Diseases of the Immune System

Immunity & the immune system

- *Immunity* refers to protection against infections,
- and *the immune system* is the collection of cells and molecules that are responsible for defending us against the countless pathogenic microbes in our environment.

Two ends

- Deficiencies in immune defenses

- result in an increased susceptibility to infections, can be life-threatening

- the immune system is capable of causing great harm

- the root cause of some of the most vexing and intractable diseases of the modern world

diseases of immunity range

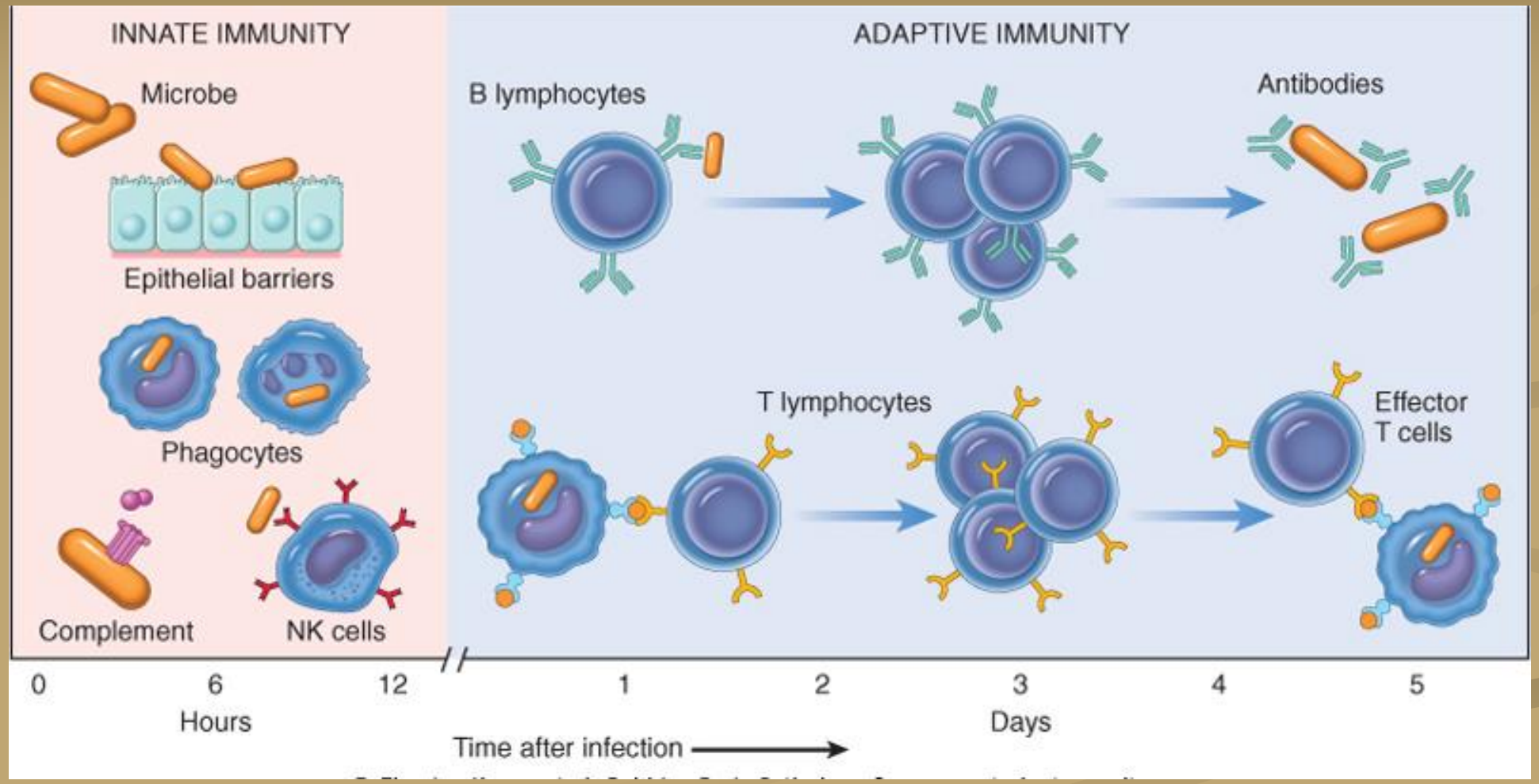
from those caused by **"too little"** to those caused by **"too much or inappropriate"** immune activity

INNATE AND ADAPTIVE IMMUNITY

Defense against microbes consists of two types of reactions:

