Reactions of innate immunity

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• Innate immune system

- Faster, but:
  ...less specific
  ...without memory

- Inflammation is one of its reactions

We will discuss:

1- Recognition (pathogen-associated molecular patterns and the receptors for them)

2- Soluble molecules...esp. interferons

3- Cellular defenses...responses of phagocytes and NK cells

4- Inflammation...briefly
Recognition

on microbes
not host cells

on host cells
not microbes

Pathogen-associated molecular patterns (PAMPs)

Pattern recognition receptors (PRRs)

By this, the innate system discriminates between self and non-self

*PRRs genes do not undergo somatic modification (they are conserved/germline)
...unlike the receptors of the adaptive immune system which are:
- Epitope-specific somatically generated
- Expressed by B and T lymphocytes
Pathogen-associated molecular patterns (PAMPs)

- Limited number—widely expressed

- May be: sugars, proteins, lipids, nucleic acids

- Recognized mainly by phagocytic cells: directly by PRRs or indirectly by complement receptors, etc.

- In phagocytosis:
  - Binding \rightarrow \text{immobilization of microbe} \rightarrow \text{phagocytosis} \rightarrow \text{phagocyte activation}
• **PAMPs on bacteria:**
  • Gram +….carbohydrates and proteins in peptidoglycan
  • Gram -….lipids and carbohydrates in LPS and to a lesser degree: also molecules of peptidoglycan

...**PRRs for the above:** -TLR2 (toll-like receptor 2) for peptidoglycan
  -TLR4 (toll-like receptor 4) for LPS

  *on phagocytes

*Phagocyte activation ➔ -Production of: -microbicidal molecules
  -Enzymes
  -cytokines
  -Activation of inflammation
**PRRs**

*Membrane-bound* or *Extracellular*

• **Examples:**
  - Toll-like receptors
  - Scavenger receptors
  - Opsonins

*Signaling transduction: synthesis of proteins:*
  - Microbicidal
  - Cytokines
  - Chemokines...recruitment of WBCs to the site...
  - Activation of inflammation

*Internalization of bacteria*
  - Phagocytosis of apoptotic host cells
  *Bind to:*
    - Modified LDL
    - Polysaccharides
    - Nucleic acids...etc.
Markers of abnormal self

- Viruses: MHC class I molecules on infected host cells
  ..........also expression of “stress signals” on cell surface

  - HSPs (heat shock proteins)
  - MICA
  - MICB

  ..........detected by:
  - TLR2
  - TLR4
  - KARs (killer activation receptors) of NK cells

this also happens to cells in cancerous transformation
Soluble mechanisms (by soluble molecules)

• Interferons type I

• Microbicidal molecules…we have discussed

• Complement…we will discuss later

• Cytokines: -by many cells
  -many functions
  -chemokines are cytokines with chemoattractant function (chemotaxis)
Type I interferons

- Produced by virus-infected cells (many cell types: dendritic cells, GI epithelial cells.....etc.), and also by injured cells
- The main producers: plasmacytoid dendritic cells...see next slide
- Produced within 5 minutes after interaction between certain PAMPs and PRRs
- Induce -production of antiviral molecules...RNA-dependent protein kinase (PKR)
  - apoptosis
  - activation of phagocytes, CD8, Th1, and NK cells

by adjacent cells
Plasmacytoid dendritic cells

• They represent a type of APCs (antigen-presenting cells)
• They have PRRs that bind to viral RNA
  
  Toll-like receptor 3 (TLR-3)

  (PAMP)

  this RNA is double stranded (not present in human)
Cellular actions...phagocytes

• Special areas in phagocyte membrane: clathrin-coated pits

Cellular extensions (pseudopodia) → Internalization (endocytosis) → Phagosome → Phagolysosome → Phagocyte activation

different receptors are in these regions

- PRRs
- complement receptors (CRs)
- Fc receptors
Cellular actions...phagocytes, cont’d

• What is macropinocytosis?

• **Phagocyte activation:**
  - Lysosomal destruction of microbe: -acid hydrolases (proteases, lipases, nucleases..etc)
    - oxygen free radicals
    ..this process is called: ....
  - nitrous oxide (NO)
  - acidity
  - ...etc

**Remember the enzymes:**
1- NADPH oxidase
2- Myeloperoxidase
Cellular actions...phagocytes, cont’d

• Phagocyte activation...cont’d
  - Secretion of cytokines and chemokines:
    - IL-1 and IL-6: fever, also vascular permeability
    - TNF-alpha: vascular permeability, also fever
    - IL-8 and IL-12: chemotaxis of neutrophils and NK cells, respectively
Cellular actions...NK cells

Killer activation receptors (KARs) **VS** Killer inhibition receptors (KIRs)

- MICA
- MICB

MHC I
How do NK cells kill the target cells?

- Perforin...creating pores
- Granzyme...proteolysis and apoptosis
- Fas ligand...apoptosis
Thank You