Advances in Cancer Immunotherapy

Immunology 101 for the Non-Immunologist

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Disclosures

- No relevant financial relationships to disclose
- This presentation does not contain discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration (FDA)

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Learning Objectives for Today

- Recall the cells and specialized lymphoid tissues that are the main components of the immune system
- Understand the basic principles of immunity: role of **innate** and **adaptive** immunity; the difference between a **primary** and a **secondary** response and **passive** and **active** immunity
- Describe in very general terms the immune response to a **pathogen** and to a **tumor** cell
- Have a basic understanding of **immune malfunction**
- Have a basic understanding of T and B-cell activation and consequences

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What is the Immune System

- A network of **organs**, **tissues**, **cells** and **proteins** all coordinated to defend the host from outside organisms/invaders
- Is an infinitely adaptable system to combat the the complex and endless variety of pathogens that it comes into contact with
- The immune response is mediated by:
  - White Blood Cells (leukocytes)
  - Soluble molecules/mediators
    - Plasma proteins such as complement and antibodies
    - Antimicrobial mediators
    - Cytokines

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Organs of the Immune System

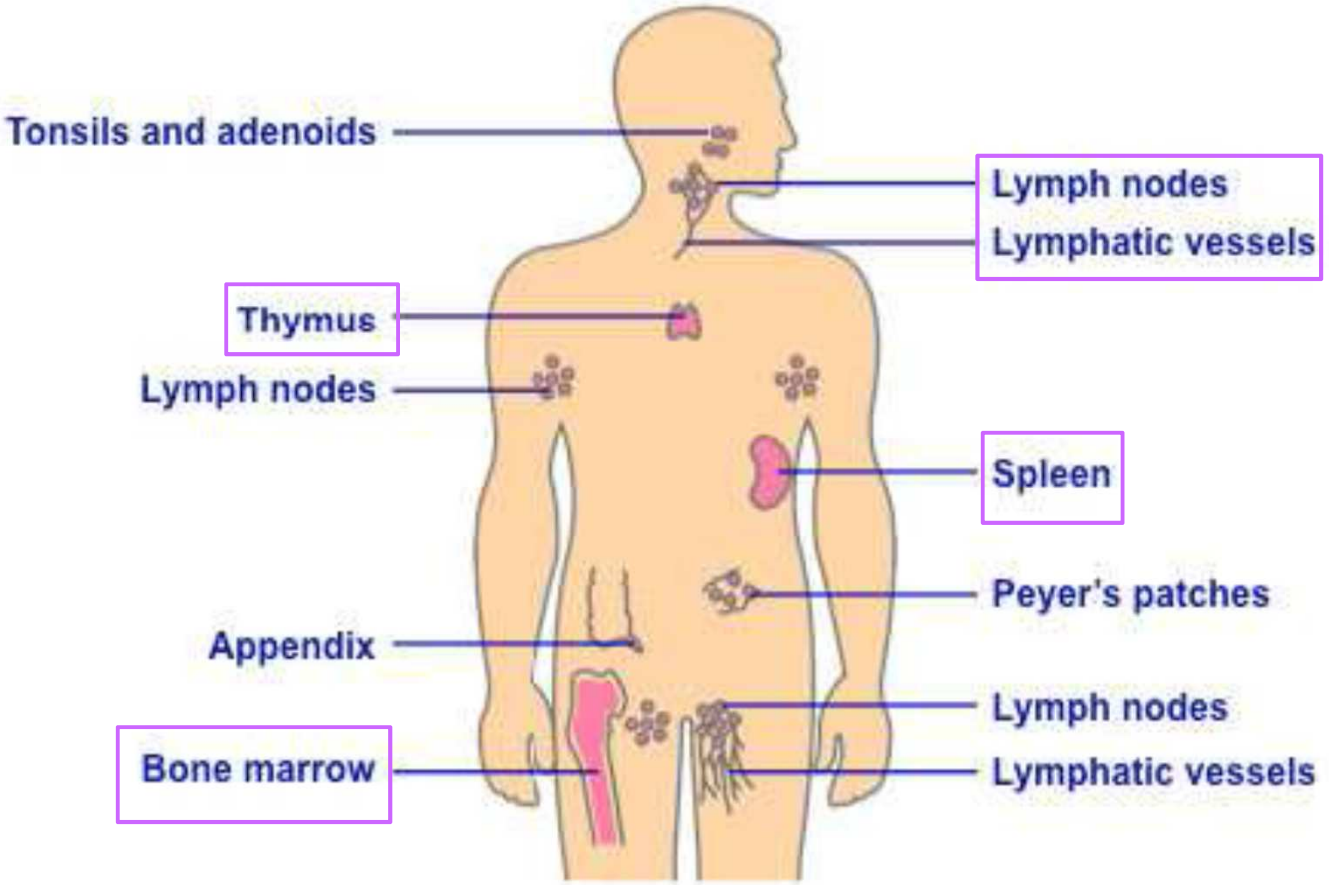

Image courtesy of the National Cancer Institute

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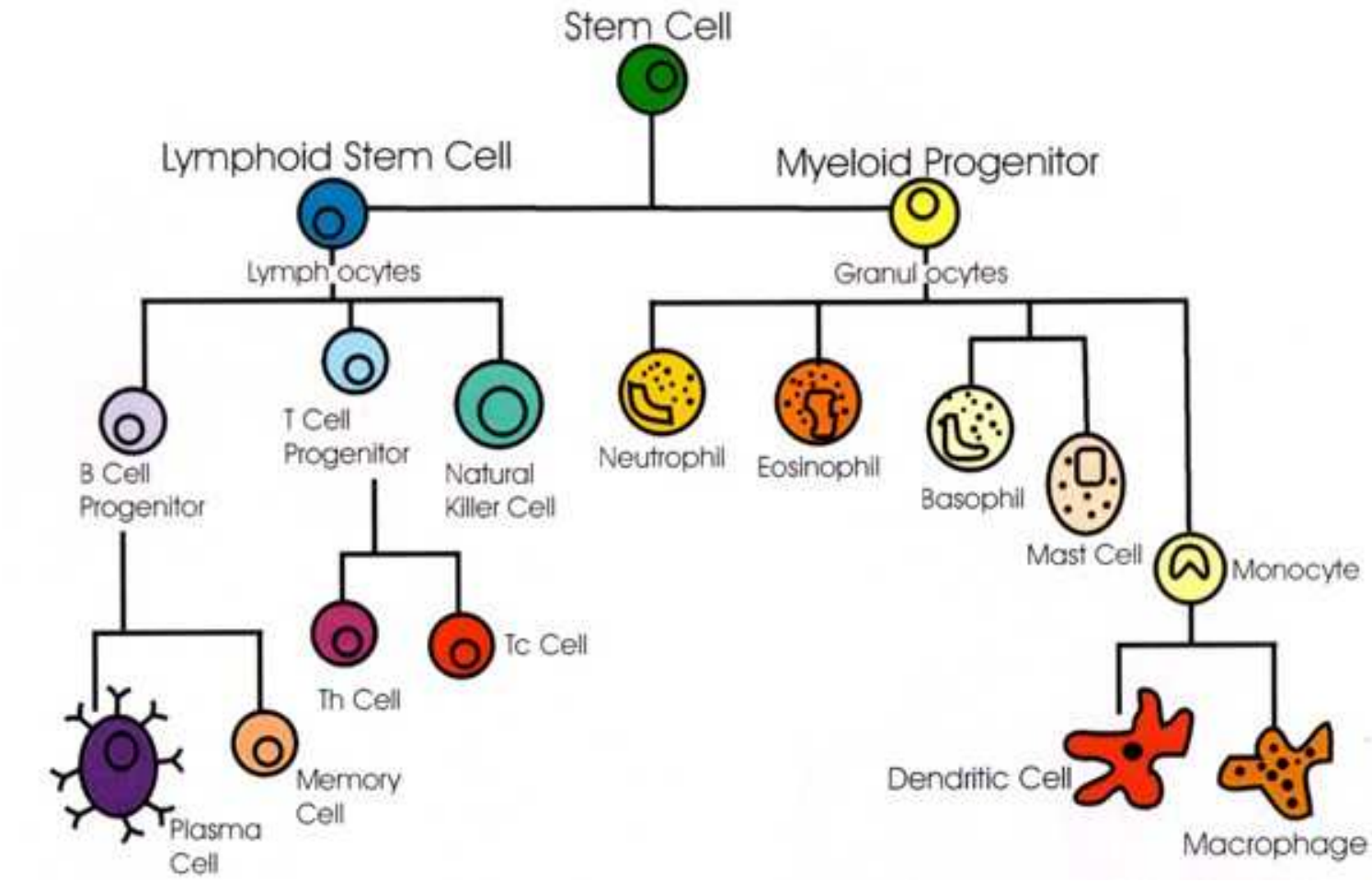
Cellular Origin of Immune Cells



Rational DiscoveryBlog.com

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The skin and mucosas form barriers against infection

- Epithelial cells and their products provide a physical and a chemical ‘barrier’ to pathogens.
- Commensal species prevent pathogens from colonizing by simple competition for space and by secretion of antibacterial factors.
- Most pathogens are eradicated by the innate immune system:
  - 1. Recognition of the pathogen
  - 2. Recruitment of effector mechanisms
  - 3. **Complement** interacts with pathogens to mark them for destruction and killing

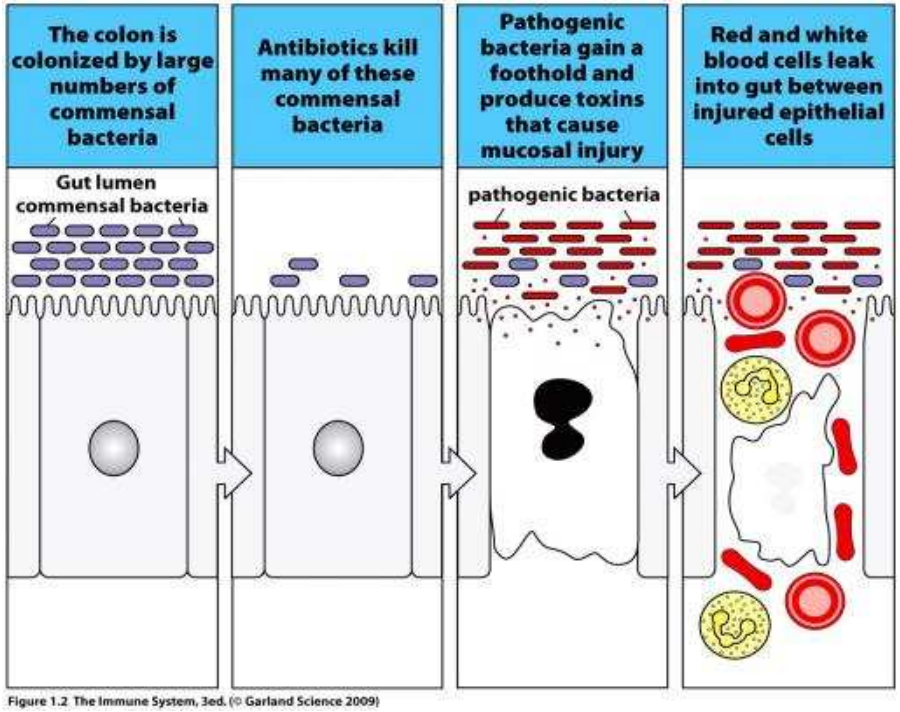

Figure 1.2 The Immune System, 3ed. (© Garland Science 2009)

