

## **Inflammation and Innate Immunity**

### **Reading materials:**

Alberts et al., Molecular Biology of the Cell  
Pgs 1284-87 and 1453-62

### **Learning objectives**

- State the key differences between innate and adaptive immune responses
- State the types of leukocytes involved in the innate immune response and describe their main functions pertaining to inflammation and host defense
- State the key components of the inflammatory response
- Describe the contribution of the inflammatory response to the host defense process

## **I. Components of Innate Immunity**

### **A. Fundamental differences between innate and adaptive immunity**

#### **Innate Immunity:**

- Consists of physical & chemical barriers and non-clonally derived cells
- Immediate/early induced responses
- Activated by infection, does not depend on hosts' prior exposure to pathogen
- Does not generate long lasting protective immunity (i.e., no "memory")
- Relies on germ-line encoded receptors (present from birth)
- Pattern recognition receptors (PRRs, i.e., TLR's, scavenger receptors, MBL) recognize conserved molecular patterns on pathogens (pathogen associated molecular patterns, PAMPS)

#### **Adaptive Immunity:**

- Consists of highly specialized, clonally derived effector cells
- Requires time to develop (days to weeks)
- Specificity (large repertoire of antigen-specific receptors)
- Requires re-arrangement of genes to recognize processed antigens/pathogens
- Results in long-term memory
- Promotes non-reactivity to self

## B. Surface or physical barriers

- Surface or physical barriers (i.e., skin, mucosa) prevent the ingress of pathogens
- Chemical barriers also exist and serve anti-microbial functions (i.e. lysozyme, pepsin, defensins, cryptidins)

## C. Leukocytes of the innate immune system

**Phagocytes:** Leukocytes that recognize, ingest, and kill microbes.

Two main types:      Neutrophils  
                                 Macrophages

### Neutrophils

- Arise from common myeloid progenitor cells in bone marrow
- Most abundant leukocyte in the circulation
- Short lived
- Rarely found in healthy tissues
- Are among the first cells recruited to sites of inflammation/infection
- Kill pathogens by phagocytosis, enzymes, defensins, and production of  $H_2O_2$ ,  $O_2^-$ , and NO (i.e., respiratory burst)
- Neutrophils generally die after one round of phagocytosis

### Macrophages

- Mature form of circulating blood monocyte
- Found in almost all tissues (i.e., resident)
  - Tissue-specific, specialized subsets exist
    - Kupffer cells (liver)
    - Alveolar macrophages (lung)
    - Dermal macrophages (skin)
    - Metallophilic and marginal zone macrophages (spleen)
- Long-lived (i.e, 10 yrs or more)
- Highly efficient at phagocytosis
- Also help initiate adaptive immunity (via MHC and co-stimulatory molecule expression)

Together, macrophages and neutrophils serve as the first-line cellular defense against invading pathogens. Combined, their main functions are 1) **recognition of pathogens**, 2) **phagocytosis, elimination, and killing of pathogens**, and 3) **production of inflammatory mediators** (i.e., chemokines & cytokines)

## Innate lymphocyte subsets

Three main types:    Natural Killer (NK) cells  
                              Natural Killer T (NKT) cells  
                              Gamma delta ( $\gamma\delta$ ) T cells

### NK cells

- Arise from common lymphoid progenitor cells in bone marrow, but do not undergo further thymic maturation
- Represent ~5% of circulating/splenic leukocytes
- Can directly kill virally infected cells and tumor cells
- Use a unique set of inhibitory/activating receptors to decide whether or not to kill targets
- Extremely abundant in the tonsils

The main mechanisms of killing by NK cells are:

- Detection of presence vs. absence of self MHC-I (missing self model)
  - i.e., virally infected cells and tumors, which can either lose MHC-I expression or express altered MHC-I
- Antibody-dependent cell-mediated cytotoxicity (ADCC)
  - Antibody coated to surfaces of cells binds to Fc receptors on NK cells, causing their activation to release cytolytic enzymes, perforin, TNF $\alpha$ , and granzymes.

Upon infection, NK cells become activated and expand. They also produce cytokines such as interferon- $\gamma$ , which can amplify the anti-microbial properties of macrophages and neutrophils and can also help initiate/promote adaptive immunity.

