

Immunology

Principles of the Adaptive Immune Response

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Objectives:

- Why adaptive immune system?
- Self/non-self discrimination: Significance
- Mediators of adaptive immunity
- Cell-mediated versus humoral immunity
- T and B cell activation
- Immunological memory
- Adaptive versus innate immunity

Discussion

What are the hallmarks of the innate immune system?

Why adaptive immunity?

Why adaptive immunity?

- **Shortcomings of innate immunity:**
 - **Non-specific**
 - **Similar pattern of response for all pathogens**
 - **Poor regulation**
 - **Control mechanisms are poor or lacking**
 - **Poor amplification**
 - **Response magnitude same for all insults**
 - **Lack of self discrimination**
 - **Harm to self results for lack of specificity**
 - **Short duration**
 - **No memory**

The enemies are different....



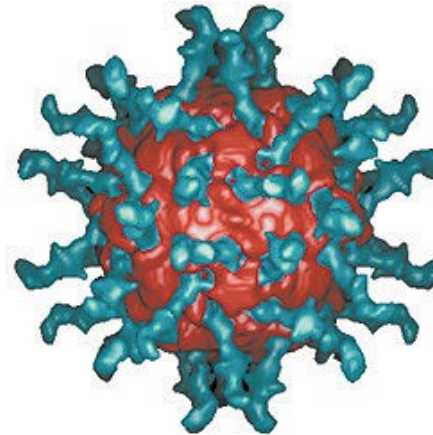
BACTERIA
-Clostridium difficile
(causes antibiotic-associated colitis & diarrhea)



FUNGUS
-Epidermophyton floccosum
(causes athlete's foot)



PARASITE -
Tapeworm



VIRUS- Polio

....therefore the responses must be tailored to specific enemies.

• Successful immune response is a huge investment!! You need to a way to remake it:

→ Faster

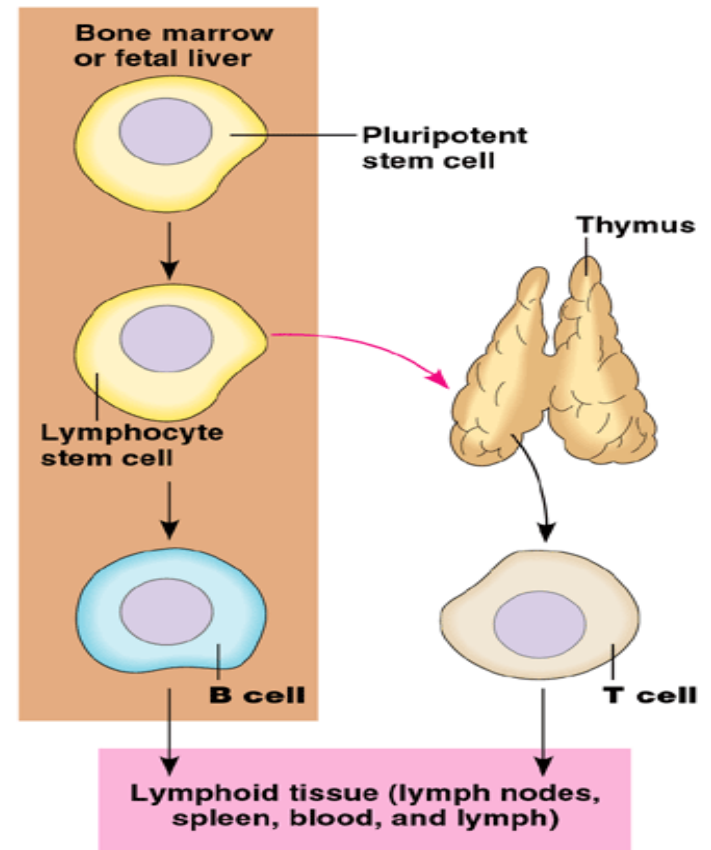
→ Larger

→ More specific

→ Less damage to self

Specific (Adaptive) Immunity

- **Lymphocytes**
 - pluripotent stem cells...
 - B Cells (bone marrow)
 - T Cells (thymus)
- **Antigen:** a foreign molecule that elicits a response by lymphocytes (virus, bacteria, fungus, protozoa, parasitic worms)
- **Antibodies:** antigen-binding immunoglobulin, produced by B cells
- **Antigen receptors:** plasma membrane receptors on B and T cells



Principles of Adaptive Immune Responses

- Specific recognition of individual antigens by immune cells via antigen receptors
- Clonal selection and expansion occurring after antigenic recognition- **PRIMARY IMMUNITY**
 - Generation of effector T cells and B cells
- Later exposure to the same antigen: **SECONDARY (MEMORY) RESPONSE**
 - Rapid proliferation of memory cells

Clonal Selection of Lymphocytes

- Lymphocytes are made randomly
 - Not directed by antigens
- Each lymphocyte bears a specific receptor
- Varied receptor specificity due to rearrangement of genes
- Antigen “selects” appropriate lymphocytes
- “Selected” cell undergoes clonal expansion
- Expansion produces clones of effector and memory cells