Complement

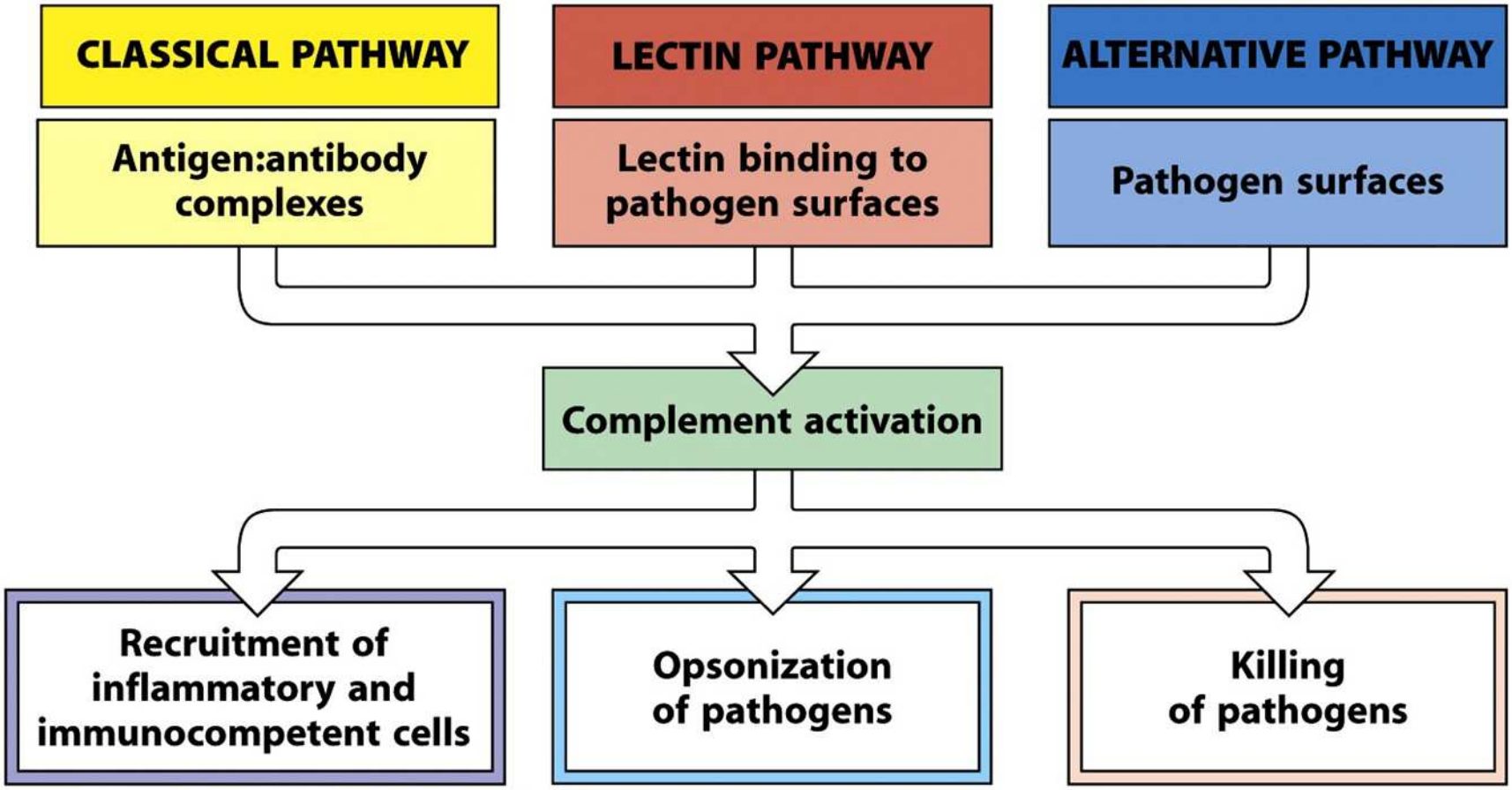

Figure 2-24 Immunobiology, 7ed. (© Garland Science 2008)

Innate Immunity

- **Innate immunity**:
  - First line of defense/Resistance before infection
  - Rapid response – minutes to hours
  - Recruits immune cells to sites of infection
  - Activation of Complement system
  - Kills pathogens and process antigen to initiate adaptive immunity
  - Not specifically directed against the invading microorganism (not antigen specific)
    - Dendritic cells/Macrophages
    - Neutrophils
    - NK cells
  - **NO IMMUNOLOGICAL MEMORY**

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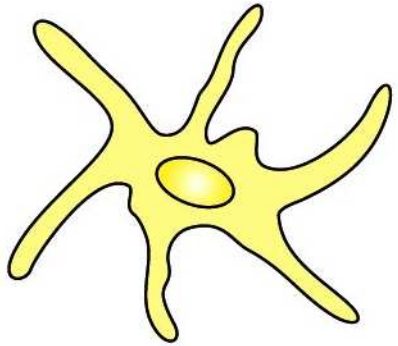
Dendritic Cells



- **Function**: Serve as the **gateway** between the innate and adaptive immune systems.
  - Sample the surrounding environment and determine whether or not to initiate an immune response
  - Multiple different functional subsets regulate and shape the ensuing immune response
  - Antigen uptake in peripheral sites
  - Antigen presentation
- **Location:** interfaces with the environment (lung, intestine and skin) and sites of immune interactions(spleen, lymph nodes, Peyer's)
- **Key Markers**: $CD11c^{+}$

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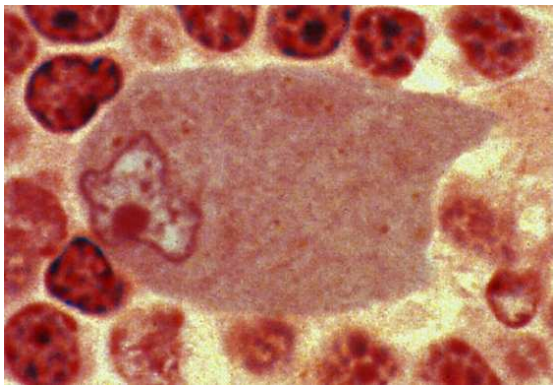
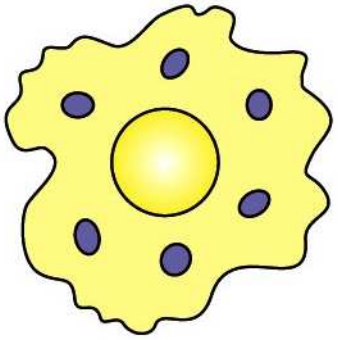
Macrophages





- **Function:** "Big Eaters" with multiple overlapping roles both at beginning and end of the immune response
  - Like DC they also sample the environment, but also have cytotoxic capabilities
  - Phagocytosis and activation of bactericidal mechanisms and antigen presentation
  - They are key regulators of wound repair and resolving an immune response
- **Location:** All tissues. Interfaces with the environment, sites of immune interactions, sites of inflammation
- **Key Markers:** $CD11b^{+}$, $CD68^{+}$, $CD14^{+}$