### NKT cells

- Arise from common lymphoid progenitor cells in bone marrow.
- An infrequent population of lymphocytes (~1% of total) that have profound immunoregulatory capacity.
- NKT cells are not so good at killing, but are called “NKT” cells because they are lymphocytes that co-express cell surface molecules normally found on NK cells.
- Undergo maturation in the thymus to ultimately express a CD1d-restricted,  $\alpha\beta$ -TCR.
- Unlike conventional T cells that express a highly variable TCR that detects peptides presented by MHC molecules, NKT cells express a highly invariant TCR that detects glycolipids in the context of CD1d molecules.

- Upon engagement of their TCR by glycolipid-CD1d complexes expressed on macrophages and dendritic cells, NKT cells rapidly release cytokines (IL-4, IFN $\gamma$ ).
- NKT cells are believed to be required for promotion of adaptive T cell immunity and maintenance of self tolerance (i.e., prevention of autoimmunity)
- NKT cells are now known to be critically involved in anti-microbial immunity

### $\gamma\delta$ T cells

- Arise from common lymphoid progenitor, express a  $\gamma\delta$ -TCR.
- Found in lymphoid tissue, skin, and mucosa of GI and reproductive tracts (mouse & human), and in airways (mouse), but generally not in the circulation.
- Are believed to recognize both self antigens (epithelial-derived) and microbial peptides (direct recognition), have some cytotoxic capabilities.
- $\gamma\delta$  T cells are known to regulate keratinocyte development/proliferation during wound healing responses.
- $\gamma\delta$  T cells are known to help limit reactivity of the airways, probably by secretion of anti-inflammatory cytokines.
- $\gamma\delta$  T cells seem important for maintaining tolerance to orally and vaginally derived antigens, but the mechanisms by which this occurs remain largely unknown.

## II. Inflammation

### A. Overview of inflammation

A generalized term, used to describe accumulation of fluid, plasma proteins, and leukocytes in tissues subjected to injury, infection, or ongoing immune responses.

Four superficial hallmarks of inflammation:

- calor (heat)
- dolor (pain)
- rubor (redness)
- tumor (swelling)

Purposes of the inflammatory response:

- To limit the spread of pathogens
- To create an incompatible environment for pathogen dissemination and growth
- To initiate tissue repair

## **B. Key events of the inflammatory response**

### **Vascular changes**

- Vasodilation
- Increased local blood flow
- Increased vascular permeability (allows leakage of serum components & inflammatory mediators to the tissue or site of infection)

### **Accumulation of leukocytes**

- Leukocytes extravasate through vasculature and into tissue along gradients of adhesion molecules and inflammatory mediators, primarily the chemokines
- The purpose of leukocyte infiltration is
  - Release of inflammatory mediators
  - Clearance (i.e. phagocytosis) of pathogens & debris
- Orderly, but overlapping sequence of leukocyte infiltration is as follows (i.e., for skin inflammation):
  - 30 minutes to 24 hours = neutrophils
  - 24 hours to 72 hours = monocyte/macrophages
  - 72 hours to 5 days = lymphocytes

### **Phagocytosis**

Phagocytosis is the primary mechanism by which pathogens (i.e., fungi and bacteria) as well as dead cells/necrotic tissue are removed.

### **Three main steps in phagocytosis:**

- Particle/pathogen recognition (can be receptor mediated via toll-like receptors, complement receptors, Fc receptors, or scavenger receptors. Or, it can be antibody mediated, called opsonization)
- Internalization (particle engulfment, creation of phagosome, fusion of phagosome with lysosome)
- Killing (occurs within lysosome, is mediated by oxygen radicals, enzymes, and nitric oxide)

### **Production of inflammatory mediators**

Engagement of receptors during phagocytosis also leads to activation of gene transcription (primarily NF- $\kappa$ B pathway) for production of inflammatory mediators including pro-inflammatory cytokines and chemokines, prostaglandins, etc.

