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Institute of Fundamental Medicine and Biology
Department of Morphology and General Pathology

Overview of the Immune System

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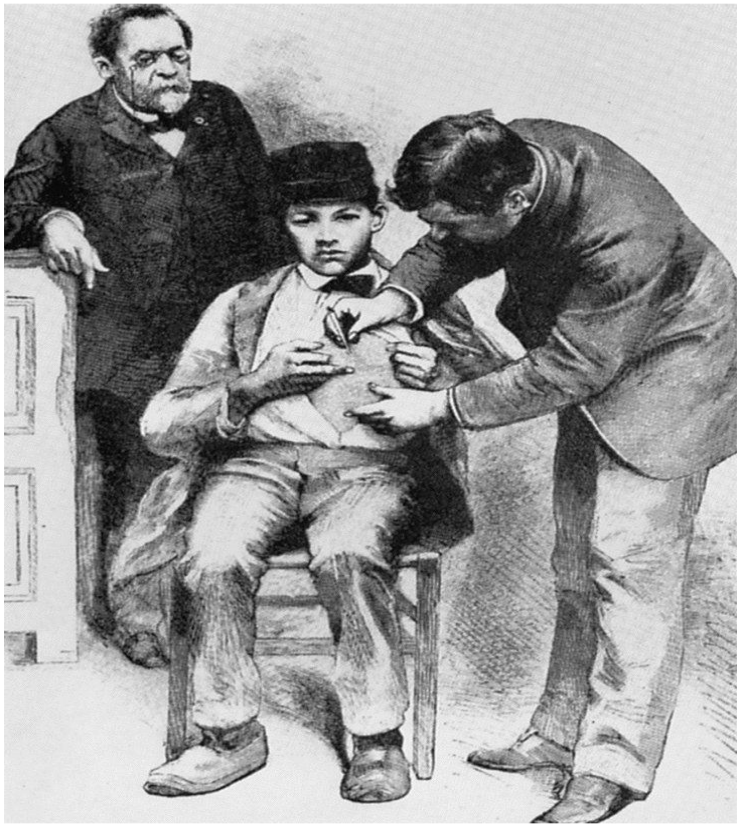
Immunology

- The Study Of Immune System
- Latin Word *immunis*=“exempt”
- Earliest Written Reference was Thucydides 430 BC
- Pasteur Was First To Successfully Apply Vaccination



Pasteur Observing Rabies Vaccination

Humoral Or Cellular Immunity?

- Pasteur Did Not Know How Vaccination Worked
- Behring and Kitasato (1890) Proposed Serum Was Responsible For Immunity
- Elvin Kabat (1930), gamma-globulin, Antibody
- Antibodies Were Present in Body Fluids=Humor
- Therefore: Humoral Immunity

Innate (Non-Specific) Immunity

- Innate Immunity Made Up Of 4 Forms
- Anatomical, physiological, phagocytic and inflammatory
- Anatomical: skin, epidermis (densely packed dead cells)
- Flow of Mucus Prevents Bacterial Entry By Washing Them Away
- Normal Flora Colonize Epithelial Cells Of Mucosal Surfaces, Pathogens Compete With Them For Attachment Sites

Cell Mediated Immunity

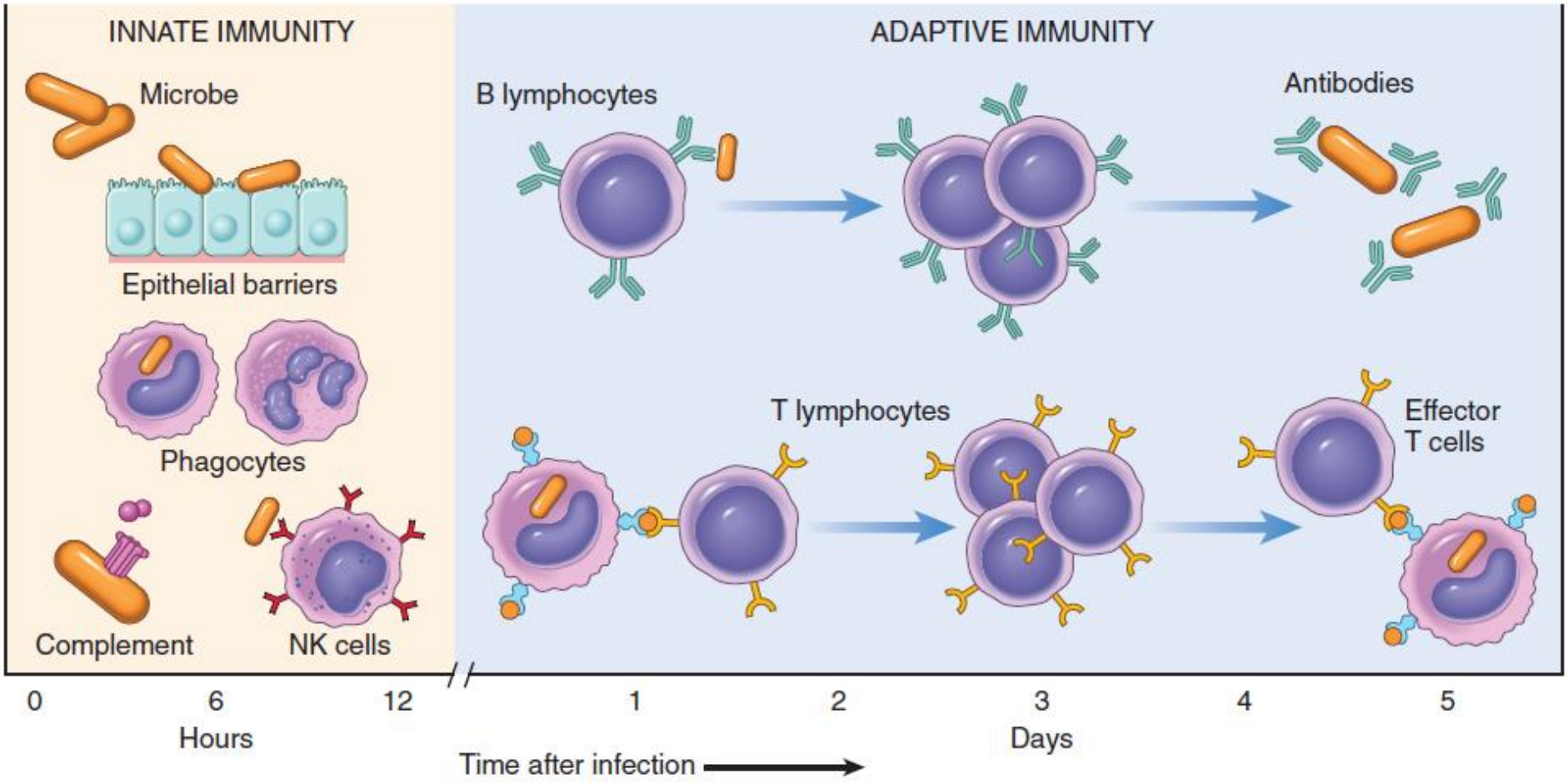
- In 1883 Ellie Metchnikoff Showed That Cells Responsible For Immune State
- Phagocytes More Active In Immune Animals
- She Hypothesized That Cells Responsible For Immunity, Not Serum Components
- Controversy Developed But Humoral School Prevailed Till 1940
- Merrill Chase Expt (1940) with Tuberculosis Infected Animals, Immunity Thru White Blood Cell Transfers

