Innate Immunity and Antigen Presentation

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Lecture outline

- Innate immunity
  - Receptors and mechanisms
  - Roles in disease

- Antigen capture and presentation to lymphocytes: the initiation of adaptive immune responses (focus on T cells)
  - Functions of dendritic cells
  - Role of HLA in antigen display to T cells
  - Antigen processing pathways
Innate Immune Responses

• The initial responses to:
  - 1. Microbes: essential early mechanisms to prevent, control, or eliminate infection;
  - 2. Injured tissues, dead cells: critical for repair and wound healing

• Limited types of responses:
  - Inflammation
  - Antiviral state

• Stimulate adaptive immunity.

Take home messages

The components of the Innate Immune System-1

• Epithelial barriers
  - Defensins and cathelicidins (antibiotics)

• Phagocytes and other cells
  - Macrophages
  - Neutrophils
  - Dendritic cells

• Specialized lymphocytes with limited diversity
  - NK cells
  - iNKT cells
  - B1 and Marginal Zone B cells
The components of the Innate Immune System-2

- **Plasma proteins**
  - Complement
  - Pentraxins (C Reactive Protein, serum amyloid protein)
  - Collectins (Mannose Binding Lectin)

- **Cytokines**
  - Inflammatory (IL-1, TNF)
  - Chemokines (IL-8, MCP-1)
  - Anti-viral (IFN α, IFN β)

**Innate Immune System**

What is recognized?

- Structures that are shared by various classes of microbes but are not present on host cells - Pathogen associated molecular patterns (PAMPs).
  - Innate immunity often targets microbial molecules that are essential for survival or infectivity of microbes (prevents escape mutants)

- Structures found in/on stressed, dying or dead host cells - “Damage associated molecular patterns (DAMPs)”.

*Take home messages*
Cellular Pattern Recognition Receptors

Functional significance of different cellular locations

Toll-like Receptors (TLRs)
Toll-like Receptors (TLRs): Clinical Relevance

- Excessive/systemic TLR signaling underlies pathophysiology of sepsis (LPS/TLR4)
- TLR signaling in B cells promotes auto-antibody production
- TLR ligands, such as CpG nucleotides, are potentially useful adjuvants to enhance effectiveness of vaccines

Activation of inflammasome by microbial products and/or host-derived molecules
Dysregulated inflammasomes and autoinflammatory diseases

- Mutations in NALP3 or other components of inflammasomes are involved in several rare “auto-inflammatory” syndromes characterized by periodic fever, skin rashes, and amyloidosis.*
- The mutations in Nalp3 lead to constitutive activation and uncontrolled IL-1 production
- IL-1 antagonists are very effective treatments for these disorders.
- IL-1 antagonists may be effective in other, “non-immune” diseases: metabolic syndrome, atherosclerosis

*Muckle–Wells syndrome, familial Mediterranean fever, others

Gout:
An inflammasome-mediated disease

- Deposition of urate crystals causes joint inflammation in gout.
- Nalp3 recognizes monosodium urate, leading to inflammasome activation and IL-1 release; IL-1 causes inflammation.
- Possibility of using IL-1 antagonists to treat severe gout that does not respond to conventional anti-inflammatory agents.
The innate immune system provides second signals required for lymphocyte activation

Second signals for T cells: "costimulators" induced on APCs by microbial products, during early innate response

Second signals for B cells: products of complement activation recognized by B cell complement receptors

Take home messages

The challenge for lymphocytes

- Very few lymphocytes in the body are specific for any one microbe (or antigen)
  - Specificity and diversity of antigen receptors: the immune system recognizes and distinguishes between $10^6 - 10^9$ antigens; therefore, few lymphocytes with the same receptors
The challenge for lymphocytes

• Very few lymphocytes in the body are specific for any one microbe (or antigen)
  – Specificity and diversity of antigen receptors: the immune system recognizes and distinguishes between $10^6 - 10^9$ antigens

• Lymphocytes must be able to locate microbes that enter anywhere in the body
  – Usual routes of entry are through epithelia, but infections may take hold anywhere

• Lymphocytes must respond to each microbe in ways that are able to eradicate that microbe; best exemplified by T cells
  - Extracellular microbes: antibodies; destruction in phagocytes (need helper T cells)
  - Intracellular microbes: killing of infected cells (need CTLs)
  - How do T cells distinguish antigens in different cellular locations?
Sites of antigen entry

Sites of initial antigen capture

Sites of antigen collection and capture

Capture and presentation of antigens by dendritic cells

Sites of microbe entry: skin, GI tract, airways (organs with continuous epithelia, populated with dendritic cells). Less often -- colonized tissues, blood

Sites of lymphocyte activation: peripheral lymphoid organs (lymph nodes, spleen), mucosal and cutaneous lymphoid tissues

Antigens and T cells come together in the same organs
Why are dendritic cells the most efficient APCs for initiating immune responses?

- **Location:** at sites of microbe entry (epithelia), tissues
- **Receptors for capturing and reacting to microbes:** Scavenger receptors, complement receptors, Toll-like receptors, others
- **Migration to T cell zones of lymphoid organs**
  - Role of CCR7
  - Co-localize with naïve T cells
- **Maturation during migration:** Conversion from cells optimized for antigen capture into cells optimized for antigen presentation and T cell activation
- **Practical application:** dendritic cell-based vaccines for tumors

**Take home messages**

What do T cells see?

- **All functions of T cells are mediated by interactions with other cells**
  - Helper T cells “help” B cells to make antibodies and “help” macrophages to destroy what they have eaten
  - Cytotoxic (killer) T lymphocytes kill infected cells

- **How does the immune system ensure that T cells see only antigens on other cells?**
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- To ensure cellular communications, T cells do NOT see free antigens in blood or fluids but only when displayed by molecules on the surface of other cells
  - These molecules are HLA (generic name: MHC) and the cells displaying the antigen are APCs

A model of T cell recognition of peptide displayed by an MHC molecule

Human MHC = HLA

Because MHC molecules are on cells and can display only peptides, T lymphocytes can recognize only cell-associated protein antigens
All MHC molecules have a similar basic structure: the tops bind peptide antigens and are recognized by T cell receptors and the bottoms bind CD4 or CD8.

Pathways of antigen processing

Protein antigen in cytosol --> class I MHC --> CTLs
Protein antigen in endosomes --> class II MHC --> helper T cells
Functions of antigen-presenting cells

• Capture antigens and take them to the "correct" place
  - Antigens are concentrated in peripheral lymphoid organs, through which naïve lymphocytes circulate

• Display antigens in a form that can be recognized by specific lymphocytes
  - For T cells: MHC-associated peptides (cytosolic peptides to class I, vesicular peptides to class II)
  - For B cells: native antigens

• Provide “second signals” for T cell activation
  - Critical for initiation of responses