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Macrophages express receptors for many microbial constituents

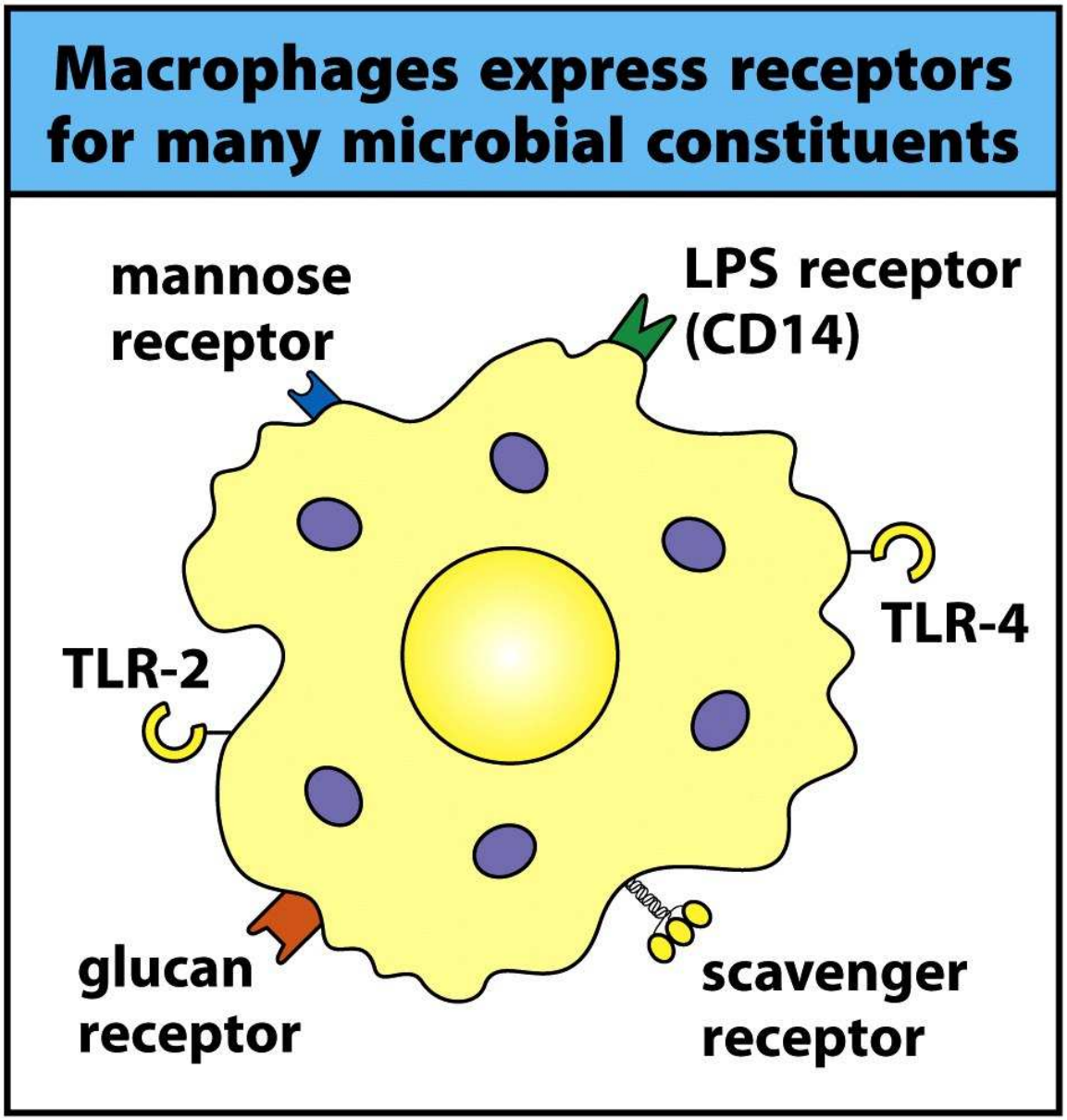

Figure 1-10 Immunobiology, 7ed. (© Garland Science 2008)

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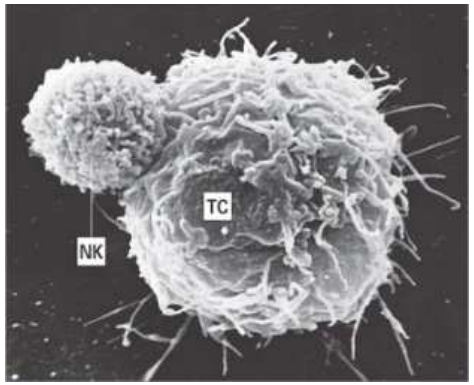
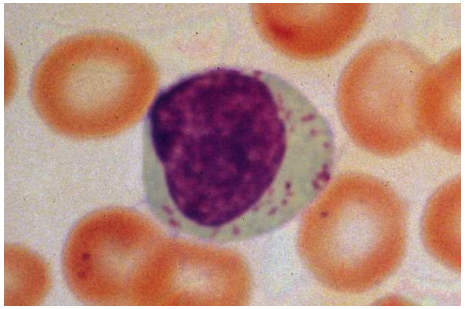
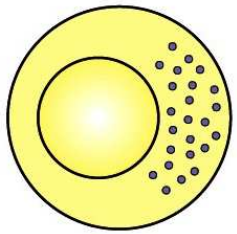
Natural Killer Cells (NK)







- **Function**: Early responders that have cytolytic potential as well as the ability to activate the immune system
  - "Natural Killing" is the ability to kill tumor cells without prior activation
  - Big sensors of altered self – e.g. loss of MHC Class I or up-regulation of stress molecules (e.g. heat shock protein)
- **Location:** bone marrow, immune sites (lymph nodes, spleen, tonsils and thymus) and the circulation
- **Key Markers:** $CD56^{+}$, $CD16^{+}$

