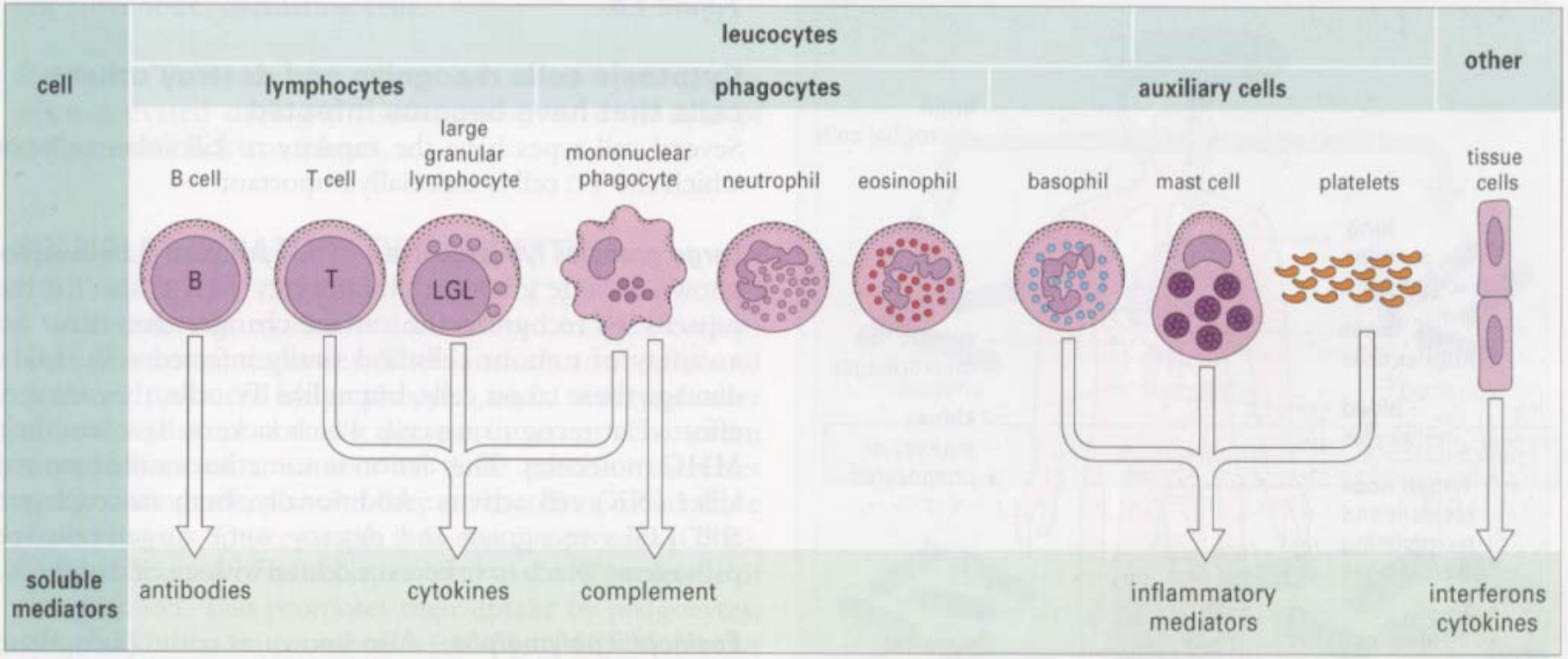
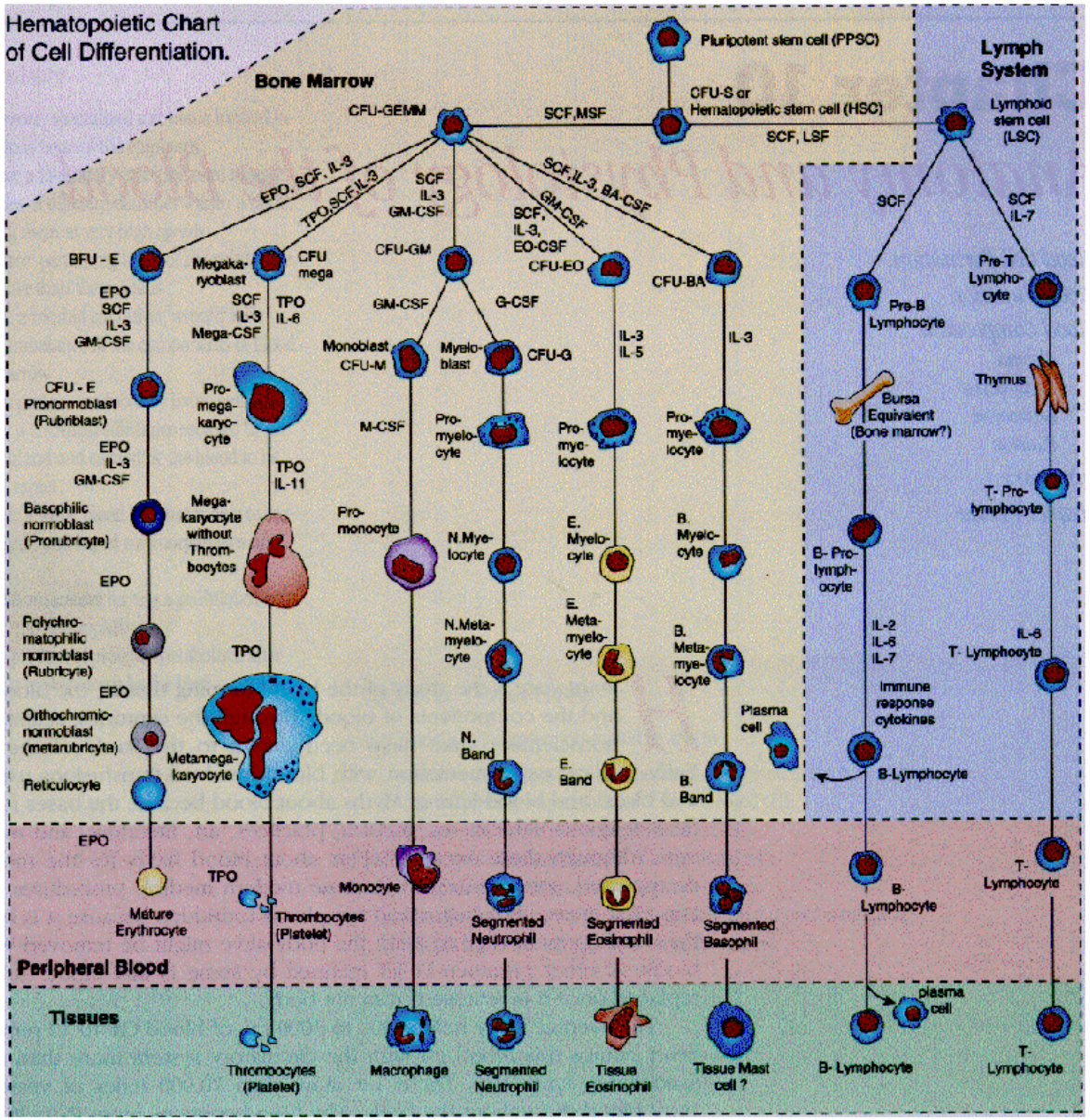