Innate (Non-Specific) Immunity

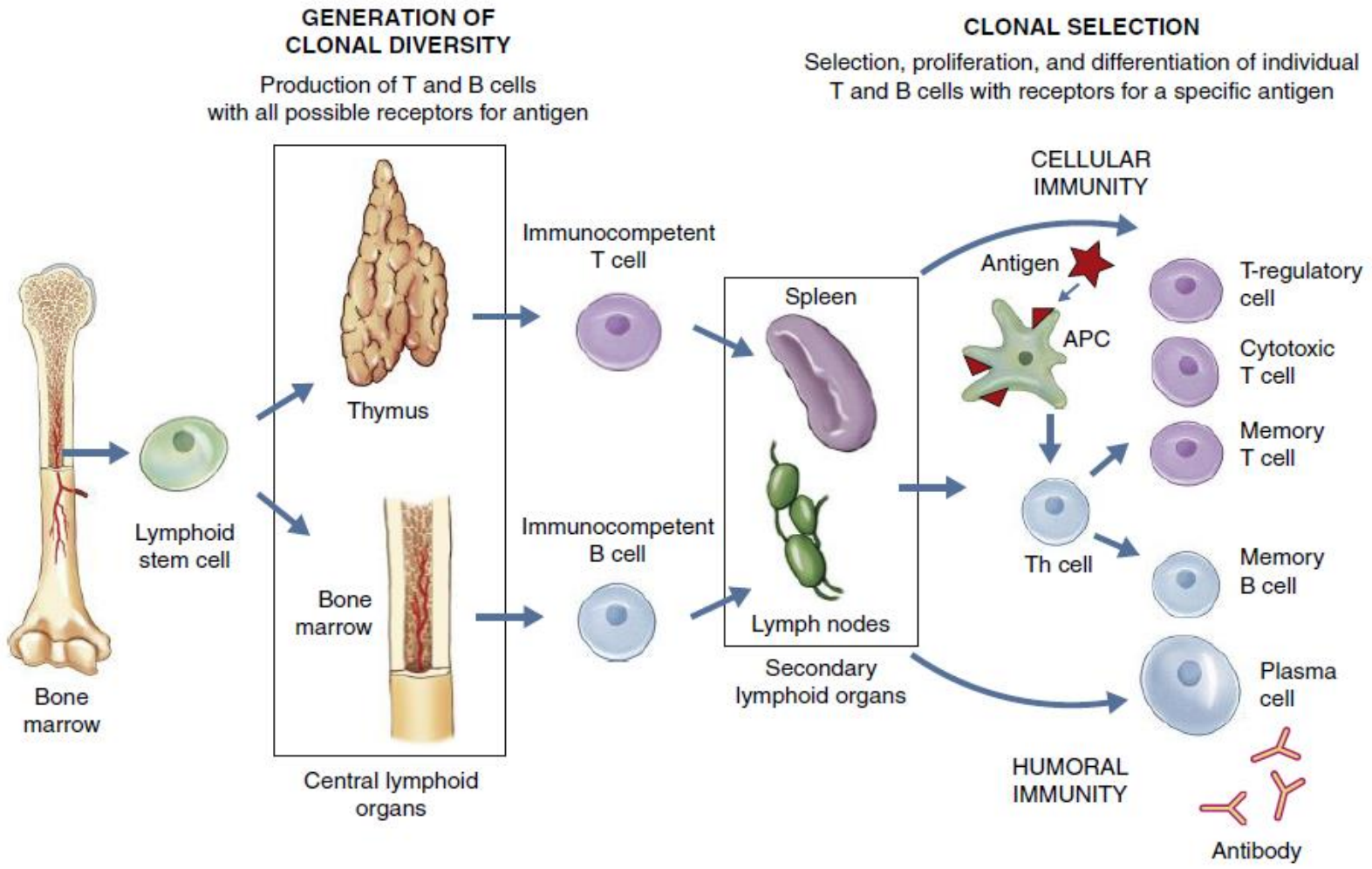
- Physiologic Barriers
  - pH (stomach)
  - Temperature (fever)
  - Soluble Factors (interferons, lysozyme)
- Phagocytic Barriers
  - Specialized Cells Perform Most Of Phagocytosis (macrophages, neutrophils)