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Summary of clonal selection

- *Each antigen, by binding to specific receptors, selectively activates a tiny fraction of cells from the body's diverse pool of lymphocytes.*
- *This relatively small number of selected cells gives rise to clones of thousands of cells, all specific for and dedicated to eliminating the antigen.”*
- *At the end of the response, a population of the expanded cells (memory) persists and are mobilized faster during subsequent encounter*
 - *Frequency of memory cells several orders of magnitude higher than naïve cells*

Self/non-self discrimination

- Property of the adaptive immune system to mount specific/targeted responses to foreign antigens without harming self
- Achieved via early and continuous presence of self-antigens
- Important for self tolerance and control of autoimmunity
- Can be broken under certain conditions

Self Tolerance

- **Central Tolerance (primary):**
 - Deletion of cells that recognize self antigen in primary lymphoid organs
- **Peripheral Tolerance (secondary):**
 - Deletion or anergy of cells that recognize self antigens in the peripheral tissues
 - Regulatory mechanisms also involved
- **Failure of tolerance results in autoimmune diseases**

Significance of Self/non-self discrimination

- Prevention of autoimmunity
- Scarce resources are all directed against “potential” enemies
- What is the price for self discrimination??
- Why do we develop autoimmune diseases anyway?

Mediators of Adaptive Immune Response

- Highly dependent on T and B cells bearing specific receptors
 - T cell receptors
 - Membrane immunoglobulin on B cells
- Antigen presenting cells (APCs)
 - Macrophages, Dendritic cells, B cells

Types of Adaptive immunity

- **Cell-mediated immunity:** Immunity mediated by T cells via:
 - Direct lysis of target (infected) cells
 - Production of cytokines that activate infected cells to kill pathogens
- **Humoral immunity:** mediated by antibodies produced by B cells
 - Antibodies bind to whole or fractions of antigens outside cells

Division of Labor, yet cooperative!!

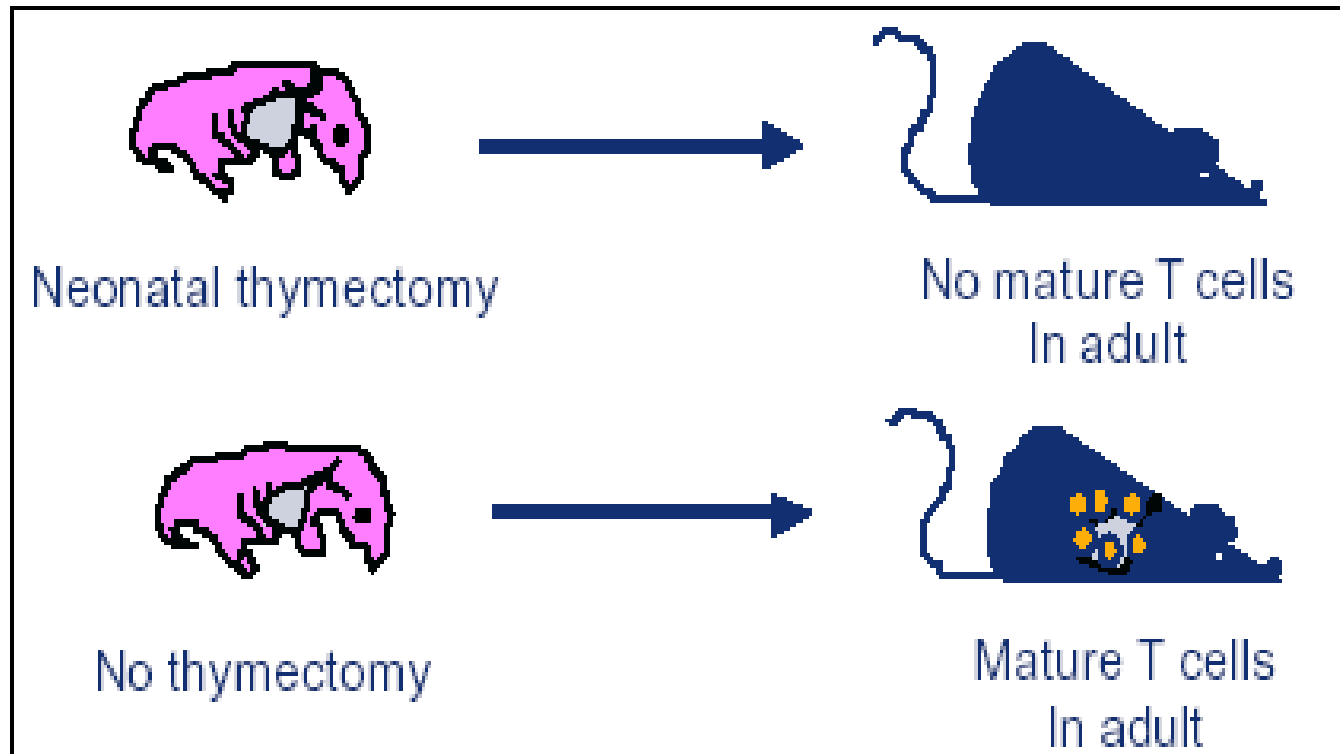
- **T cells mediate cellular immunity:**
 - **Control of intracellular pathogens**
 - **Control of tumors**
- **B cells mediate Humoral immunity:**
 - **Control of extracellular pathogens**
 - **Mediates allergy and hypersensitivity**
- **T and B cells cooperate for effective immunity**
 - **T cell help may be needed for B cell activation and B cells may present Ag to T cells**