Fig. 1.4 The principal components of the immune system are shown, indicating which cells produce which soluble mediators. Complement is made primarily by the liver, although there is some synthesis by mononuclear phagocytes. Note that each cell produces and secretes only a particular set of cytokines or inflammatory mediators.

Immunology-Basics

- **Hematopoiesis:** all the cells in the blood develope from common precursor cells (pluripotent stem cells).



Courtesy R. Zenz

Immunology-Basics

- Phagocytes:
  - **Mononuclear phagocytes:**
    - Derived from the bone marrow.
    - Migrate into the tissues where they develope 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 particulary at sites of inflammation.
    - Short-lived (engulf material, destroy it, and then die).

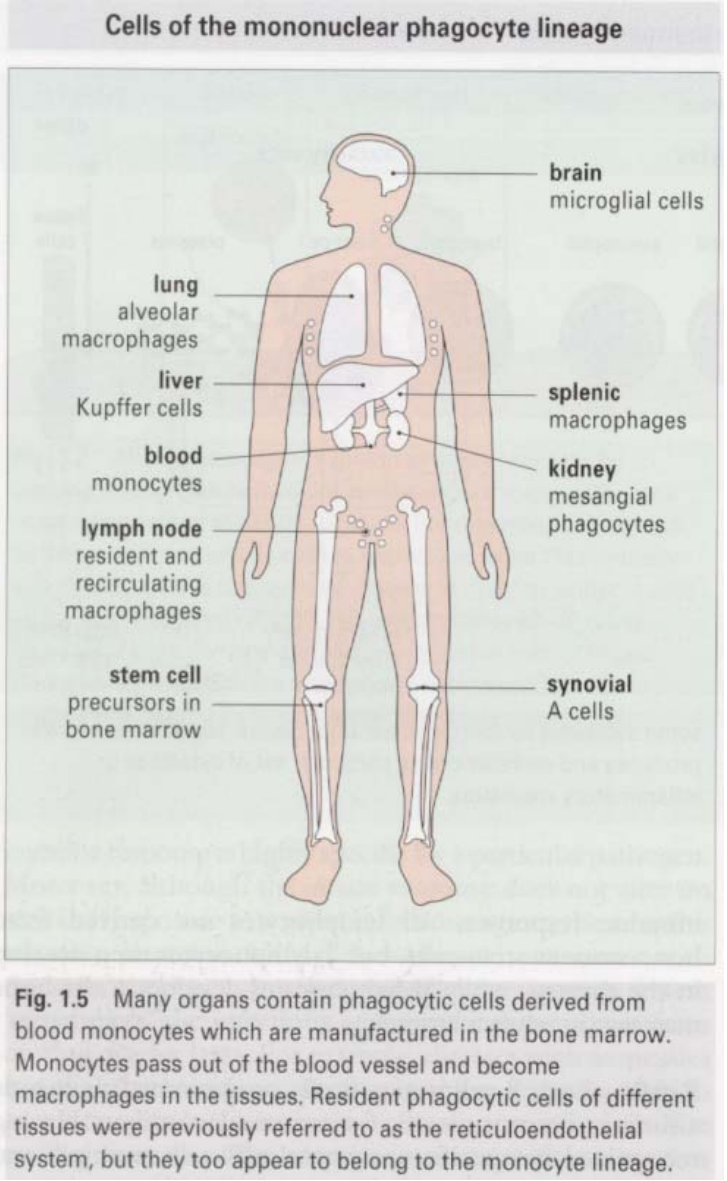
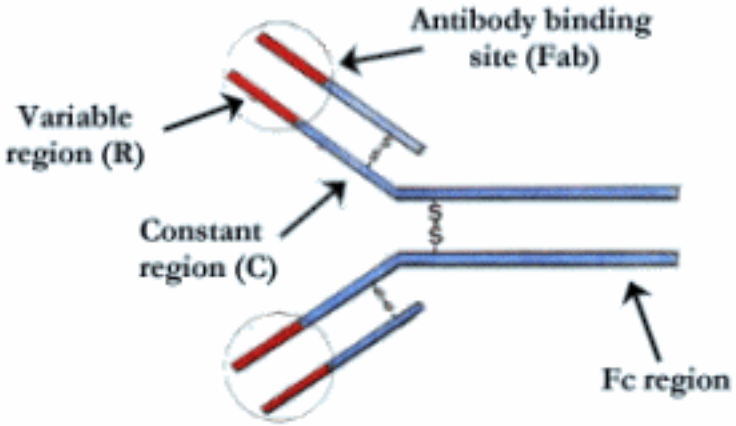