Innate (Non-Specific) Immunity

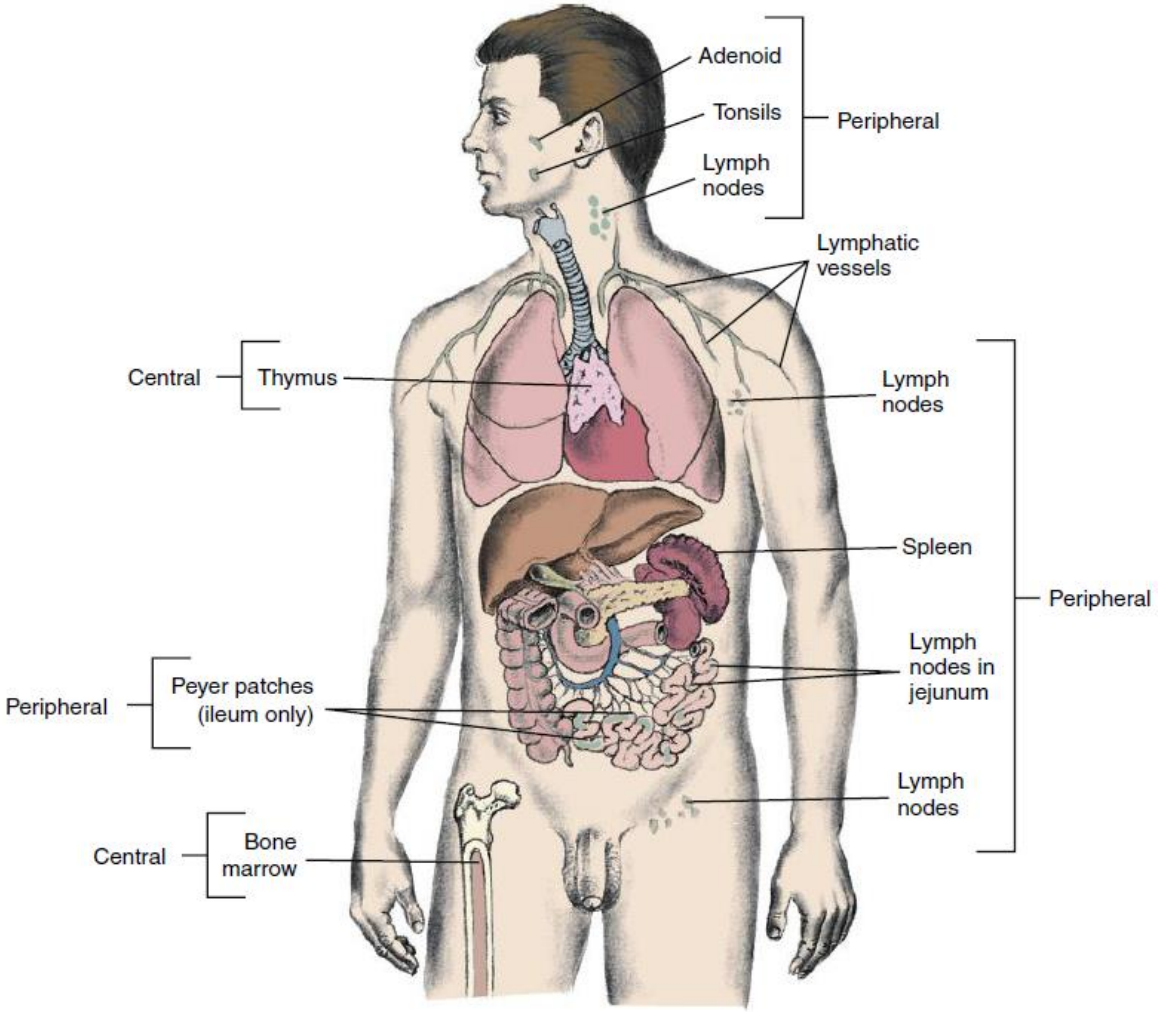
- Inflammatory Barriers
  - Vasodilation
  - Cappillary permeability
  - Leukocyte Infiltration
    - Chemotactic means
    - Increased Adherence
    - Leaky capillaries


INNATE IMMUNITY
ADAPTIVE IMMUNITY
Microbe
B lymphocytes
Antibodies
Epithelial barriers
Phagocytes
T lymphocytes
Effector
T cells
Complement
NK cells
0
6
12
1
2
3
4
5
Hours
Days
Time after infection