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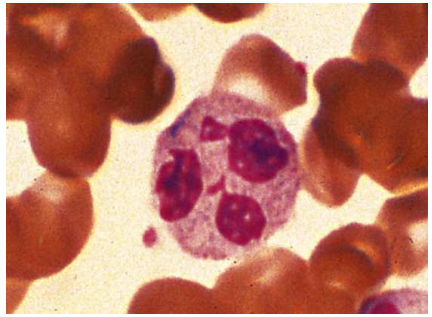
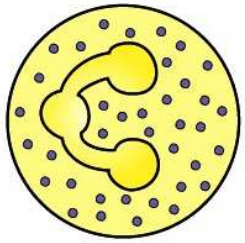
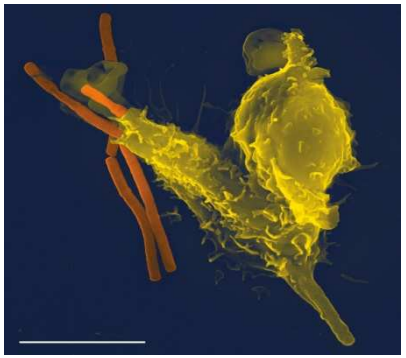
Neutrophils







- **Function:** Leave the blood and migrate to sites of infection in a multi-step process involving adhesive interactions that are regulated by macrophage-derived cytokines and chemokines.
  - Rapidly recruited to site of infection
  - Functions in anaerobic conditions
  - Capture, engulf and kill cells
  - Are the hallmark of acute inflammation
- **Localization:** Blood stream
- **Key Markers:** $CD15^{+}$, $CD66^{+}$, HLA-Class I

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Adaptive Immunity

- **Cellular Immunity**
  - Mediated by T lymphocytes
  - Requires Ag presentation by professional APCs
  - $CD4^+$ (helper): cytokine production for activation of other cells
  - $CD8^+$ (cytotoxic): recognizes and kills specific target cells
- **Humoral Immunity**
  - Mediated by B lymphocytes
  - Antibody-mediated immunity
  - B cells require dendritic and T helper cells to produce antibodies against soluble Ags

– **MEMORY CAN LAST A LIFETIME**

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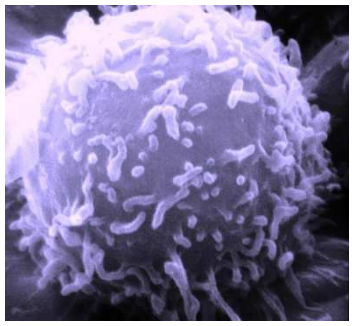
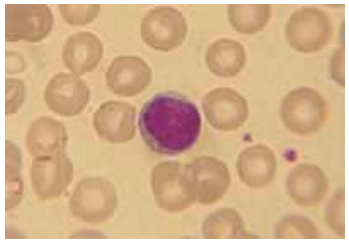
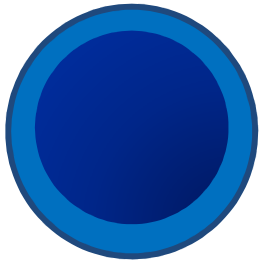
T-Cells







- **Function: Antigen-specific killing and orchestrate** an immune response through direct killing ($CD8^+$) and cytokine release ($CD4^+$)
  - Two main types: **$CD4^+$ and $CD8^+$ T cells that recognize antigens** presented in MHC Class II and Class I respectively
- **Location:** Immune sites (lymph nodes, spleen, tonsils and thymus) and sites of inflammation
- **Key Markers:** $CD3^+$, $CD4^+$, $CD8^+$, $CD28^+$
- $CD152^+$ (CTLA-4) and PD1

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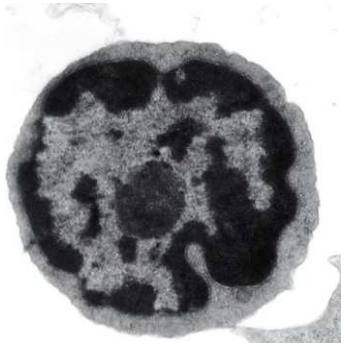
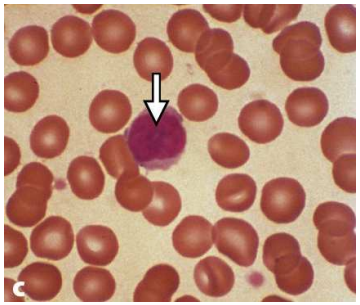
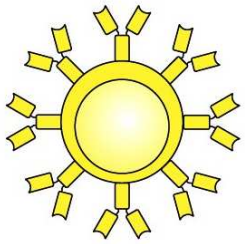
B-cells







- **Function: Antigen-specific production of antibodies**
  - They also help propagate an immune response by presenting antigens and producing cytokines
- **Location:** immune sites (lymph nodes, spleen, tonsils and thymus) and sites of inflammation
- **Key Markers**: $CD19^+$, $CD20^+$, $CD21^+$, HLA Class II

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Antigen

- **Antigen (Ag)**: molecule recognized by receptors on B and T lymphocytes
- **Ags** are the driving force of adaptive immunity which responds to **Ag** stimulation with proliferation and differentiation
- Lymphocytes are extremely sensitive to their specific **Ags**
- T and B cell receptors bind to their cognate **Ags** with a high degree of specificity
  - The part of the antigen bound by receptor is the **antigenic determinant** or **EPITOPE** (not the whole antigen)

