Basic immunological concepts and
Cells of the immune system

BBS755 Infection and Immunity
Feb 6, 2014
Lecture 2
Prof. Stern
Immunology: study of how an organism responds to pathogens
What does the immune system need to do to deal with these threats?

- See everything
  - Viruses, bacteria, fungi, protozoa, helminths
- Look everywhere
  - All tissues, extracellular, intracellular
- Mount an appropriate response
- Make a self-nonself discrimination
The Responses

- Innate immune response
  - Rapid
  - Indiscriminate

- Adaptive immune response
  - Slower
  - Precise

Innate response
(e.g. inflammation)

Adapted immune response
Characteristics of innate vs adaptive responses

Inflammation (Innate immunity):
• Stereotyped response
• Same cell - same receptor
• Germ-line encoded receptors
• Immediate effect
• More easily subverted
• Evolutionarily older

Adaptive immunity:
• Specialized responses
• Each cell has a different receptor
• Somatic cell receptor variation
• Slower to respond, but “always gets their man”
• Evolutionarily more recent
Specificity of innate versus adaptive immunity

**Innate**: Limited # specificities
- “Each policeman is looking for about the same thing”
- Limited number of different receptors looking for conserved features of pathogens or injury (e.g. bacterial cell wall components, DNA in cytosol)

**Adaptive**: Numerous highly selective specificities
- “Each soldier is looking for a different thing”
- Many different receptors & each cell has a different receptor
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Specificity and Memory

Two key features of the \textit{adaptive immune system} have puzzled, fascinated, and inspired researchers:
The immune system is amazingly specific

![Isoleucine](image1) vs. ![Leucine](image2) vs. [Dinitrophenyl hapten](image3)

Hapten: a small molecule covalently coupled to a macromolecule to make it “foreign” so it can be recognized by the immune system.
Nitrophenyl serum albumin
Immunological memory

The immune system responds more quickly and more effectively to pathogens to which it has been previously exposed.
Immunological memory

Thucydides, on the plague of Athens, 430 BC

“Yet is was with those who had recovered from the disease that the sick and the dying found most compassion. These knew what is was from experience, and had now no fear for themselves, for the same person was never attacked twice - never at least fatally.”
Definition: **immunogen**

Something that provokes an immune response

Related terms:

- **antigen**: a substance that binds to a particular immune receptor (often the receptor is an antibody)

- **epitope**: the part of the antigen actually recognized by an immune receptor, i.e. antibody or B-cell epitopes, T-cell epitopes
Immune defenses
Immune defenses

First line of defense: barriers (epithelial surfaces)
To deal with diverse threats, many different defenses are needed

What are the components of the immune response?

**Soluble defenses:** antibodies, complement proteins, cytokines, chemokines, lipid mediators

**Cells:** lymphocytes, macrophages, dendritic cells, granulocytes, mast cells
Immune defenses

- Soluble molecules

**Humoral immunity**, from “humor”: according to ancient theory, four bodily fluids or humors (blood, phlegm, black bile, yellow bile) determined health and temperament, with imbalances among the humors responsible for pain and disease

- serum antibodies (Abs)
- serum complement (C’ )
Immune defenses

- Antibodies

Immunoglobulin G
Immune defenses

- Antibody-mediated immunity

Opsonize:
fr. Greek *opson*, condiment, delicacy

Complement:
a cascade of serum proteins that results in bacterial lysis and immune recruitment
The complement system

Recognition of microbial surface

Proteolytic signaling cascade

All pathways lead to:
1) Covalent deposition of complement components on surface
2) Generation of pro-inflammatory peptides

Membrane damage
Target for destruction by phagocytes "opsinization"
Inflammation
Immune defenses

• Cellular responses - T cells (CTL and NK cells) directly lyse infected cells...

... by induction of apoptosis to destroy infected cells and their contents
Immune defenses

- Cellular responses – macrophages phagocytose bacteria and fungi …

... and kill them by phagosome-lysosome fusion (pH ~5: proteases, lipases, lysozyme, antimicrobial peptides, iron chelators)
Immune defenses

- Cellular responses: neutrophils phagocytose and kill bacteria...