Overview of Immune Response



Lymphoid Tissues: Sites of B-Cell and T-Cell Differentiation



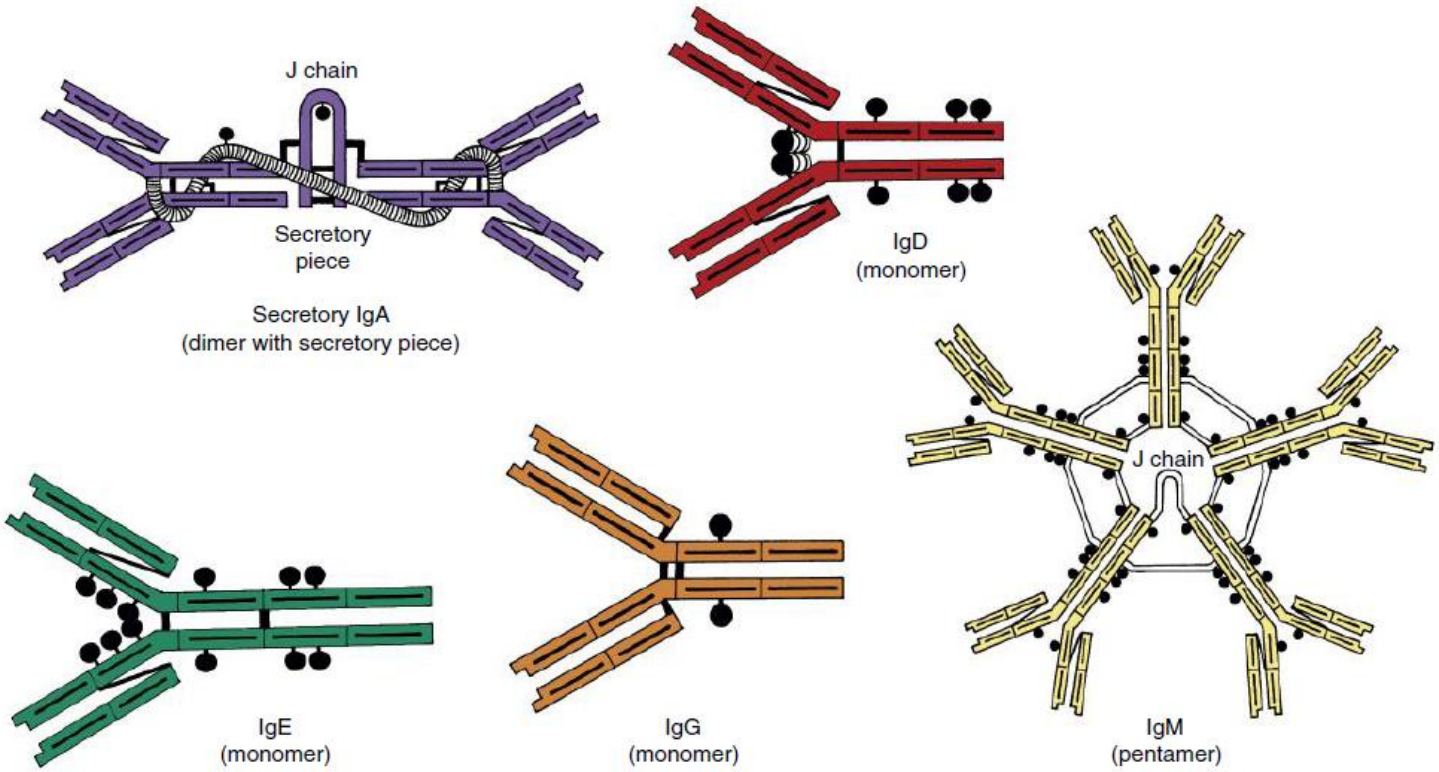


FIGURE 8-6 Structure of Different Immunoglobulins. Secretory IgA, IgD, IgE, IgG, and IgM. The black circles attached to each molecule represent carbohydrate residues.

TABLE 8-5 KEY CYTOKINES AND RECEPTORS THAT INFLUENCE THE IMMUNE RESPONSE

CYTOKINE	PRIMARY SOURCE	PRIMARY FUNCTION
Interleukin (IL)		
IL-1	APCs	Stimulates T cells to proliferation and differentiation; induces acute-phase proteins in inflammatory response; endogenous pyrogen
IL-2	Th1 cells, NK cells	Stimulates proliferation and differentiation of T cells and NK cells
IL-4	Th2 cells, mast cells	Induces B-cell proliferation and differentiation; up-regulates MHC class II expression; induces class-switch to IgE
IL-5	Th2 cells, mast cells	Induces eosinophil proliferation and differentiation; induces B-cell proliferation and differentiation
IL-6	Th2 cells, APCs	Induces B-cell proliferation and differentiation into plasma cells; induces acute-phase proteins in inflammatory response
IL-7	Thymic epithelial cells, bone marrow stromal cells	Major cytokine for induction of B- and T-cell proliferation and differentiation in central lymphoid organs
IL-8	Macrophages	Chemotactic factor for neutrophils
IL-10	Th cells, B cells	Inhibits cytokine production; activator of B cells
IL-12	B cells, APCs	Induces NK-cell proliferation; increases production of IFN-γ
IL-13	Th2 cells	IL-4–like properties; decreases inflammatory responses
IL-17	Th17 cells	Increases inflammation; increased influx of neutrophils and macrophages; increased epithelial cell chemokine production
IL-22	Th17 cells	Increases inflammation; increased epithelial cell production of antimicrobial peptides
Interferon (IFN)		
IFN-α, IFN-β	Macrophages, some virally infected cells	Antiviral; increases expression of MHC class I; activates NK cells
IFN-γ	Th1 cells, NK cells, Tc cells	Increases expression of MHC class II; activates macrophages and NK cells
Tumor Necrosis Factor (TNF)		
TNF-α (cachectin)	Macrophages	IL-1–like properties; induces cellular proliferation
TNF-β (lymphotoxin)	Tc cells	Kills some cells; increases phagocytosis by macrophages and neutrophils
Transforming Growth Factor (TGF)		
TGF-β	Lymphocytes, macrophages, fibroblasts	Chemotactic for macrophages; increases macrophage IL-1 production; stimulates wound healing

CYTOKINE RECEPTORS	LIGAND	ADDITIONAL INFORMATION
Class I receptor dimers (α- and β-chains)	IL-3, IL-5, IL-6, IL-11, IL-12, IL-13	IL-3 and IL-5 share a common α-chain; IL-6 and IL-11 share a common β-chain
Trimers (α-, β-, and γ-chains)	IL-2, IL-4, IL-7, IL-9, IL-15	All share a common γ-chain
Class II receptors	IFN-α, -β, and -γ	Two chains
TNF receptors	TNF-α, TNF-β, CD40, Fas	Single chain
Immunoglobulin-like receptors	IL-1	Single chain with immunoglobulin-like characteristics

Chemical Mediators Of Inflammation

- C-Reactive Protein (liver)
- Histamine (vasodilation, increased permeability
- Kinins
  - Small peptides normally inactive in blood
  - Ex. Bradykinin (causes pain)

Innate and Adaptive Immunity Collaborate

- Close collaboration
  - Macrophages can secret cytokines that affect the type of adaptive immunity
- Macrophages/DCs Present Antigen
- Lymphocytes Increase Effectiveness of Macrophages

Adaptive Immunity

- 4 Characteristics
  - Memory
  - Diversity
  - Antigenic Specificity
  - Self/nonself recognition