Fig. 1.5 Many organs contain phagocytic cells derived from blood monocytes which are manufactured in the bone marrow. Monocytes pass out of the blood vessel and become macrophages in the tissues. Resident phagocytic cells of different tissues were previously referred to as the reticuloendothelial system, but they too appear to belong to the monocyte lineage.

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**



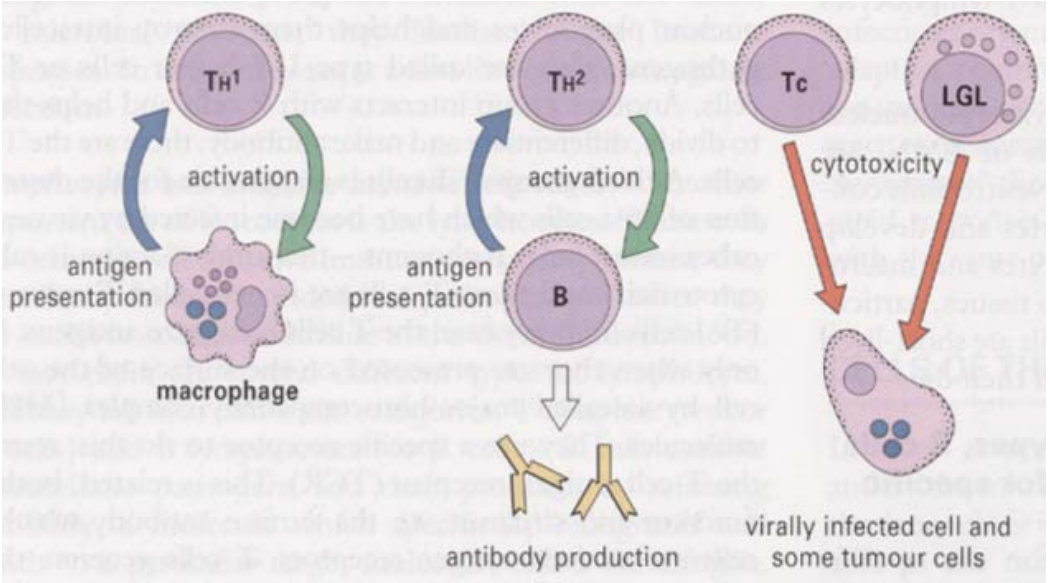
Immunology-Basics

- **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

Courtesy R. Zenz

Immunology-Basics

- **T-cells:** There are several types
  - **Type-1 T-helper cells** (T_H^1): interact with phagocytes and help them to destroy interacelluler pathogens.
  - **Type-2 T-helper cells** (T_H^2): interact with B-cells and help them to divide, differentiate and make antibody.
  - **Cytotoxic T-cells** (T_C): 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.

Courtesy R. Zenz

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

Courtesy R. Zenz

Immunology-Basics

- 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 per-meability of capillaries to plasma molecules.
  - Damage to plasma membrane on Gram-negative bacteria and enveloped viruses.
  - Release of further inflammatory mediators from mast cells.