T cells

- 70% of lymphocytes in peripheral blood
- Lymphoid progenitor in bone marrow
- Maturation in the thymus
 - Positive and negative selection
 - Absent in nude (athymic) and SCID mice
- T cell receptor complex
- T cell types
- MHC restriction
- **Function: T cells mediate cellular immunity**

The thymus is important for T cell development

- **Athymic mice (nude) and humans (DiGeorge syndrome) are immunodeficient due to lack of T cells**



MHC Molecules

- Major histocompatibility antigen
 - Body cell surface proteins coded by a family of highly polymorphic genes
 - MHC class I: found on all nucleated cells
 - MHC class II: found only on APCs
- T cell receptors recognize antigenic peptide/MHC complexes
 - CD4⁺ T cells: restricted by class II
 - CD8⁺ T cells: restricted by class I

MHC Restriction:

- Property of T cells to recognize antigens presented **only** by self-MHC molecules
- Vital aspect of self/non-self discrimination and hence adaptive immunity
- A marker of T cell that has been positively selected
- Selection occurs in the thymus

T cell selection/education:

Positive selection

Selection by retention in the repertoire of thymocytes that express TcR restricted in their recognition of antigen by self MHC

Negative selection

Removal from the repertoire of thymocytes that express TcR that recognise self peptide antigens presented by self MHC

Types of T cells

- **Conventional:**
 - Uses $\alpha\beta$ TCR
 - Helper (CD4+) and cytotoxic (CD8+) T cells
 - More abundant and highly specific
 - Restricted by classical MHC (I and II) molecules
- **Non-conventional:**
 - Uses $\gamma\delta$ TCR
 - Primitive with broad specificity
 - Restricted by non-classical molecules

CD4+ T cells

- T cells with CD4 marker (glycoprotein)
- 70% of T cells in the periphery
- T helper cells
- Play central role in modulating cellular immunity via secretion of cytokines that modulate:
 - B cell activation
 - Immunoglobulin secretion (quality)
 - Macrophage and dendritic cell activation
 - Cellular chemotaxis and inflammation
- Th1 versus Th2 cells

Th1 and Th2 cells

- **CD4+ T helper cells can be classified into two based on their cytokine profiles: T helper cell type 1 (Th1) and T helper cell type 2 (Th2).**
 - **Cytokine profile is influenced by several factors:**
 - **Nature and dose of antigen**
 - **Route of infection**
 - **Initial cytokine environment**
 - **Type of antigen presenting cell/costimulation**
 - **Genetic background**
 - **The cytokine profile determines the effector function of the helper cell**

Differences b/w Th1 and Th2 cells

Th1 cell

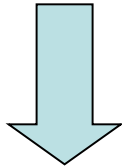
- Produces type 1 cytokines
 - IL-2, IFN- γ , TNF- α , TNF- β
- Activates macrophages and DCs for intracellular killing of pathogens
- Mediates CMI

Th2 cell

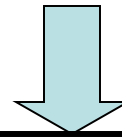
- Produces type 2 cytokines
 - IL-4, IL-5, IL-10, IL-13
- Provides help to B cells in antibody response
- Mediates allergy and immunity to extracellular pathogens, including parasites