... by releasing reactive oxygen (ROI) and nitrogen (RNI) species that react with proteins, lipids and DNA.
- Superoxide (\(O_2^-\)) generated by the NADPH oxidase complex
- Nitric oxide (NO) produced by inducible nitric oxide synthase (iNOS)
How do we learn about the immune system?

Many branches of experimental science have contributed to our current understanding of immunology:

- Chemistry
- Biochemistry
- Molecular biology
- Microbiology
- Microscopy
- Cellular biology
- Genetics
- Population biology
Levels of immunological investigation:

- **molecular**
  - Antigen receptor on T cell surface
  - Viral antigen from influenza virus
  - MHC protein on surface of infected cells
Levels of immunological investigation: cellular

- bacteria
- macrophage
- T cell
Intravital imaging of a lymph node

Alex YC Huang, Hai Qi, Ronald Germain

**Illuminating the landscape of in vivo immunity: insights from dynamic in situ imaging of secondary lymphoid tissues**

Two-photon microscopy of a murine lymph node. Images taken at 30s intervals at a depth of ~100um below the capsule. Total length of movie = 25min (300x).

Image shows capture of CD4+ T cells (red) and CD8+ T cells (green) specific for chicken ovalbumin by dendritic cells (yellow) expressing ovalbumin peptides bound to cell surface MHC II molecules.
Levels of immunological investigation: organism

Transgenic mice and gene knockout technology allow the function of a gene to be tested in vivo at the whole organism level.
Levels of immunological investigation: population

The shaping of modern human immune systems by multiregional admixture with archaic humans.


Department of Structural Biology, Stanford University School of Medicine, Stanford, CA 94305, USA.

Abstract

Whole genome comparisons identified introgression from archaic to modern humans. Our analysis of highly polymorphic human leukocyte antigen (HLA) class I, vital immune system components subject to strong balancing selection, shows how modern humans acquired the HLA-B*73 allele in west Asia through admixture with archaic humans called Denisovans, a likely sister group to the Neandertals. Virtual genotyping of Denisovan and Neandertal genomes identified archaic HLA haplotypes carrying functionally distinctive alleles that have introgressed into modern Eurasian and Oceanian populations. These alleles, of which several encode unique or strong ligands for natural killer cell receptors, now represent more than half the HLA alleles of modern Eurasians and also appear to have been later introduced into Africans. Thus, adaptive introgression of archaic alleles has significantly shaped modern human immune systems.

PMID: 21868630 [PubMed - indexed for MEDLINE]
Did sex with Neanderthals and Denisovans shape our immune systems? The jury’s still out
Summary of key points

• Diverse threat from infectious agents
  numerous, ubiquitous, adaptable

• Innate (rapid, germ-line encoded) and adaptive (slower, encoded by rearranged/mutated receptors) responses

• Flexible, multilevel protection strategy
  soluble defenses (humoral immunity)
  phagocytes and cytotoxic cells (cellular immunity)
Cells of the immune system

There are a variety of types of immune cells, but all arise from a common bone-marrow progenitor
How can we tell the various immune cells apart from one another?

1. Morphology
2. Surface molecules that are cell type-specific

- **Macrophage**
  - Phagocytosis and killing of microorganisms.
  - Activation of T cells and initiation of immune responses.

- **Mast cell**
  - Expulsion of parasites from body through release of granules containing histamine and other active agents.
Differentiation of immune cells

- **Pluripotent hematopoietic stem cell**
  - **Bone marrow**
    - Common lymphoid progenitor
    - Common myeloid progenitor
    - Granulocyte/macrophage progenitor
    - Megakaryocyte/erythrocyte progenitor
  - **Blood**
    - Granulocytes (or polymorphonuclear leukocytes)
      - Neutrophil
      - Eosinophil
      - Basophil
      - Immature dendritic cell
    - Monocyte
    - Platelets
    - Erythrocyte
    - B cell
    - T cell

Lymphocytes
(adaptive immunity)
B and T Lymphocytes

- Mediators of adaptive immunity
- distinguish self / non-self
- resting and activated appearance is different
Type of Lymphocytes