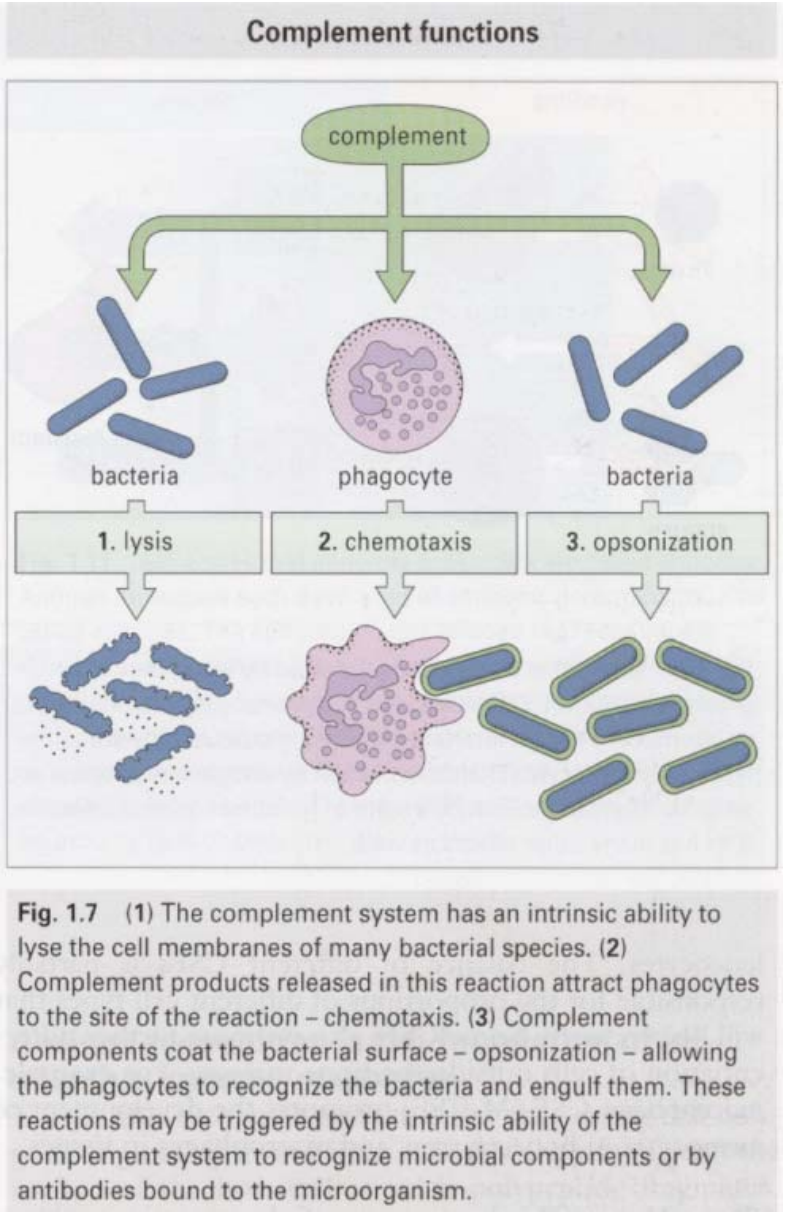


Fig. 1.7 (1) The complement system has an intrinsic ability to lyse the cell membranes of many bacterial species. (2) Complement products released in this reaction attract phagocytes to the site of the reaction – chemotaxis. (3) Complement components coat the bacterial surface – opsonization – allowing the phagocytes to recognize the bacteria and engulf them. These reactions may be triggered by the intrinsic ability of the complement system to recognize microbial components or by antibodies bound to the microorganism.

Courtesy R. Zenz

Immunology-Basics

- Cytokines: Glycoproteins signaling between lympho-cytes, 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 anti-viral resistance in uninfected cells; are produced early in infection.

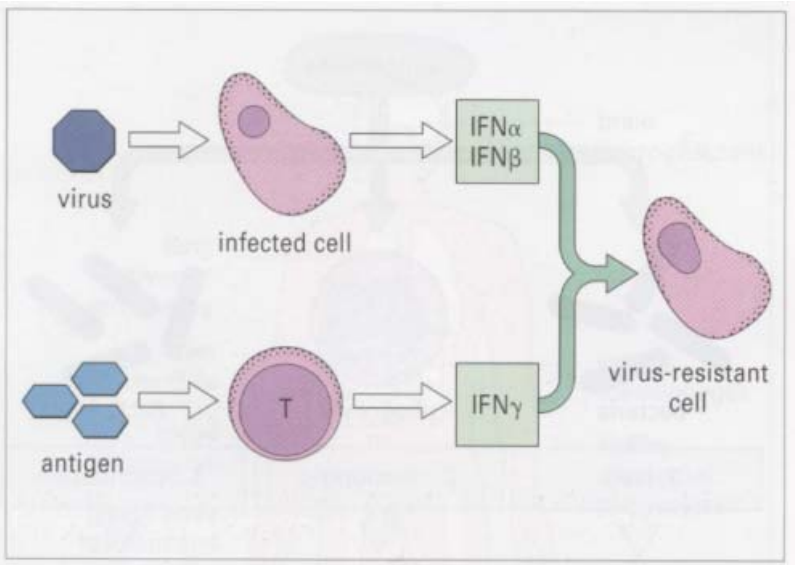


Fig. 1.8 When host cells become infected by virus, they may produce interferon. Different cell types produce interferon-α (IFNα) or interferon-β (IFNβ); interferon-γ (IFNγ) is produced by some types of lymphocyte (T) after activation by antigen. Interferons act on other host cells to induce a state of resistance to viral infection. IFNγ has many other effects as well.

Immunology-Basics

- 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: TNFα, TNFβ, TGFβ having a variety of functions; mediating inflammation and cytotoxic reactions.

Courtesy R. Zenz

Immunology-Basics

- 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.