CD4+ Th1 vs. Th2 cells

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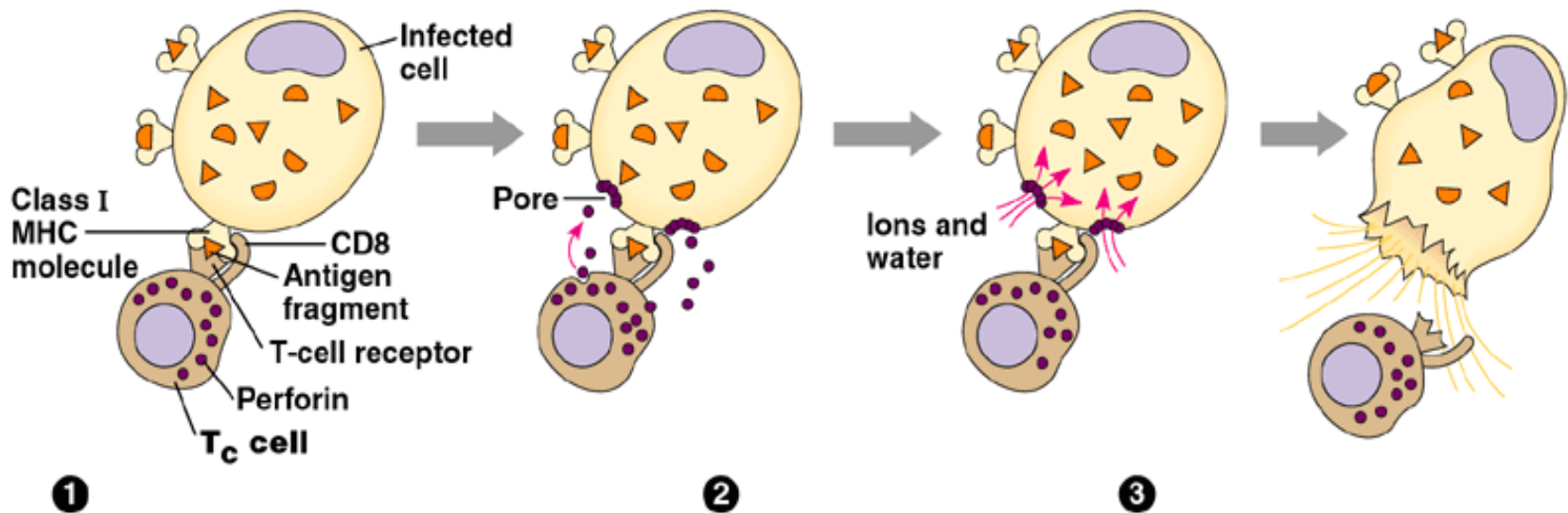
Intracellular pathogens



**Antibodies for extracellular
pathogens and allergy**

Cytotoxic T cells

- T cells that express CD8 molecule on their surface
- 30% of T cells in the periphery
- Destroy cells infected by intracellular pathogens and cancer cells
- Class I MHC molecules (nucleated body cells) expose foreign proteins
- T_c cell releases perforin and granzymes, proteins that form pores in the target cell membrane; causing cell lysis and/or apoptosis



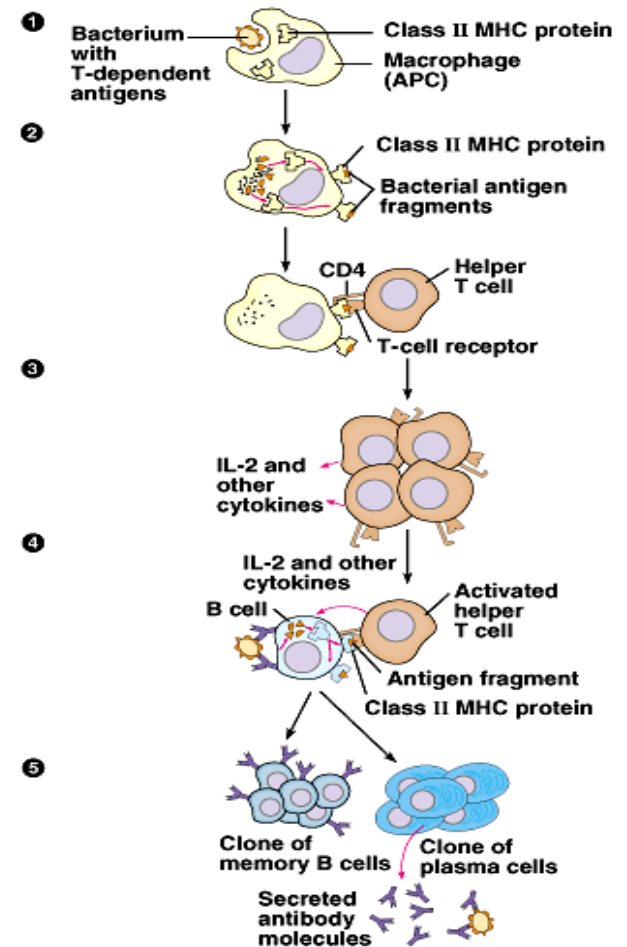
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Humoral immunity

