Immune System Basics

From Friend to Foe: What Happens When Your Immune System Goes Bad?

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ἥξει Δωριακὸς πόλεμος καὶ λοιμὸς ἃμ’ αὐτῶ.
Plague of Athens – 430 B.C.

…it was with those who had recovered from the disease that the sick and the dying found most compassion.

These knew what it was from experience, and had now no fear for themselves; for the same man was never attacked twice - never at least fatally.

And such persons not only received the congratulations of others, but themselves also, in the elation of the moment, half entertained the vain hope that they were for the future safe from any disease whatsoever.

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The immune system is armed against...

Pathogens

Altered self (e.g., cancer)
Two major types of immunity

**Innate Immunity**
- Genetically hardwired
- Germline evolution
- Stereotypic responses
- First line of defense

**Adaptive Immunity**
- Plastic
- Somatic evolution
- Idiosyncratic responses
- Delayed, efficient
Innate Immunity: Immediate, Hardwired Responses

- **Detectors**: Macrophage, Dendritic cell
  - Bacterial infection, other

- **Mediators**:
  - IL-1
  - TNF
  - IL-6

- **Responders**:
  - **CNS**: Fever, somnolence, anorexia
  - **Liver**: Acute phase proteins
  - **Other**
Innate Immune Cells Detect Shared Properties of Pathogens

- Bacterial cell wall components
- Components of flagella
- Modified DNA
- Double-stranded RNA

Phagocytosis
Target cell lysis
Inflammation
Adaptive Immune Cells Express Receptors of Exquisitely High Specificity and Diversity
T cells Play a Central Role in Adaptive Immune Responses

Helper T Cell

Cytolytic T Cell

B cell, Macrophage
T cells and B cells Collaborate to Make Antibodies
Mutual Activation: T cell and B cell

Negulescu et al. Immunity 4, 421-430
Emil von Behring - Antitoxins

Transfer of immunity to tetanus and diphtheria toxins by serum
Christmas Eve, 1890
Mouse, human and hybrid antibodies are widely used as therapeutic agents.

- "-omab" ibritomomab Zevalin B cell NHL
- "-umab" adalimumab Trudexa Crohn’s, RA
- "-ximab" infliximab Remicade Crohn’s, RA
- "-zumab" omalizumab Xolair asthma
Antibody Diversity and the Coding Paradox

Number of different antibodies in a typical mammal: \( > 10^9 \)

Coding sequence required if each the product of distinct genes: \( 2 \times 10^{12} \text{ bp} \)

Total size of human genome: \( 3 \times 10^9 \text{ bp} \)
The Solution: Let’s Hit the Slots!
Antigen Receptor Genes are Assembled from Discrete Gene Segments to Make Many Combinations
Recombination is Initiated by a Molecular Scissors Called RAG

Binding

Cutting

Joining

New Antibody Gene
Shuffling of antigen receptor genes: frequent and dangerous

- A major cause of leukemia and lymphoma
- Two protective mechanisms:
  - No recombination at “dangerous” times
  - No recombination without the ignition key
Cutting of Antibody Genes is Strictly Timed in Developing Immune Cells

- **RAG On**: Repair by non-homologous end-joining, in the G1 phase.
- **RAG Off**: Repair by homologous recombination with sister chromatid, in the S-G2 phase.
Mistimed Recombination Disrupts the Genome and Causes Lymphoma

(7;14;15)

(7;14;15;5)

(16;14)

(7;16;15)
Only Active Genes Carry the Ignition Key

Inactive gene

RAG-1

RAG-2

RAG Off
Only Active Genes Carry the Ignition Key

Inactive gene

Active gene

RAG-1

RAG-2

RAG Off

RAG On
Mistakes in DNA Rearrangement are a Major Cause of Leukemia and Lymphoma

- More than 10 million DNA rearrangements per hour in each of us
- 40 – 70 percent of all B cell progenitor cancers are caused by mistakes in recombination
- Regulatory mechanisms restrict recombination to protect against genomic damage.
- When these mechanisms fail the cancer-causing potential of V(D)J recombination is unmasked.
Going Rogue

- Cancer
- Allergy and Asthma
- Autoimmune Diseases
- Immune Deficiency Diseases