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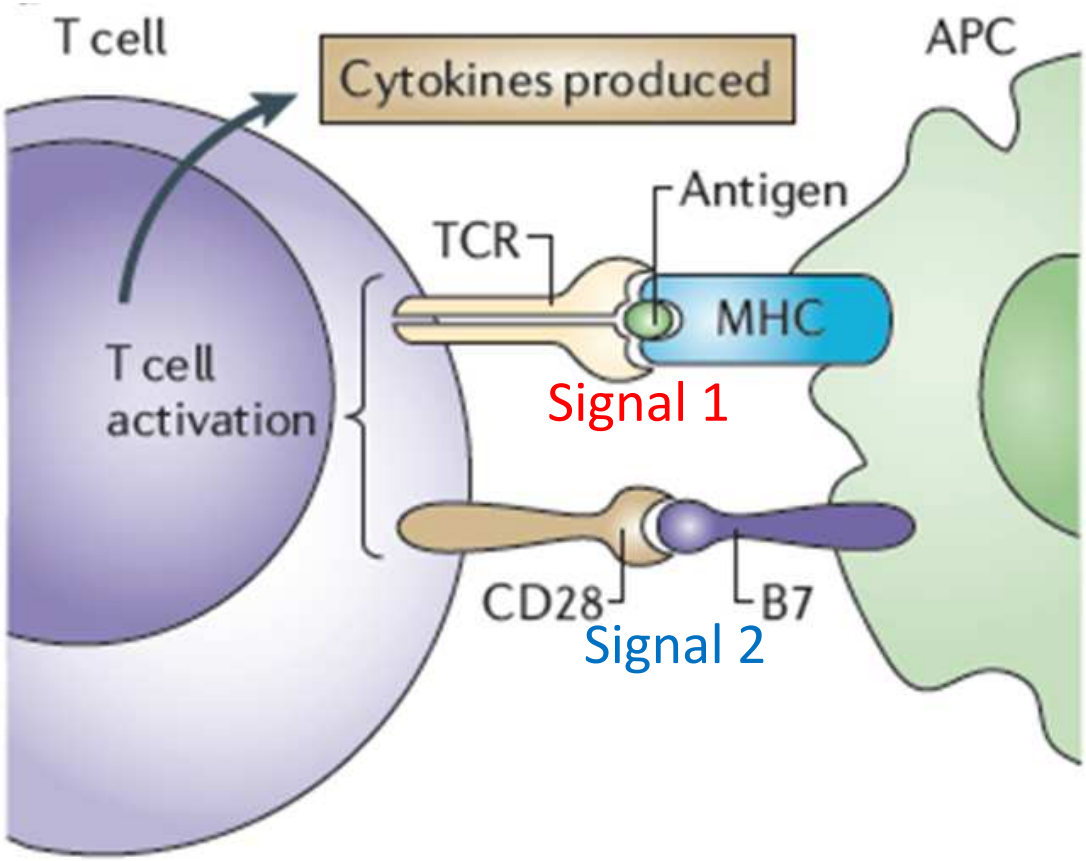
T-cell Activation



Signaling between CD28 cells and B7.1/B7.2 on APC

Leads to production of IL-2 required for T cell survival and proliferation

Sharma, Nature Reviews-Cancer, 2011

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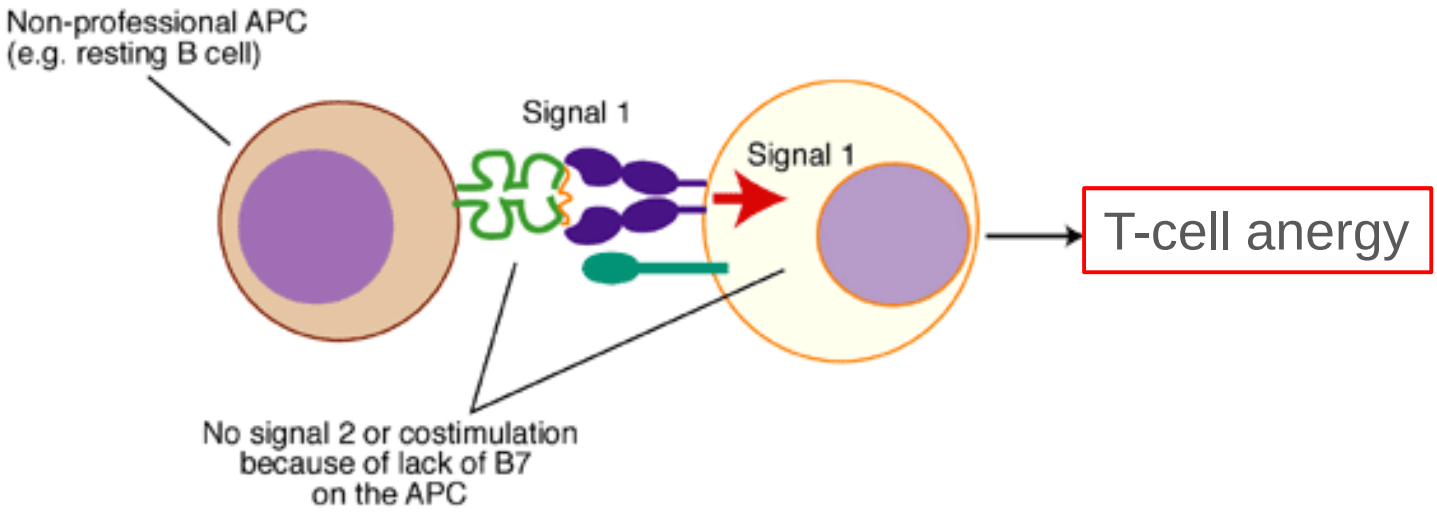
Anergy



- Initial signal for T cell activation
- In the absence of signal 2, T cells will not be activated, and may undergo under **anergy** or **apoptosis**