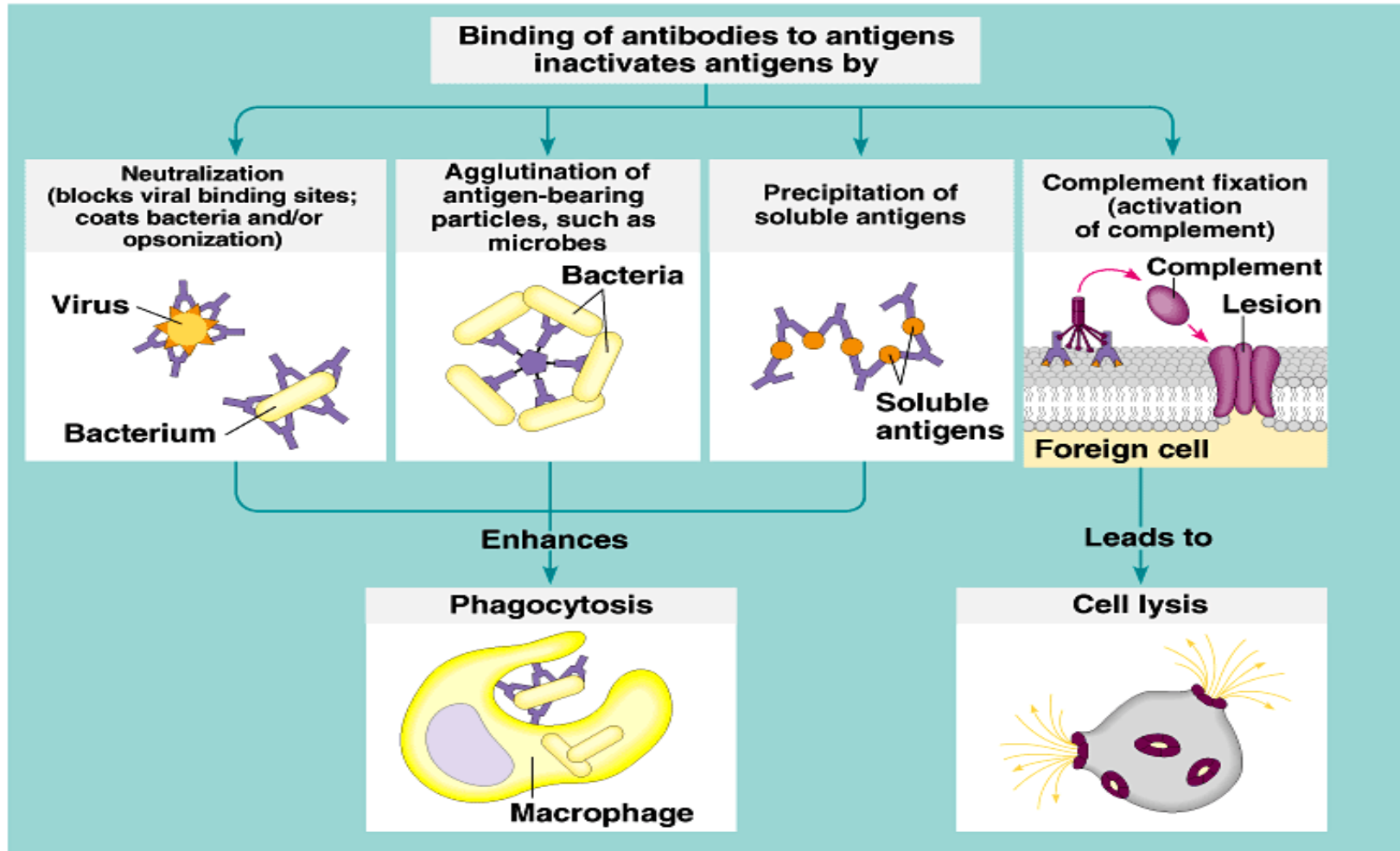
- Mediated by B cells
- B cell development starts in fetal liver
- At birth, bone marrow (mammals) or bursa of fabricius (birds)
- B cells produce antibodies (5 classes)
 - IgM, IgD, IgG, IgA and IgE
- Antibody production may/may not depend on T cells

Humoral response: B cells

- Stimulated by T-dependent antigens (help from TH cells)
- APCs with class II MHC proteins process and present antigen to CD4+ T cells (helper cells)
- Helper T cell become activated
- Activated T cell secretes cytokines that in turn activate B cell
- B cell differentiates into effector and memory (plasma) cells and produce antibodies



Antibody-mediated effector mechanisms



COMPARISON OF T CELLS AND B CELLS

| T CELLS | B CELLS |
|------------------------------|-----------------------------|
| Origin: Bone marrow | Bone marrow. |
| Maturation: Thymus | Bone marrow; Bursa in birds |
| Long-lived | Short-lived/long-lived |
| Highly mobile | Fairly mobile/stationary |
| No complement receptors | Complement receptors |
| No surface Ig | Surface immunoglobulins |
| No antibody synthesis | Antibody synthesis |
| Effector: cellular & humoral | Effector: humoral only |

Reproduced from Brock et al, Biology of microorganisms, 4th ed.

Antigen presenting cells (APC)

- Cells with the capacity to capture, process and present antigenic peptides to T cells
- Antigens are presented in the context of MHC class I or II
- Also deliver co-stimulatory signal (signal II) to T cells leading to proper activation
- Only APCs can activate a naïve T cell
 - **Dendritic cells, Macrophages, B cells**

Dendritic Cell

- Most potent APC for naïve T cells
- Many long membrane extensions
- Highly variable depending on location
 - Langerhan cells in the skin
 - Interdigitating cells in the thymus
 - FDC in germinal centers
 - Veiled cells in lymphatics
 - Blood dendritic cells in circulation