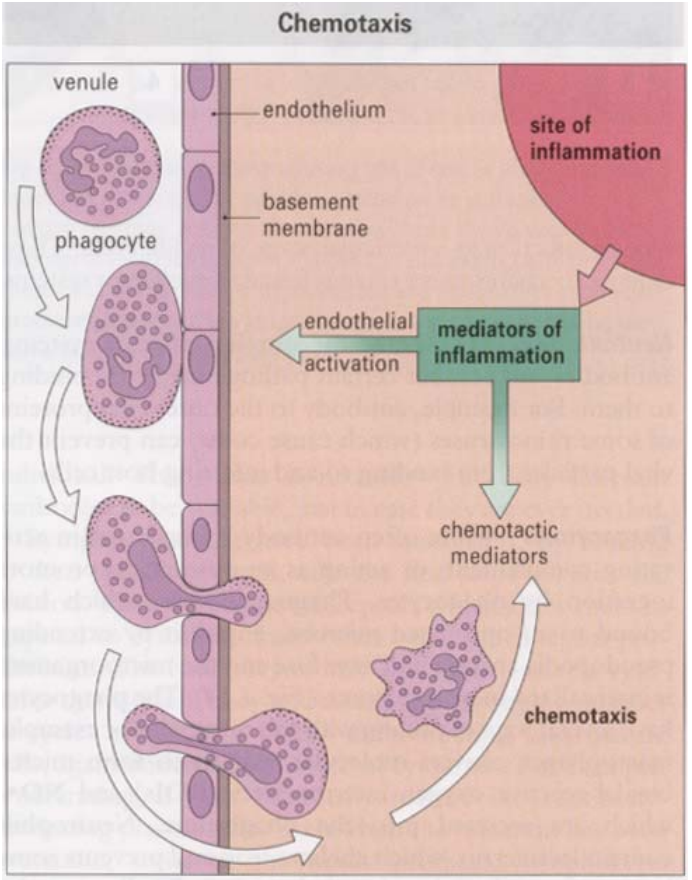


Fig. 1.17 At a site of inflammation, tissue damage and complement activation by the infectious agent cause the release of mediators of inflammation (e.g. C5a, a fragment of complement and one of the most important chemotactic peptides). These mediators diffuse to the adjoining venules, causing passing phagocytes to adhere to the endothelium. The phagocytes insert pseudopodia between the endothelial cells and dissolve the basement membrane. They then pass out of the blood vessels and move up the concentration gradient of the chemotactic mediators in the direction of the site of inflammation (chemotaxis).

Courtesy R. Zenz

Immunology-Basics

- 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.

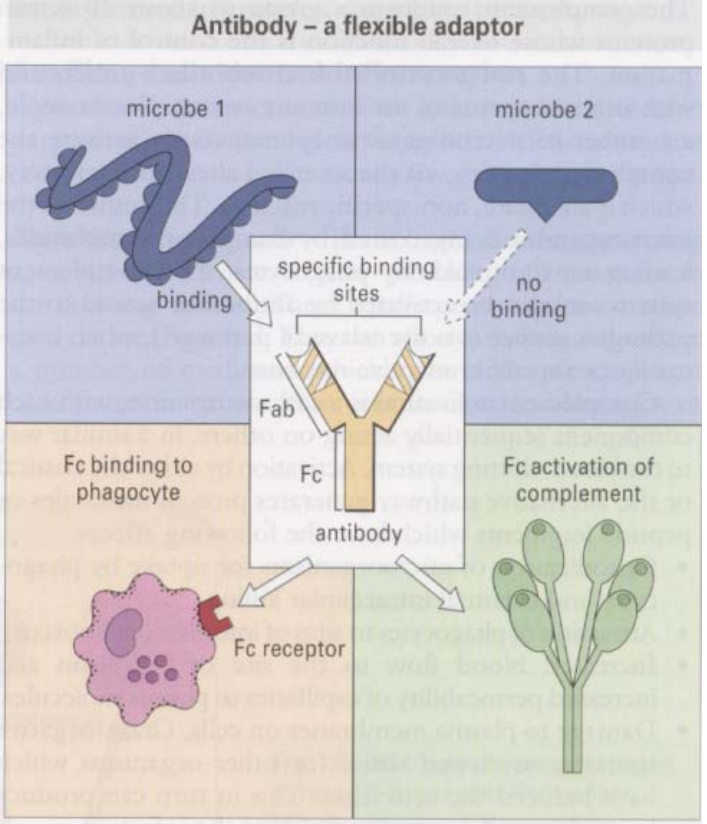


Fig. 1.9 When a microorganism lacks the inherent ability to activate complement or bind to phagocytes, the body provides antibodies as flexible adaptor molecules. The body can make several million different antibodies able to recognize a wide variety of infectious agents. Thus the antibody illustrated binds microbe 1, but not microbe 2, by its 'antigen-binding portion' (Fab). The Fc portion may activate complement or bind to Fc receptors on host cells, particularly phagocytes.

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“).

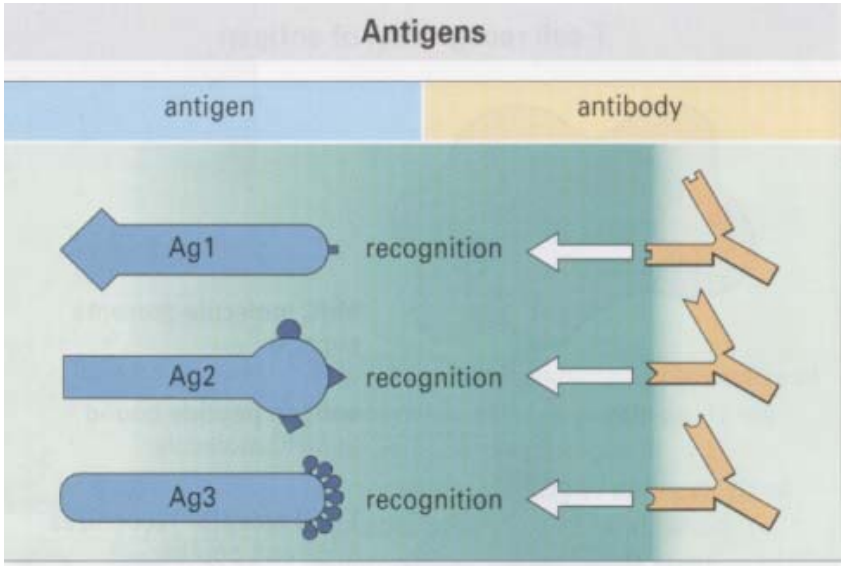


Fig. 1.11 Molecules that generate antibodies are called antigens. Antigen molecules each have a set of antigenic determinants, also called epitopes. The epitopes on one antigen (Ag1) are usually different from those on another (Ag2). Some antigens (Ag3) have repeated epitopes. Epitopes are molecular shapes recognized by antibodies of the adaptive immune system. Each antibody recognizes one epitope rather than the whole antigen. Even simple microorganisms have many different antigens which may be protein, lipid or carbohydrate.