Cell Frequency of Different Leukocytes in Healthy Individuals

~ 60% neutrophils (50% - 70%)
~ 3% eosinophils (>0% - 5%)
~ 0.5% basophils (>0% - 2%)
~ 5% monocytes (1% - 9%)
~ 30% lymphocytes (20% - 40%)

Cells Of The Immune System

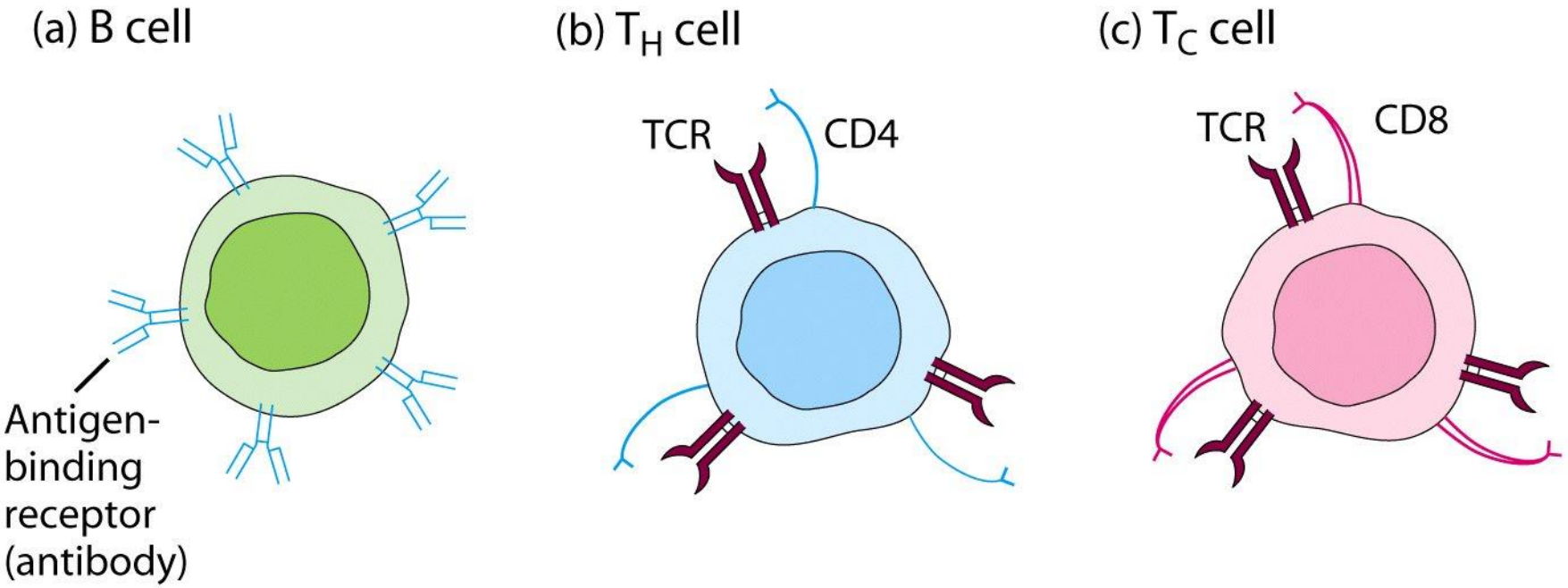
- Lymphocytes
  - B cells, mature in Bone Marrow (CD19, CD20)
    - in periphery they express a unique surface antibody
    - Plasma cells differentiated B cell, short lifespan, antibody factory
    - Memory B cell (CD45RO), long life span