• Killer T cells (CTL): recognition and lysis of infected cells
• Helper T cells ($T_{H1}$, $T_{H2}$, $T_{H17}$, $T_{reg}$): recognize infection, coordinate response, activate or inhibit effector cells
• B cells: antibody production
• NK cells: lyse infected cells
• Innate-like lymphocytes: B-1 cell, $\gamma$δ T cells, NKT cells

Fig 1.5 © 2001 Garland Science
Myeloid cells
phagocytes, granulocytes
(innate immunity)
Myeloid cells

- Mediators of innate immunity
- Secrete toxins to kill pathogens
- Release signals to alert and attract other cells (cytokines, chemokines, vasodilators)
Antigen presenting cells
(bridge between adaptive and innate immunity)
Antigen presenting cells

Functions of APC
- sentinels / warning
- sample environment by phagocytosis and surface receptors
- process antigens and “present” them to helper T cells

Other functions
- \( M\phi \): phagocytic effector cells
- DC: carry antigens to lymph nodes
Where are immune cells in the body?

**Primary immune organs**
- Bone marrow
- Thymus

**Peripheral (secondary) Lymphoid tissue**
- Lymphocytes
- Macrophages
- Dendritic cells

**Blood**
- Granulocytes
- Monocytes
- Lymphocytes

**Tissues**
- Macrophages
- Dendritic cells
- Mast cells
Summary of key points

• Immune cells arise from a common precursor
• Different types of immune cells have different functions
• Phagocytic and secretory myeloid cells (neutrophils, PMN, mast cells, basophils, mφ) provide immediate response, sound alarm
• Lymphocytes (B, T, NK cells) are specialized for specific antigen recognition
  – Activated B cells secrete Ab
  – Activated CTL lyse infected cells
  – Activated TH cells recognize infection, coordinate response
Stages of response to infection

Adherence to epithelium
- Normal flora and local chemical factors inhibit microbial growth
- Phagocytes activated (especially in lung)

Local infection, penetration of epithelium
- Wound healing induced
- Antimicrobial proteins and peptides, phagocytes, and complement destroy invading microorganisms
- Activation of γδ T cells?

Local infection of tissues
- Complement activation
- Dendritic cells migrate to lymph nodes
- Phagocytosis and phagocyte action
- NK cells activated
- Cytokines and chemokines produced

Lymphatic spread
- Pathogens trapped and phagocytosed in lymphoid tissue
- Adaptive immunity initiated by migrating dendritic cells

Adaptive immunity
- Infection cleared by specific antibody, T-cell dependent macrophage activation and cytotoxic T cells
Classic signs of inflammation

*Calor, dolor, tumor, rubor*

warmth, pain, swelling, redness

Aulus Cornelius Celsus
25 – 50 AD
De Medicina
Inflammation

- Induced by resident leukocytes, complement activation, or tissue damage

- Results in:
  - Increased vascular diameter, local blood flow
  - Upregulation of endothelial cell adhesion molecules
  - Recruitment of leukocytes from blood (extravasation)
  - Plasma leakage (edema)
Dendritic cells deliver tissue antigen to lymph nodes and present it to lymphocytes.
Lymphocytes circulate between blood and lymphatic fluid.

Antigen-presenting cells carry antigens from tissues to lymph nodes.
Lymph nodes - and other peripheral lymphoid tissue - where lymphocytes meet antigens
T cells searching for antigen in lymph node
Meeting of lymphocytes and antigen is important in the conversion of naïve lymphocytes to active forms that can perform their respective immune functions.

**Naïve:** simple and guileless, unsuspecting
In immunology, having been never exposed to antigen
Summary of key points

• Inflammation is a rapid response to penetration of the epithelial barrier, and serves to deliver effector molecules and cells to sites of infection
• Inflammation is triggered by soluble mediators released by tissue-resident leukocytes: mΦ, mast cells, and causes monocytes, neutrophils, and lymphocytes to extravasate near sites of infection
• antigen presenting cells acquire antigens and carry them to lymphatic tissue to initiate adaptive responses
• naïve lymphocytes (B cells and T cells) meet antigens on APC in lymph nodes, inducting lymphocyte maturation
• yin/yang of immunity:
  possibility of collateral damage by innate system
  possibility of autoreactivity by adaptive system
The end