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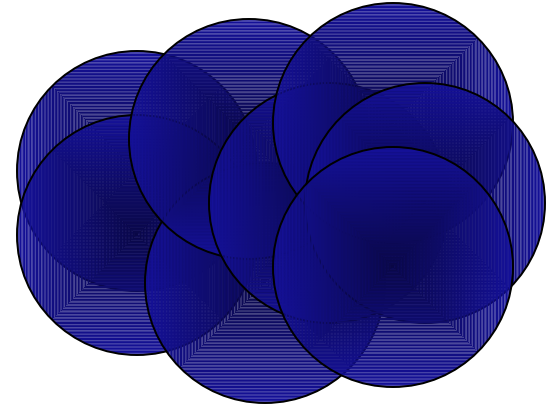
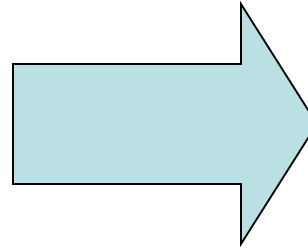
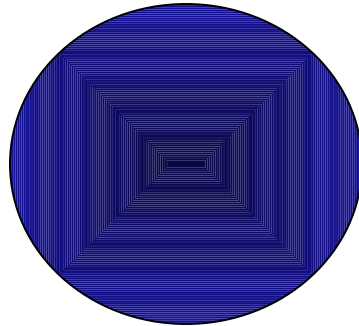
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Maturation of dendritic cell

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Only mature DC activates T cells

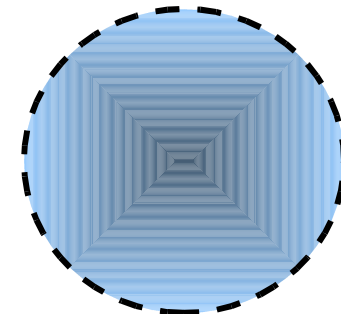
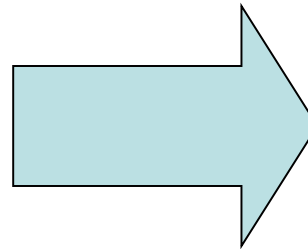
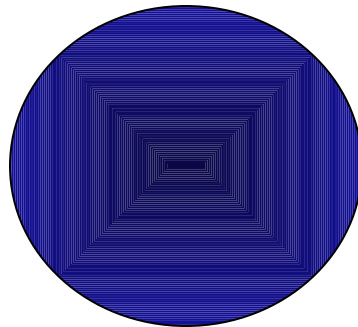
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Mature DC

T cell

Activation/Proliferation



Immature DC

T cell

**Anergy/Apoptosis/
Deletion**

Functions of APCs

- T cell selection in the thymus (only DCs)
- Trap and capture antigen in the periphery
- Process antigen into peptides
- Store antigens
- Transport antigens to peripheral lymphoid tissues
- Present antigenic peptides to T cells
- Co-stimulate T cells

T Cell Activation

- **Requirements: Two signals**
 - **Signal 1: specific recognition of antigen (peptide-MHC complex) via antigen receptor**
 - **Signal 2: costimulatory signals from APC**

- **Signal 1 alone leads of unresponsiveness**
 - **Anergy, Deletion, Apoptosis**

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B Cell Activation

- **Requirements: Antigenic structure determines the rules**
- **T cell dependent antigen:**
 - **Signal 1: specific recognition of native antigen via receptor**
 - **Antigen processed into peptides and presented to helper T cells via MHC class II**
 - **Signal 2: costimulatory signals from helper T cell**
 - **Signal 2 results in affinity maturation and isotype switching**

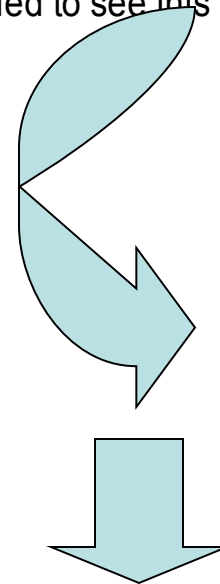
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B Cell Activation contd:

- **T cell independent antigen:**
 - Repetitive epitopes
 - **Signal 1: specific recognition of native antigen via receptor**
 - **Cumulative binding energy enough to trigger activation**
 - **No Signal 2 required!!**
 - **Poor inducers of affinity maturation and isotype switching**