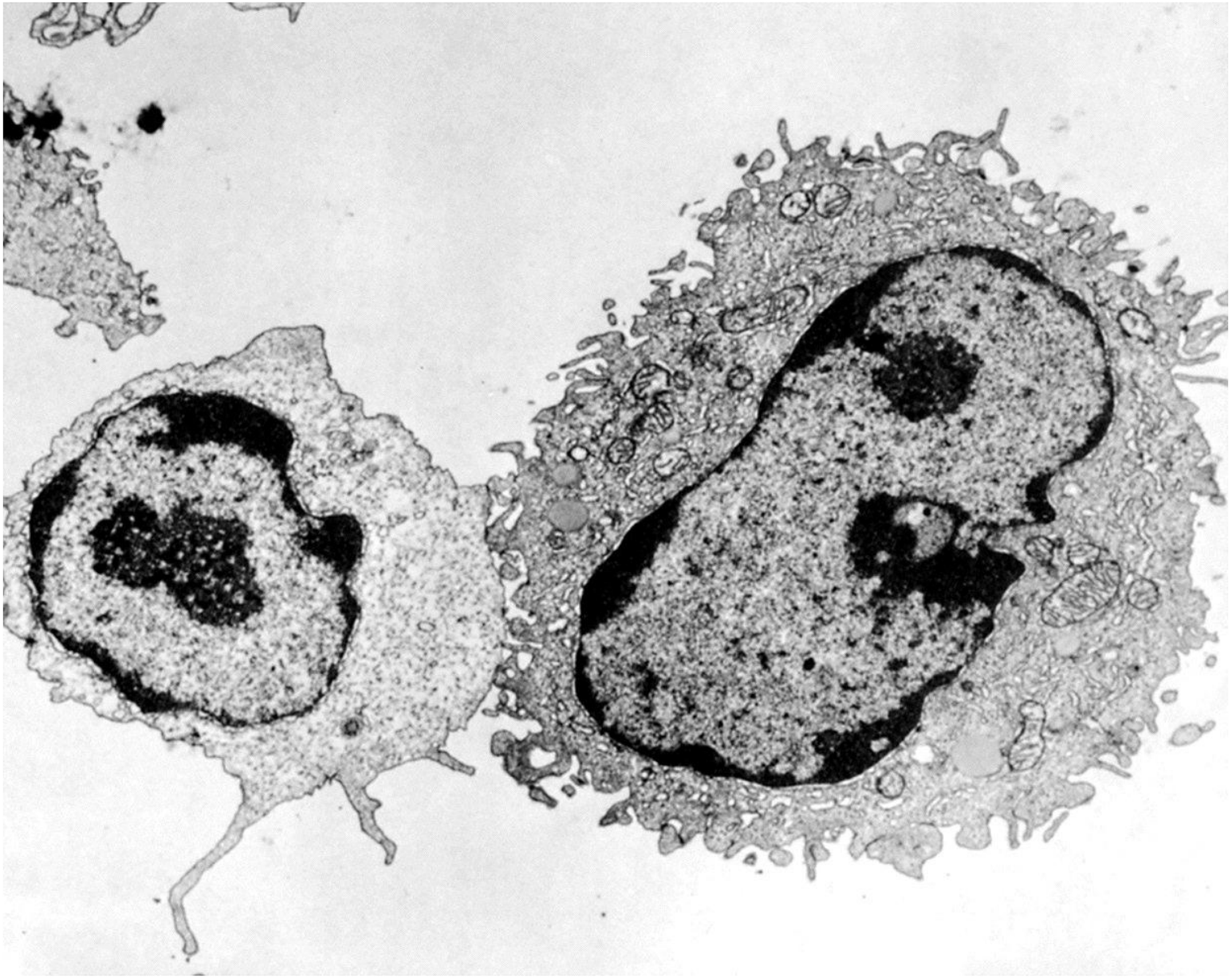
Cells Of Immune System

- T cells, mature in Thymus (CD3, CD4, CD8)
  - Two Major subsets, T_H (CD4) and T_C (CD8)
  - Third type T_S not as clear
  - Mature T cell expresses TCR
  - TCR cannot recognize antigen on its own
  - MHC I (all nucleated cells) or MHC II (APCs) is required
  - T_H cells secrete cytokines
  - T_C less cytokines, more cytotoxic (virus and tumor survailance)

Cells Of Immune System

- Antigen Presenting Cells
  - Number of Cells capable of Antigen Presentation
  - Dendritic Cell (DC) professional APC
  - Macrophages, B cells
  - Besides Antigen They Provide Co-stimulation
  - APCs are a safeguard against autoimmunity


(a) B cell
(b) T_H cell
(c) T_C cell
Antigen-binding receptor (antibody)
TCR
CD4
TCR
CD8



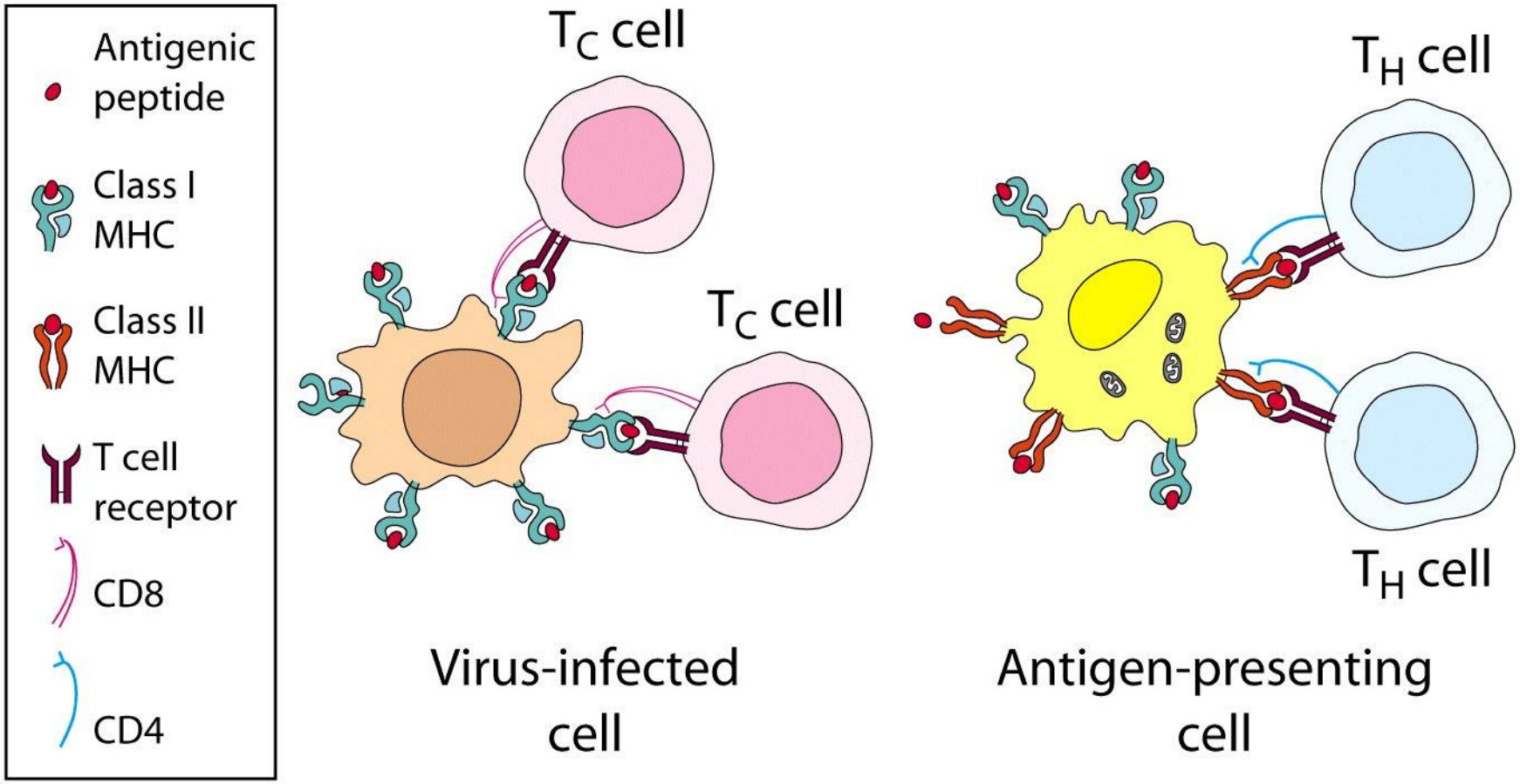
APC INTERACTING WITH T CELL

Specificity and Diversity

- B cells are specific, 100,000 identical antibodies on 1 B cell
- 10^8 different B Cells in Bone Marrow, Enormous Diversity
- Reduction To Avoid Auto-antibodies
- Same for T Cells, Elimination in Thymus