### **Resolution of the inflammatory response**

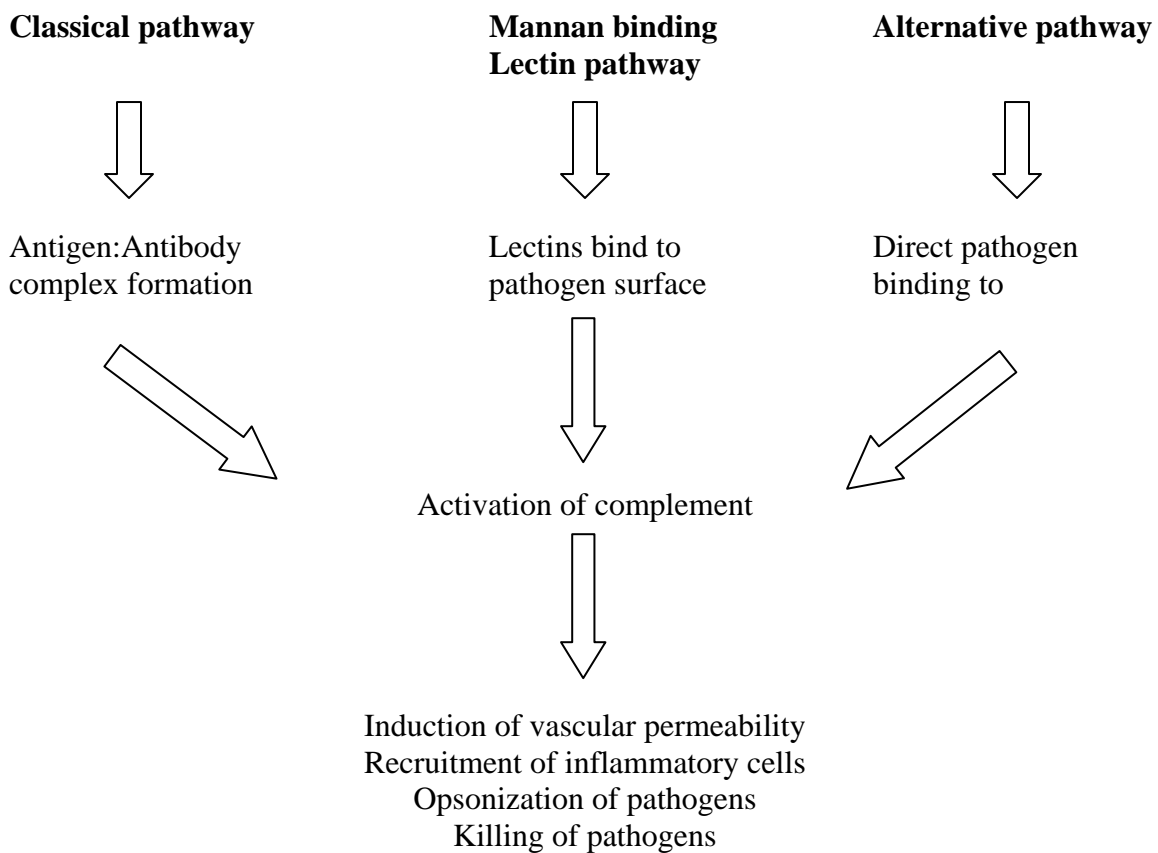
In the absence of continued infection or further tissue damage, the inflammatory response is for the most part, self-limiting and resolves over a matter of days. Chronic or un-

resolved inflammatory responses can pose serious health problems and will be discussed in the Immunopathology block.

### C. Complement

A group of >30 plasma and membrane associated proteins that react with one another to opsonize pathogens and induce an inflammatory response. Many complement proteins are proteases. At sites of infection, components of the complement cascade are activated locally to trigger inflammation. There are three pathways of complement activation. All three pathways can be initiated independently of antibody. The early events in all pathways consist of a sequence of cleavage reactions in which the larger cleavage product binds to the surface of a pathogen, contributing to the activation of the next component in the pathway (See pgs 1456-57 in Alberts text).

#### Three pathways of complement activation



## **End results of complement activation**

### **Cell lysis via the membrane attack complex (MAC)**

- Activation of terminal complement components leads to formation of a “membrane attack complex”. This complex creates a pore in the membrane of target cells (or bacteria or enveloped viruses) causing disrupted cell homeostasis, leading to cell lysis and death. Healthy mammalian cells are resistant to MAC formation.

### **Opsonization**

- Macrophages and neutrophils express classes of receptors for complement (i.e., Fc receptors). Bacteria and other pathogenic particles can become coated with complement components, targeting them for phagocytosis by macrophages and neutrophils.

### **Clearance of immune complexes**

- Antigen:antibody complexes (i.e., on cell surfaces) can bind complement directly

### **Induction of inflammation**

- The small fragments of complement that are produced during the cleavage processes can induce vascular permeability, vasodilation, activation of endothelium, etc. Some small cleavage products can serve as chemoattractants that initiate recruitment of inflammatory cells to sites of injury or infection.