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 polypetide fragments.

  The antigens are presented by MHC molecules (major histokompatibility complex).

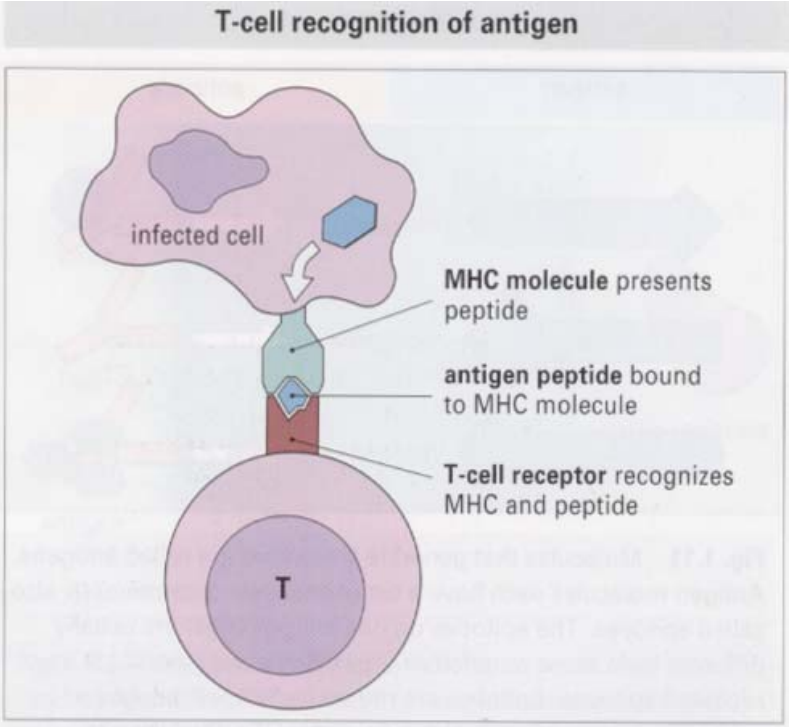


Fig. 1.12 T cells recognize antigens that originate within other cells, such as viral peptides from infected cells. They do this by binding specifically to antigenic peptides presented on the surface of the infected cells by molecules encoded by the major histocompatibility complex (MHC molecules). The T cells use their specific receptors (TCRs) to recognize the unique combination of MHC molecule plus antigenic peptide. Unlike B cells, which recognize just a portion of the antigen, a T cell recognizes residues from both the MHC molecule and the antigen peptide.

Immunology-Basics

- 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.

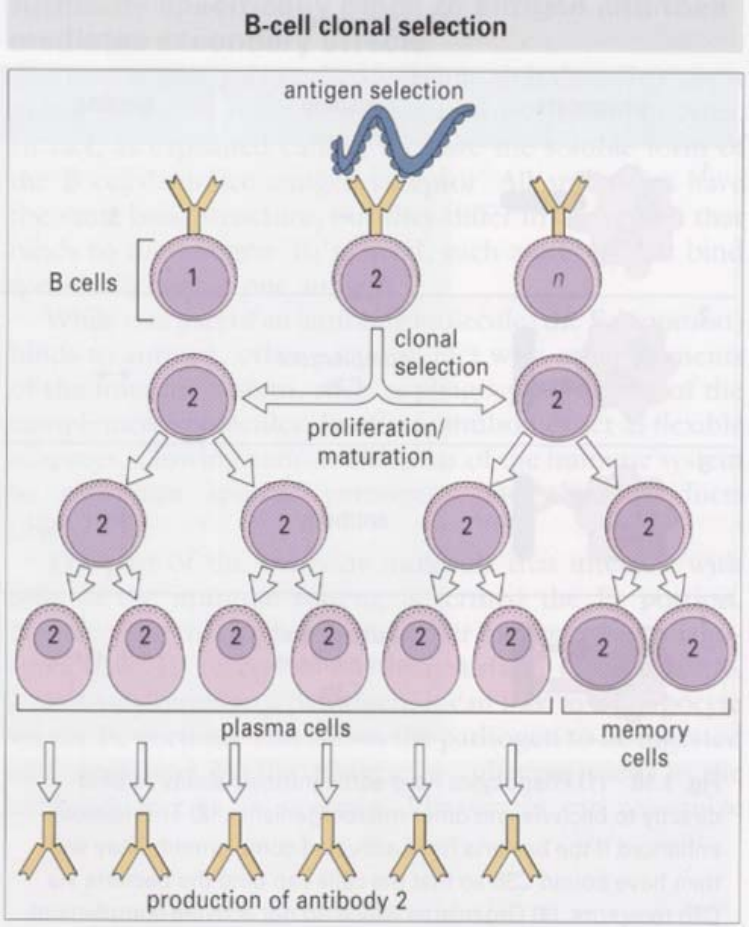


Fig. 1.13 Each antibody-producing cell (B cell) is programmed to make just one antibody, which is placed on its surface as an antigen receptor. Antigen binds to only those B cells with the appropriate surface receptor – B cell 2 in this example. In this way these cells are stimulated to proliferate and mature into antibody-producing cells, and the longer-lived memory cells, all having the same antigen-binding specificity.