Expert Reviews in Molecular Medicine, 2000

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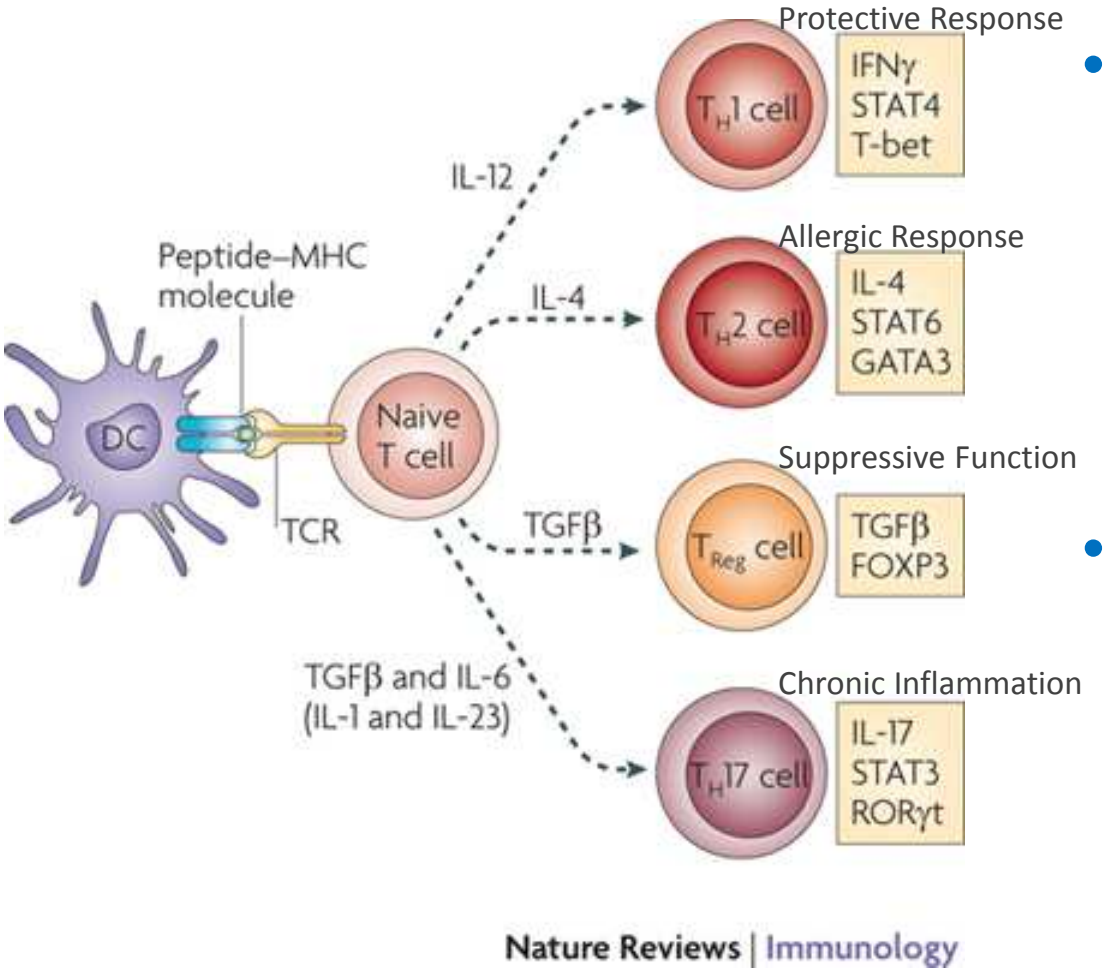
APCs and MHC Complex

- **MHC class I (HLA-A/B/C)**
  - Typically peptides derived from endogenous proteins
- **MHC class II (HLA-DR)**
  - Typically peptides derived from exogenous proteins

Tissue	MHC class I	MHC class II
Lymphoid tissues		
T cells	+++	+*
B cells	+++	+++
Macrophages	+++	++
Dendritic cells	+++	+++
Epithelial cells of the thymus	+	+++
Other nucleated cells		
Neutrophils	+++	–

T-cell Differentiation



- DC maturation results in the development of functionally different effector DC subsets that selectively promote T helper 1 (T_H1)-, T_H2- or regulatory T-cell responses.
- The differentiation of each of these effector T cell subsets is controlled by distinct sets of transcription factors

Zou, Nature Reviews-Immunology, 2010

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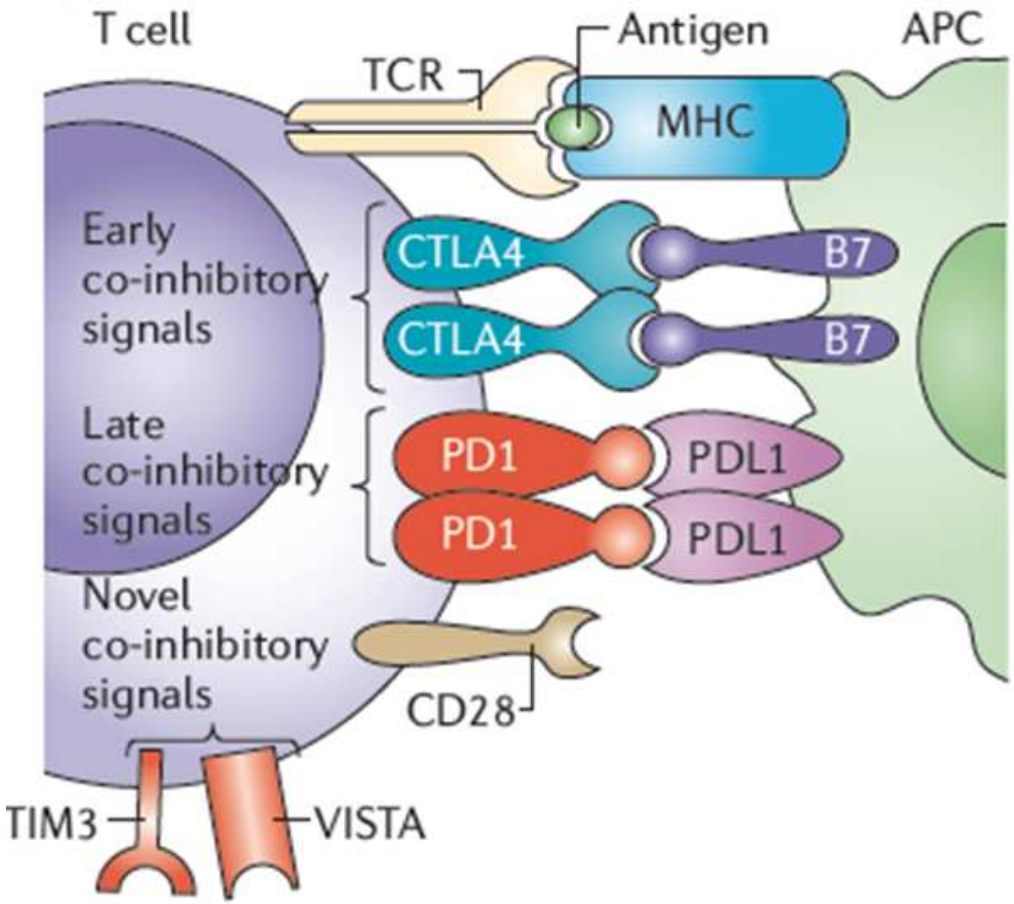
Inhibitory Signals