Repeating epitopes e.g. LPG

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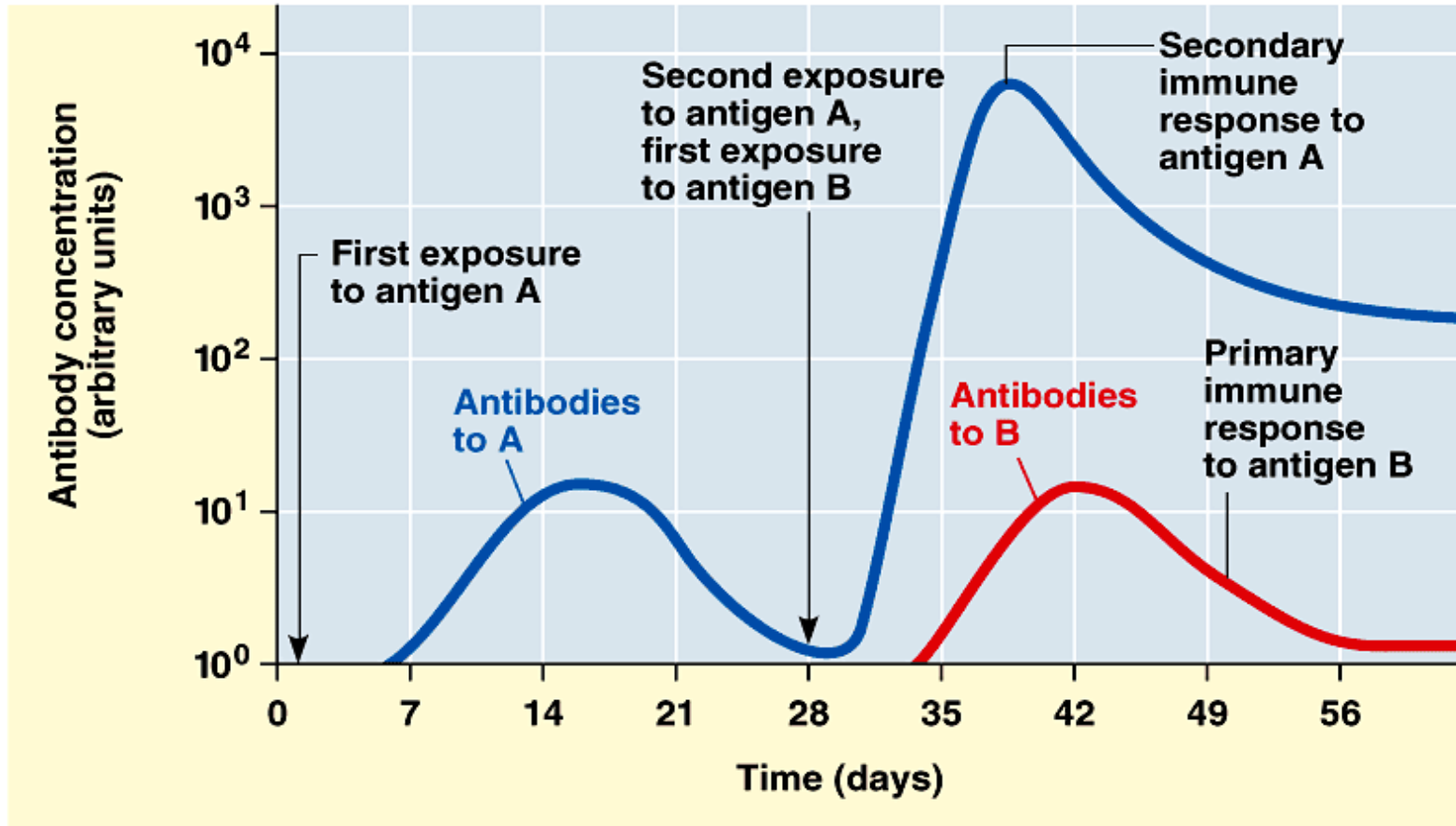


ACTIVATION

Immunological Memory

- Ability of the immune system to respond **more rapidly and effectively** to pathogens that have been **encountered previously** – either by previous infection or by vaccination
- This reflects the pre-existence of clonally expanded lymphocytes with specificity for the antigen.
- Hallmark of adaptive immunity

Schematic representation of memory response (B cell)



Effectiveness of memory

- **More responder cells available**
 - Frequency higher than naïve cells
- **More efficient antigen recognition/activation**
 - May not require costimulatory signals for activation
- **Rapid and effective migration to tissues and lymph nodes**
 - Expresses different homing/chemokine receptors than naïve T cells
- **More effective function**
 - Produce qualitatively and quantitatively more cytokines (T cells) or antibodies (B cells)
- **Longer lasting**
 - Naïve cells live for few days/months; memory cells persist for years

Maintenance of Memory

- **Long-lived memory cells persist in the absence of antigen**
 - Experiments with transgenic mice
 - MHC deficient animals
- **Memory cells are perpetually stimulated by residual antigen**
 - Antigens trapped for years in FDC (> 35 yr)
 - Chronic infections (clearance of infection leads to loss of resistance)
 - Cross-reactive environmental antigens