Courtesy R. Zenz

Immunology-Basics

- 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.

Lysosoms release enzymes into the phagosom to digest the content.

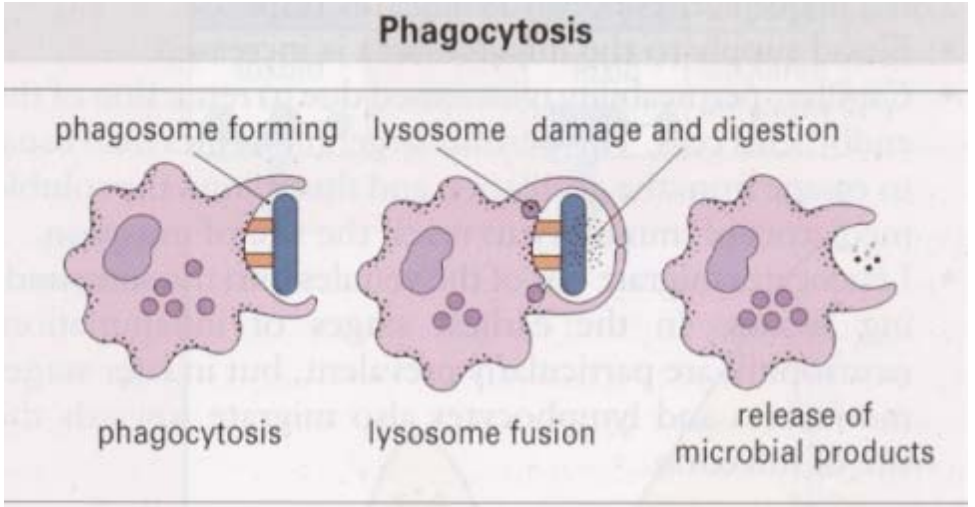


Fig. 1.15 Phagocytes arrive at a site of inflammation by chemotaxis. They may then attach to microorganisms by way of their non-specific cell surface receptors. Alternatively, if the organism is opsonized with a fragment of the third complement component (C3b) and/or antibody, attachment will be through the phagocyte's receptors for C3b and/or Fc (see *Fig. 1.10*). If the phagocyte membrane now becomes activated, microbicidal oxygen metabolites are formed and the infectious agent is taken into a phagosome by pseudopodia extending around it. Once inside, lysosomes fuse with the phagosome to form a phagolysosome and the infectious agent is killed. Undigested microbial products may be released to the outside.

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.

TABLE 1 Sequence of Local Events Following Implantation

Injury
Acute inflammation
Chronic inflammation
Granulation tissue
Foreign body reaction
Fibrosis

  - 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.

Courtesy R. Zenz

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.

TABLE 2 Cells and Components of Vascularized Connective Tissue

Intravascular (blood) cells
Neutrophils
Monocytes
Eosinophils
Lymphocytes
Basophils
Platelets
Connective tissue cells
Mast cells
Fibroblasts
Macrophages
Lymphocytes
Extracellular matrix components
Collagens
Elastin
Proteoglycans
Fibronectin
Laminin

Courtesy R. Zenz

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.

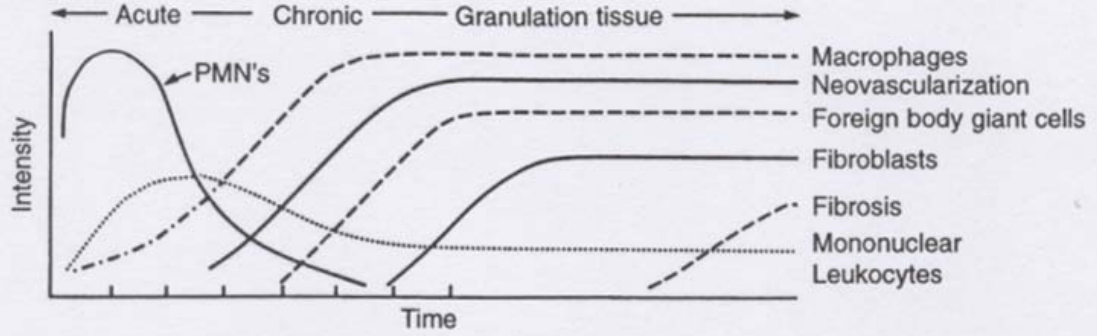


FIG. 1. The temporal variation in the acute inflammatory response, chronic inflammatory response, granulation tissue development, and foreign body reaction to implanted biomaterials. The intensity and time variables are dependent upon the extent of injury created by implantation and the size, shape, topography, and chemical and physical properties of the biomaterial.

  - Neutrophils predominate during the first several days.
    - Neutrophils are short-lived, disintegrate and disapear 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.