Sharma, Nature Reviews-Cancer, 2011

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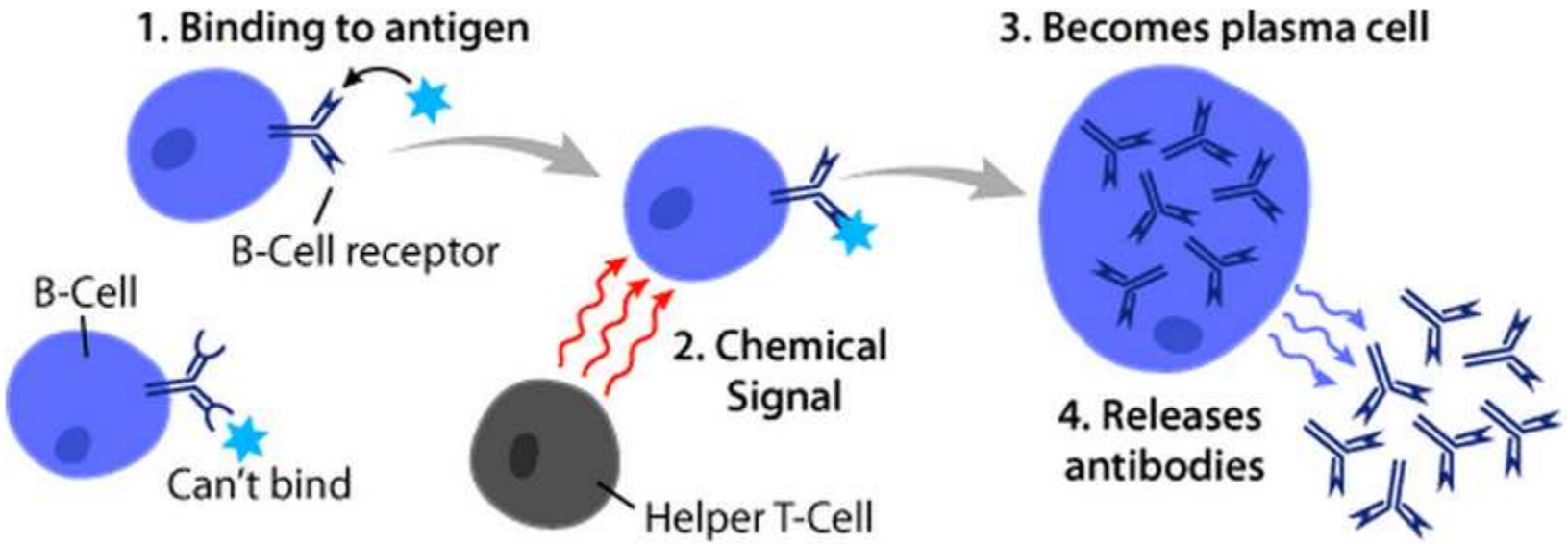
B-cell Activation



- Bind an antigen, receive help from a cognate helper T-cell, and differentiate into a plasma cell that secretes large amounts of antibody

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Secreted Antibodies

- Antibodies themselves are not inherently destructive to pathogens.

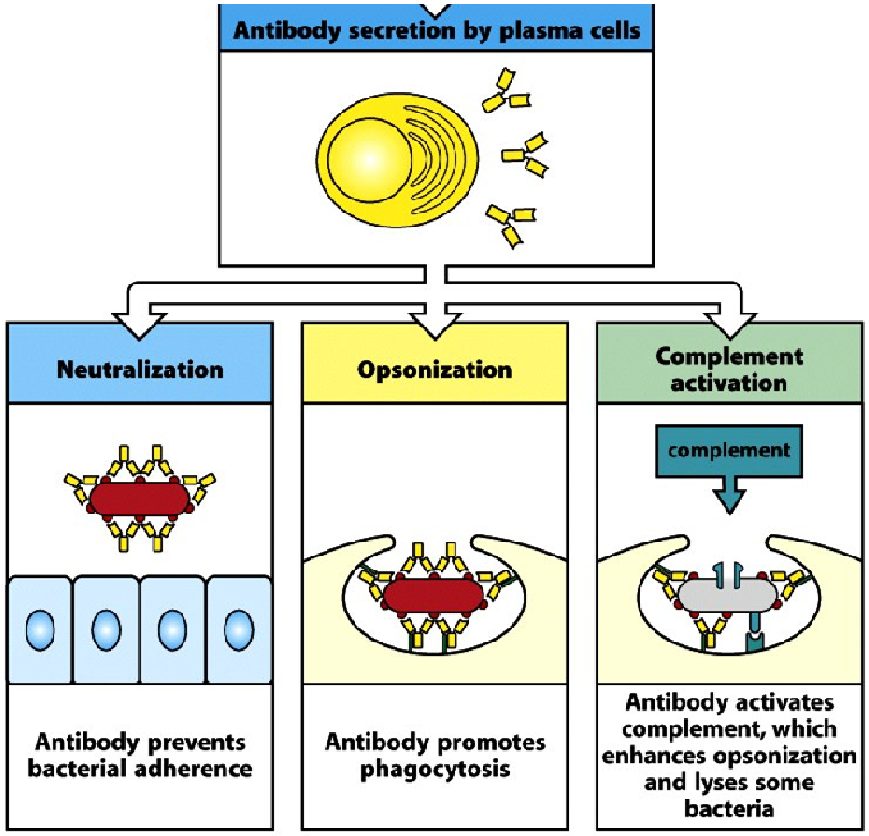

Figure 9-1 Immunobiology, 7ed. (© Garland Science 2008)

Summary

- There are four key “organs” of the immune system: *Bone Marrow, Lymph Node, Spleen and Thymus* that give it system wide access to protect against a variety of targets
- There are five major immune cells: Dendritic cells, Macrophages, NK Cells, T cells and B cells
- There are two broad categories of the immune system: **Innate Immunity** (antigen non-specific) and **Adaptive Immunity** (antigen-specific)
- **Innate** and **adaptive** immunity are equally important and can not properly respond to a pathogen invasion without another.

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Summary

- The immune response involves a series of specific steps starting from detection of a target to its elimination and finally returning the body to its normal state

- T cells are required to potently activate B cells to proliferate and synthesize antibodies. T-cells and B-cells must recognize components of the same antigen to interact effectively

- Many disease states, particularly cancer, arise from failed immune responses, and retraining the immune system is the goal of all immunotherapy from vaccination to checkpoint inhibitors

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Thank You!


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