Major Histocompatibility Complex (MHC)

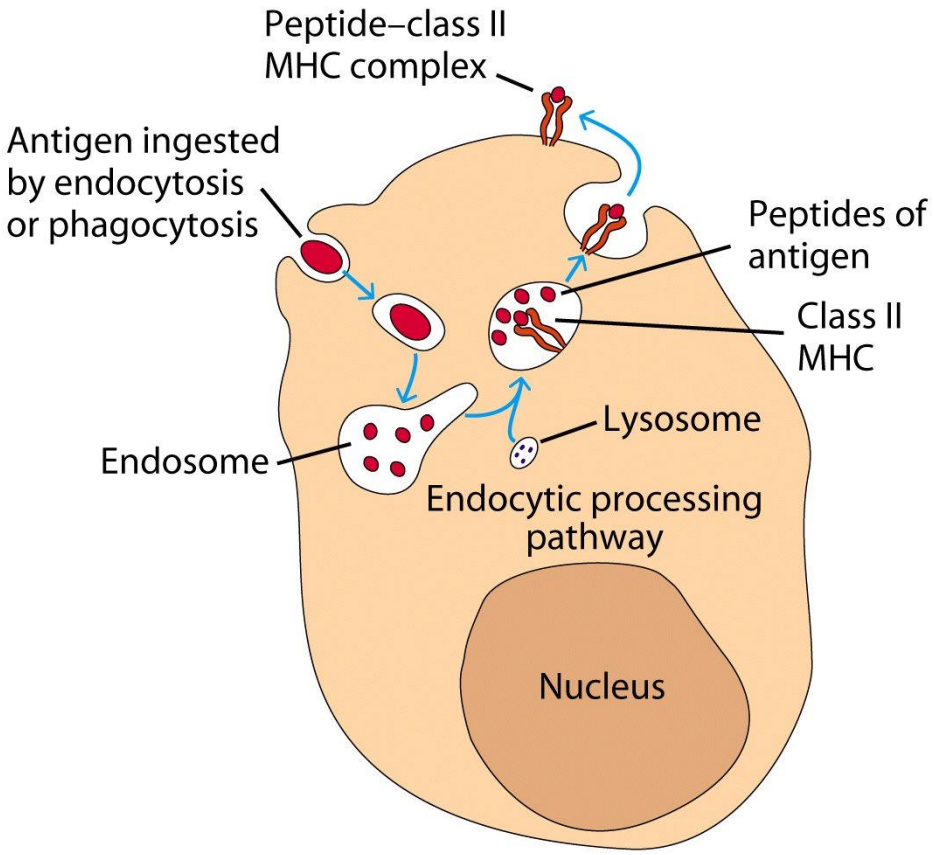
- Genetic Complex With Multiple Loci
- MHC I - CTLs
- MHC II - T_H
- MHC I+β_2-microglobulin
  - 3 classes A, B, C (human)
  - 2 classes K and D (mouse)
- MHC II
  - 3 classes DP, DQ, DR (human)
  - 2 classes IA, IE (mouse)
- Highly Polymorphic in Humans

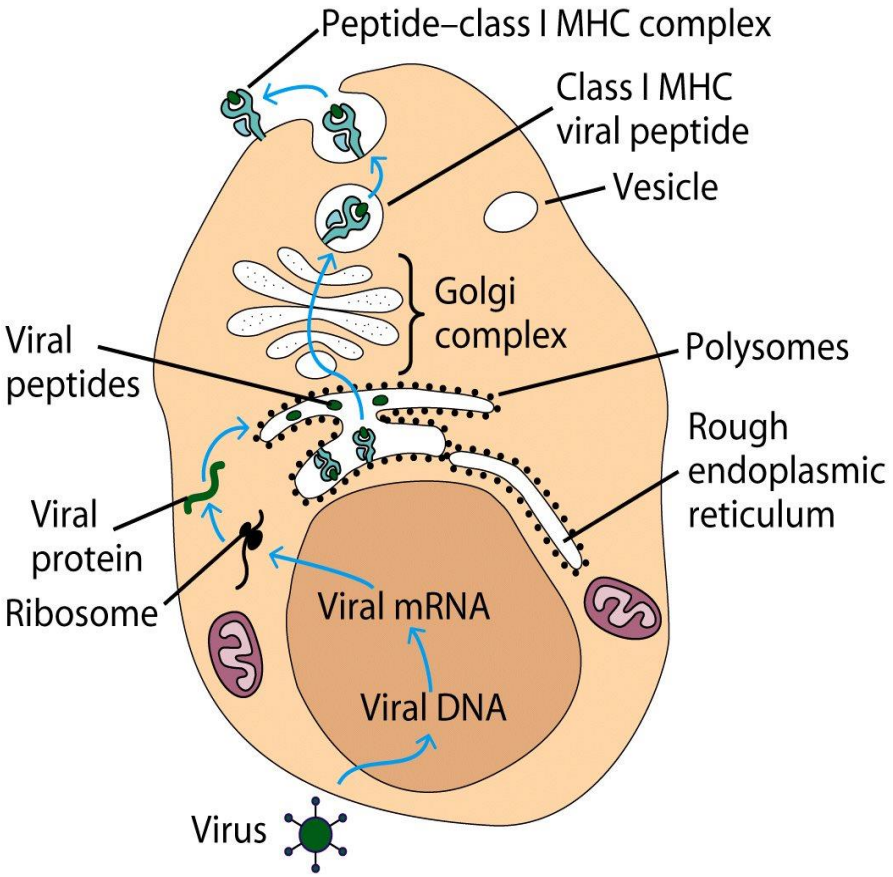

Antigenic peptide
Class I MHC
Class II MHC
T cell receptor
CD8
CD4
T_C cell
T_C cell
Virus-infected cell
T_H cell
T_H cell
Antigen-presenting cell

