20.380 S10
Introduction: the Immune System— the basics, inflammation in health and disease
Overview of the immune system
Two arms of immunity: the innate and adaptive immune systems
KEY EFFECTORS OF ADAPTIVE IMMUNITY

Diagram of how B lymphocytes, Helper T lymphocytes, and Cytolytic T lymphocytes recognize particular antigens and effect immunity has been removed due to copyright restrictions.
THE CLONAL IMMUNE SYSTEM

• $10^{12}$ total T cells in adult human
• 25-100 million distinct clones
• Only several thousand T cells at most respond to any individual antigen (von Andrian and Mackay 2000)

• Precursor frequency of antigen-specific cells:
• CD8+ T cells: 1 in 200,000 cells specific for any given antigen (0.0005% antigen-specific cells)

The immune system: evolved to eliminate infectious disease

B cell activation

Diagram of antigen recognition, B cell proliferation, and Ig secretion and isotype switching has been removed due to copyright restrictions.
Biology of dendritic cells in T cell activation

Classical pathways of antigen processing and presentation:

- **Classical Class I antigen loading pathway**
- **Class II antigen loading pathway**
- **Exogenous ANTIGEN**

CD8+ T cells

CD4+ T cells
interactions in the lymph node

Three electron micrographs of T cells and dendritic cells interacting with reticular fibers have been removed due to copyright restrictions.
T-cell activation

(1) antigen recognition

infected cell or tumor cell

peptide-MHC

T cell receptor (TCR)

target cell

(2) immunological synapse (IS) formation


Two electron micrographs removed due to copyright restrictions.
The immune system: a distributed network
lymphocyte trafficking is “addressed” by combinations of adhesion molecules and chemokine signals

Diagram of lymphocyte trafficking removed due to copyright restrictions.
There are four steps: rolling adhesion, tight binding, diapedesis, and migration.
See Figure 2-44 part 3 of 3, Janeway, Charles, et al. Immunobiology. 6th ed.
chemokines and chemotaxis: how the immune system gets around

Figure "Known and proposed functions for homeostatic chemokines and their receptors in lymphocyte development, trafficking, and function" has been removed due to copyright restrictions.
unique combinations of chemokine/adhesion molecule “addressins” lead immune cells to different tissue sites, both in “healthy” immune responses and in inflammatory diseases:


Diagram of chemotaxis directing cell migration has been removed due to copyright restrictions.
chemokines also direct cells to their appropriate locations within tissues


Katakai et al. JEM, 200, 783-792 (2004)

Figure of T cell/B cell removed due to copyright restrictions.
Steps in the immune response to infection
innate immune sentinels

HIV illustration removed due to copyright restrictions.

http://www.northwestern.edu/newscenter/images/2008/12/hiv-illustration.jpg
(1) chemoattraction of dendritic cells/DC precursors to sites of infection/inflammation

(2) dendritic cells collect antigen and become activated

(3) DCs travel to lymph nodes

(4) DCs activate lymphocytes by cell-cell contact

Dendritic cells and initiation of adaptive immune responses


Electron micrograph of resident dendritic cells in skin has been removed due to copyright restrictions.

Diagram of gram-negative bacterium removed due to copyright restrictions.


www.invivogen.com


PAMP recognition of microbes by dendritic cells

Immune cells integrate many signals to ‘fingerprint’ pathogens:

Diagram from Science magazine removed due to copyright restrictions.

Huang et al., Science 294 3870 (2001)


Lecture 20 Spring 2006
TLR signaling is likely one of the earliest steps in the host response to infection
what we typically think of as inflammation: recruitment of innate and adaptive immune cells to peripheral tissue sites:

inflammatory agent applied to epithelium:

Figure removed due to copyright restrictions.
See Figure 2 from Luster, Andrew D. "Chemokines — Chemotactic Cytokines That Mediate Inflammation." New England Journal of Medicine 338 (2006).

Le Borgne, Dubois et al. Immunity 24 191-201 (2006)

Diagram explaining process of inflammation removed due to copyright restrictions.
recruitment of DCs: chemotaxis into inflammation sites

chemoattractants bring monocytes and DCs to sites of infection

Two electron micrograph images removed due to copyright restrictions.
(1) chemoattraction of dendritic cells/DC precursors to sites of infection/inflammation

(2) dendritic cells collect antigen and become activated

(3) DCs travel to lymph nodes

(4) DCs activate lymphocytes by cell-cell contact


Antigen is one of (at least) two signals that must be delivered by a vaccine:

- Signal 1 - antigen
- Signal 2 - costimulation
- Signal 3 - cytokines

+DC ACTIVATION

+ANTIGEN

• NO T CELL ACTIVATION
• T CELLS TOLERIZED
• MAXIMAL T CELL PROLIFERATION
• GENERATION OF FULL EFFECTOR FUNCTIONS
• GENERATION OF MEMORY T CELLS
(1) antigen carried to lymph nodes:

ORCHESTRATION OF THE PRIMARY IMMUNE RESPONSE

(2a) B cells encounter antigen, likely in follicles:

(Pape et al. *Immunity* 26, 491 (2007))

(2b) T cells encounter antigen in T zones:


(3) Antigen-specific T and B cells meet at follicular border:

Figure from New England Journal of Medicine removed due to copyright restrictions. See Figure 3 from Ada, Gordon. "Advances in Immunology: Vaccines and Vaccination." *New England Journal of Medicine* 345 (2001).
Adaptive immune cell effectors home back to infection site:
molecular warfare involved in clearing infections:

Figure of chemical processes within a blood vessel removed due to copyright restrictions.
Turning off the immune response as infection is cleared:

Cells play a key role in preventing activation of immune responses in the steady state. These cells are thought to help regulate the close of immune responses in infection:

![Diagram showing interactions between immune cells and the regulation of immune responses.](image-url)
Turning off the immune response as infection is cleared: role of hypoxia/adenosine receptor signaling

Figure 3 | The hypothesis: role of hypoxia in local tissues in the regulation of T cells in inflamed and hypoxic areas. We think that excessive collateral immune damage to the local-tissue microcirculation, and therefore to the oxygen (O₂) supply, creates deepening tissue hypoxia, which functions as a signal to stop immune responses. Hypoxia, in turn, inhibits adenosine kinase (AK) and upregulates 5’-nucleotidase (NT5) activity, which results in the accumulation of extracellular adenosine. Adenosine signals through the immunosuppressive adenosine receptors A₂₅R and/or A₂₆R at the surface of surrounding activated T cells, and it downregulates T-cell-receptor (TCR)-mediated responses in a delayed negative-feedback manner. The regulatory effects of hypoxia-inducible factor 1α (HIF1α) on T cells remain to be directly established, but it is expected that the increased expression of HIF1 in response to hypoxia will also be inhibitory.


Induction of immunological memory (the basis of vaccination)

Figure removed due to copyright restrictions.