TABLE 3 Important Chemical Mediators of Inflammation Derived from Plasma, Cells, and Injured Tissue

Mediators	Examples
Vasoactive amines	Histamines, serotonin
Plasma proteases	
Kinin system	Bradykinin, kallikrein
Complement system	C3a, C5a, C3b, C5b–C9
Coagulation/fibrinolytic system	Fibrin degradation products; activated Hageman factor (FXIIA)
Arachidonic acid metabolites	
Prostaglandins	PGI_2, TxA_2
Leukotrienes	HETE, leukotriene B_4
Lysosomal proteases	Collagenase, elastase
Oxygen-derived free radicals	H_2O_2, superoxide anion
Platelet activating factors	Cell membrane lipids
Cytokines	Interleukin 1 (IL-1); tumor necrosis factor (TNF)
Growth factors	Platelet-derived growth factor (PDGF); fibroblast growth factor (FGF); transforming growth factor (TGF-α or TGF-β)

Courtesy R. Zenz

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.

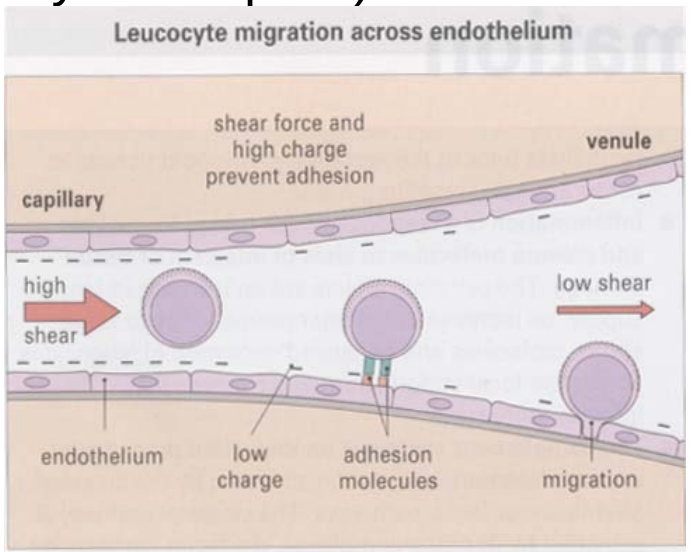


Fig. 3.2 Leucocytes circulating through a vascular bed may interact with venular endothelium via sets of surface adhesion molecules. In the venules, haemodynamic shear is low, surface charge on the endothelium is lower and adhesion molecules are selectively expressed.

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 to big a „mouthfull“ for the cells).
- But: instead „frustrated phagocytosis“: release of leucocyte products occur in an attempt to degrade the biomaterial.

Courtesy R. Zenz

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 vessls 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.

Courtesy R. Zenz

Host reactions to biomaterials

- Monocytes and macrophages belong to the MPS (mono-nuclear phagocytosis system), aslo called RES (reticulo-endothelial system)

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

TABLE 4 Tissues and Cells of MPS and RES

Tissues	Cells
Implant sites	Inflammatory macrophages
Liver	Kupffer cells
Lung	Alveolar macrophages
Connective tissue	Histiocytes
Bone marrow	Macrophages
Spleen and lymph nodes	Fixed and free macrophages
Serous cavities	Pleural and peritoneal macrophages
Nervous system	Microglial cells
Bone	Osteoclasts
Skin	Langerhans' cells
Lymphoid tissue	Dendritic cells

Courtesy R. Zenz

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

Courtesy R. Zenz

Host reactions to biomaterials

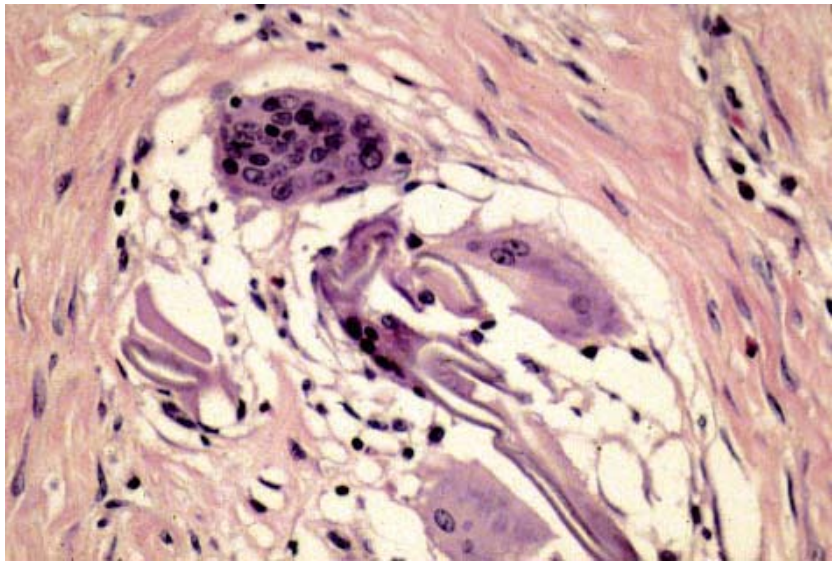
- Granulation tissue:
  - Within one day the healing response is initiated by the action of monocytes and macrophages.
  - Fibroblasts and vascular endothelial cells proliferate and begin to form granulation tissue (specialized type of tissue that is the hallmark of healing inflammation).
  - New small blood vessels are formed by budding or sprouting of preexisting vessels (neovasculation 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 phago-cytose material:

- The form and topography of the surface of the biomaterial determines the composition of the foreign body reaction.



Courtesy R. Zenz

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.

Courtesy R. Zenz

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 inocculated 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.

Courtesy R. Zenz

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.

Courtesy R. Zenz

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,..)