Processing and Presentation of Antigens

- First Protein Antigens Must Be Broken Down
- Form Complexes With MHC I or II
- Exogenous Antigens
  - Antigens Processed Thru Endocytic Pathway
  - Binding of Ags To MHC II
  - Expression of MHC II+Ags On Surface
  - CD4 T Cells Recognize Ag Thru Class II MHC
- Endogenous Antigens
  - Antigens Processed Thru Cytosolic Pathway
  - Produced Within Cell, Ex. Virus Ag, Cancer Ag
  - MHC I Molecules Bind Ag in ER
  - CD8 T Cells Recognize Ag Thru MHC I

Processing and Presentation of Antigens



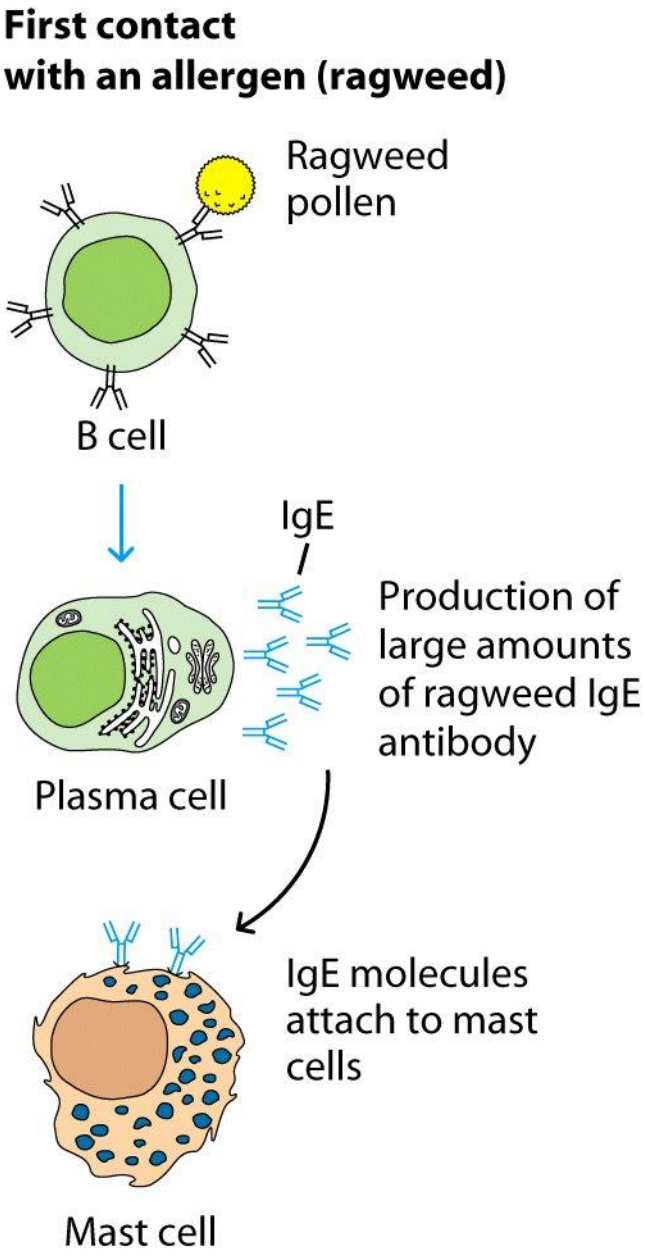


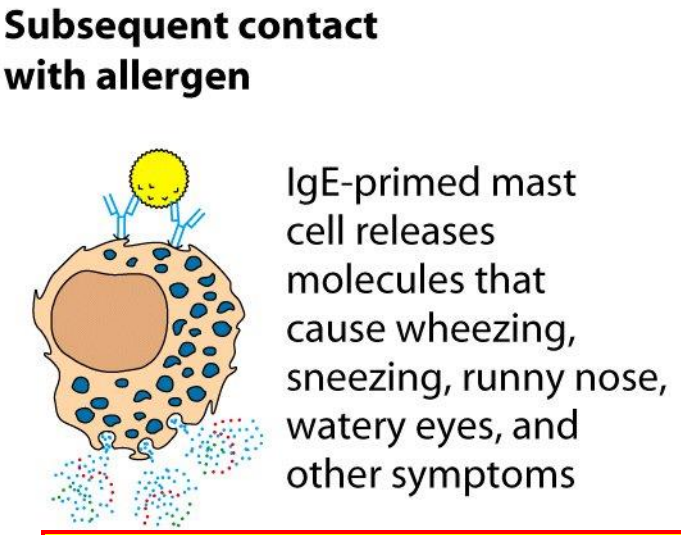
Clonal Selection of Lymphocytes and Memory

- Ag Reactivity Determines Clonal Expansion
- Immunologic Memory is By-product of Clonal Expansion
- Humoral Primary Response
  - 7 Days Before Antibody Levels Rise
  - Antibody Titer is Low Compared to Secondary
- Humoral Secondary Response
  - 1-2 Days Antibodies Are Detected
  - Antibody Titer Higher (100-1000 fold higher)
  - Lasts Longer

Clonal Selection of Lymphocytes and Memory

- Cell Mediated Response (T_H or CTL) is Similar
  - Primary Response 10-14 Days For Skin Rejection
  - Secondary Response Starts Immediately





Aberrant Respones – Allergy, Asthma, Anaphylaxis

- Asthma/Allergies Attacks Are Very Common
- Mediated Thru IgE
- IgE Binds Mast Cells, Basophils
- Re-exposure Cross Links IgE
- Causes Degranulation, Histamine, prostanoids