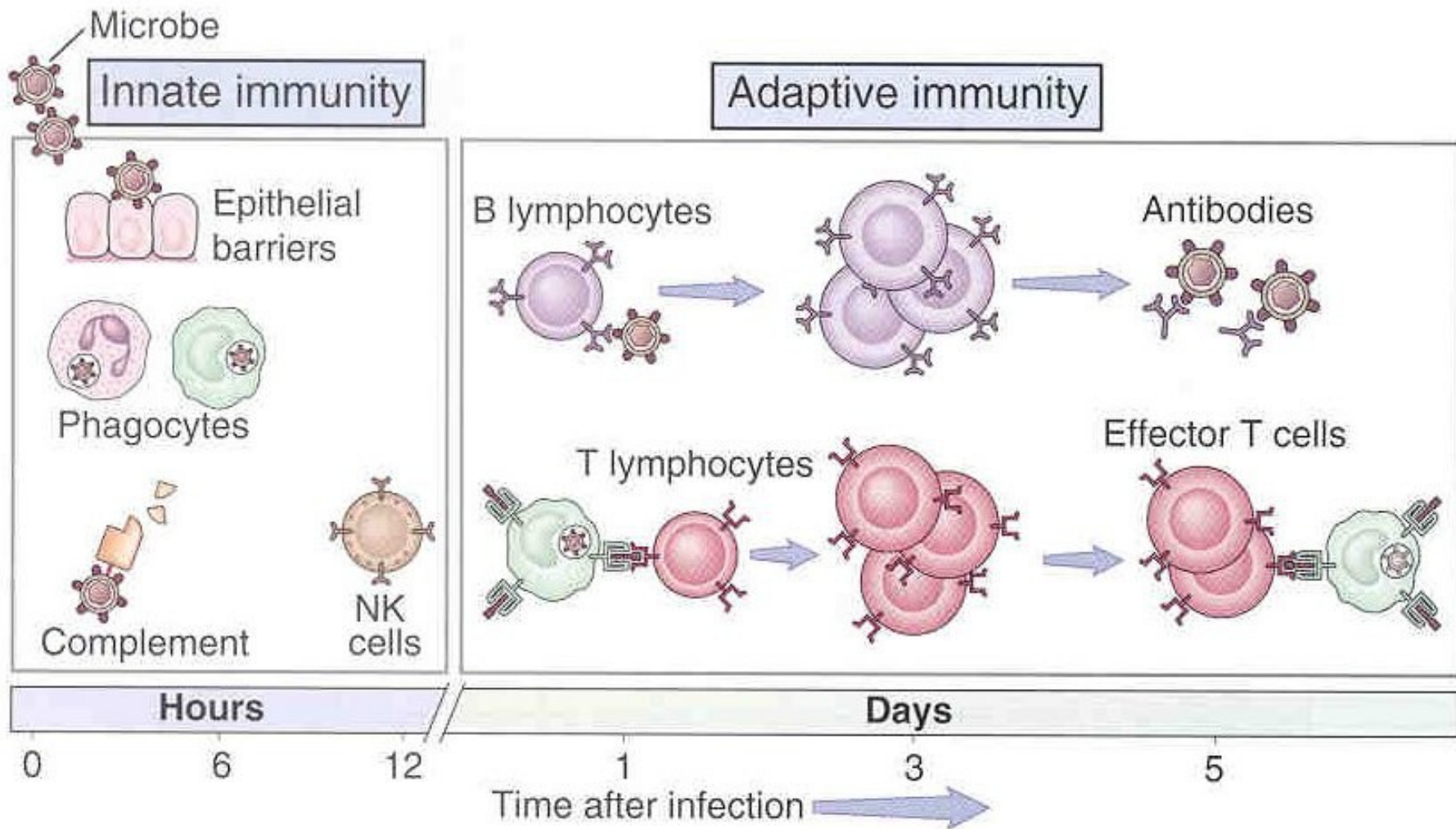
Innate versus Adaptive immunity

| | Innate | Adaptive |
|---------------------|---------------------|--|
| Receptors | Primitive and broad | Highly specific (T and B cell receptors) |
| Kinetics | Fast (hours-days) | Slow (days-wks) |
| Regulation | +/- | ++++ |
| Amplification | No (insignificant) | Yes |
| Self discrimination | - | ++++ |
| Duration | Short (days) | Long (months/yr) |
| Memory | - | ++++ |

Innate immunity shapes adaptive immunity

- Cells of the innate immunity participate in both priming and effector phases of the adaptive immunity
 - Macrophages and DCs present antigens to T cells
 - IFN- γ produced by NK cells can activate macrophages to kill intracellular pathogens
 - NK cells can directly lyse infected cells
- Innate immune responses generate molecules (including cytokines) that act as costimulatory (second) signals for T and B cell activation
 - APCs express costimulatory molecules for T cell activation
 - Production of cytokines (eg IL-1, IL-2, IL-4, IL-10, IL-12, TNF- α , IFN- γ)

The big picture...Integration of innate and adaptive immunity



Courtesy: Abbas and Litchman; Basic Immunology

Summary

- **Evolutionary need for adaptive immunity:**
 - Self/non-self discrimination, specificity, amplification, regulation, duration and memory
- **T and B cells are mediators of adaptive immunity**
 - T cells: cell-mediated immunity
 - B cells: humoral immunity
 - Cells of innate immunity also participate (DCs, Macrophages)
- **Activation of T and B cells are different:**
 - T cells: specific recognition of peptide/MHC complex (signal 1) and costimulatory signals by APC (Signal 2)
 - B cells: recognize native proteins (signal 1). May/may not require signal 2 from CD4⁺ Th cells (TD and TI antigens)
- **Immunological memory: an important hallmark**
 - Faster and rapid response on a second antigen encounter
- **Innate immune response shapes the adaptive immunity**