- **Innate immunity** (also called natural, or native, immunity)
- **adaptive immunity** (also called acquired, or specific, immunity)

The principal mechanisms of innate immunity and adaptive immunity



Innate immunity

- also called natural, or native, immunity
- is mediated by cells and proteins that are always present and poised to fight against microbes
- are called into action immediately in response to infection

The major components of innate immunity

- epithelial barriers of the skin, gastrointestinal tract, and respiratory tract,

- which prevent microbe entry (and have to be breached for a microbe to establish infection);

- phagocytic leukocytes, neutrophils and macrophages
- a specialized cell type called NK cell
- several circulating plasma proteins

- e.g. the complement system

adaptive immunity

- The innate immune response is able to prevent and control many infections
- many pathogenic microbes have evolved to overcome innate immune defenses, and protection against these infections requires the more powerful mechanisms
- also called acquired, or specific, immunity
- is normally silent and responds (or "adapts") to the presence of infectious microbes by becoming active, expanding, and generating potent mechanisms for neutralizing and eliminating the microbes

By convention,

the terms
"immune system"
and "immune response"
refer to
adaptive immunity

The components of the adaptive immune system

- Lymphocytes
- their products

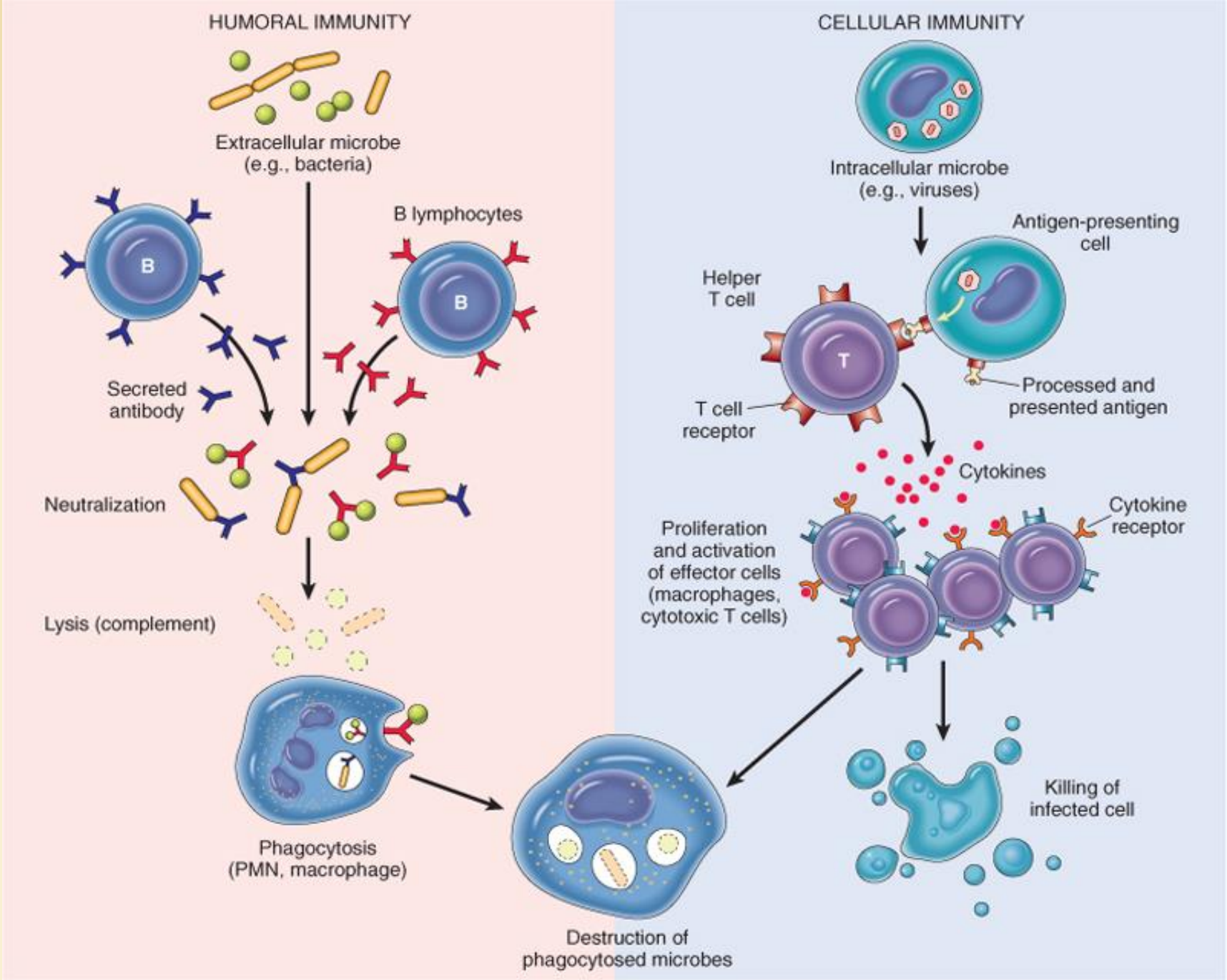
Two types of adaptive immune responses:

- *humoral immunity,*

- mediated by soluble antibody proteins that are produced by B lymphocytes (also called B cells), and

- *cell-mediated (or cellular) immunity,*

- mediated by T lymphocytes (also called T cells)



Humoral and cell-mediated immunity

- ***In humoral immunity, B lymphocytes secrete antibodies that eliminate extracellular microbes***
- ***In cell-mediated immunity, T lymphocytes either activate macrophages to destroy phagocytosed microbes or kill infected cells***

Functions of these

- **Antibodies** provide protection against extracellular microbes in the blood, mucosal secretions, and tissues.
- **T lymphocytes** are important in defense against intracellular microbes.

T lymphocytes work:

- by either directly killing infected cells

- accomplished by cytotoxic T lymphocytes

- by activating phagocytes to kill ingested microbes

- via the production of cytokines, made by helper T cells

CELLS AND TISSUES OF THE IMMUNE SYSTEM

CELLS AND TISSUES OF THE IMMUNE SYSTEM

- Lymphocytes (T, B, NK Cells)

- MHC Molecules: the Peptide Display System of Adaptive Immunity

- Antigen-Presenting Cells

- Effector Cells

- Lymphoid tissue

Lymphocytes

Lymphocytes

- are present in the:
  - Circulation
  - Lymphoid organs
- appear morphologically identical
- there are several functionally and phenotypically distinct populations
- develop from precursors in the generative lymphoid organs

two populations

- **T lymphocytes** are so called because they mature in the thymus
- **B lymphocytes** mature in the bone marrow

antigen receptors

- Each T or B lymphocyte expresses receptors for a single antigen
- the total population of lymphocytes (10^12 in humans) is capable of recognizing **tens or hundreds of millions of antigens**

antigen recognition

- enormous diversity
- is generated by the somatic **rearrangement of antigen receptor genes** during lymphocyte maturation
- during the joining of different gene segments

Two applications

- classification of lymphoid malignancies
- distinguish neoplastic expansions

classification of lymphoid malignancies

- These antigen receptors are rearranged and **expressed in lymphocytes**, but not in any other cell.
- The demonstration of antigen receptor gene rearrangements by molecular methods (e.g. **PCR**) is a definitive marker of T or B lymphocytes

distinguish neoplastic expansions

- **each lymphocyte has a unique DNA rearrangement,** hence a unique antigen receptor
- molecular analysis of the rearrangement in a cell population can be used to distinguish **polyclonal** (non-neoplastic) lymphocyte proliferations from **monoclonal** (neoplastic) expansions.

T Lymphocytes

T Lymphocytes

- are the effector cells of cellular immunity
- provide important stimuli for antibody responses to protein antigens
- constitute 60-70% of the lymphocytes in peripheral blood
- are the major lymphocyte population in splenic periarteriolar sheaths and lymph node interfollicular zones

T Lymphocytes

- do not detect free or circulating antigens
- >95% of T cells recognize only peptide fragments of protein antigens that are displayed on other cells bound to proteins of the MHC (in humans, HLA complex)

MHC

- was discovered on the basis of studies of graft rejection or acceptance (tissue, or "histo," compatibility)
- the normal function of MHC molecules is to display peptides for recognition by T lymphocytes

forcing T cells to see MHC-bound peptides

- the system ensures that T cells can recognize antigens in other cells
- thus perform their function of:
  - killing infected cells
  - activating phagocytes or B lymphocytes that have ingested protein antigens

MHC restriction

- In every individual, T cells recognize only peptides displayed by that individual's MHC molecules
- of course, they are the only MHC molecules that the T cells will encounter normally

the TCR

- is a heterodimer composed of disulfide-linked α and β protein chains
- each chain has a **variable region** that participates in binding a particular peptide antigen and a **constant region** that interacts with associated signaling molecules

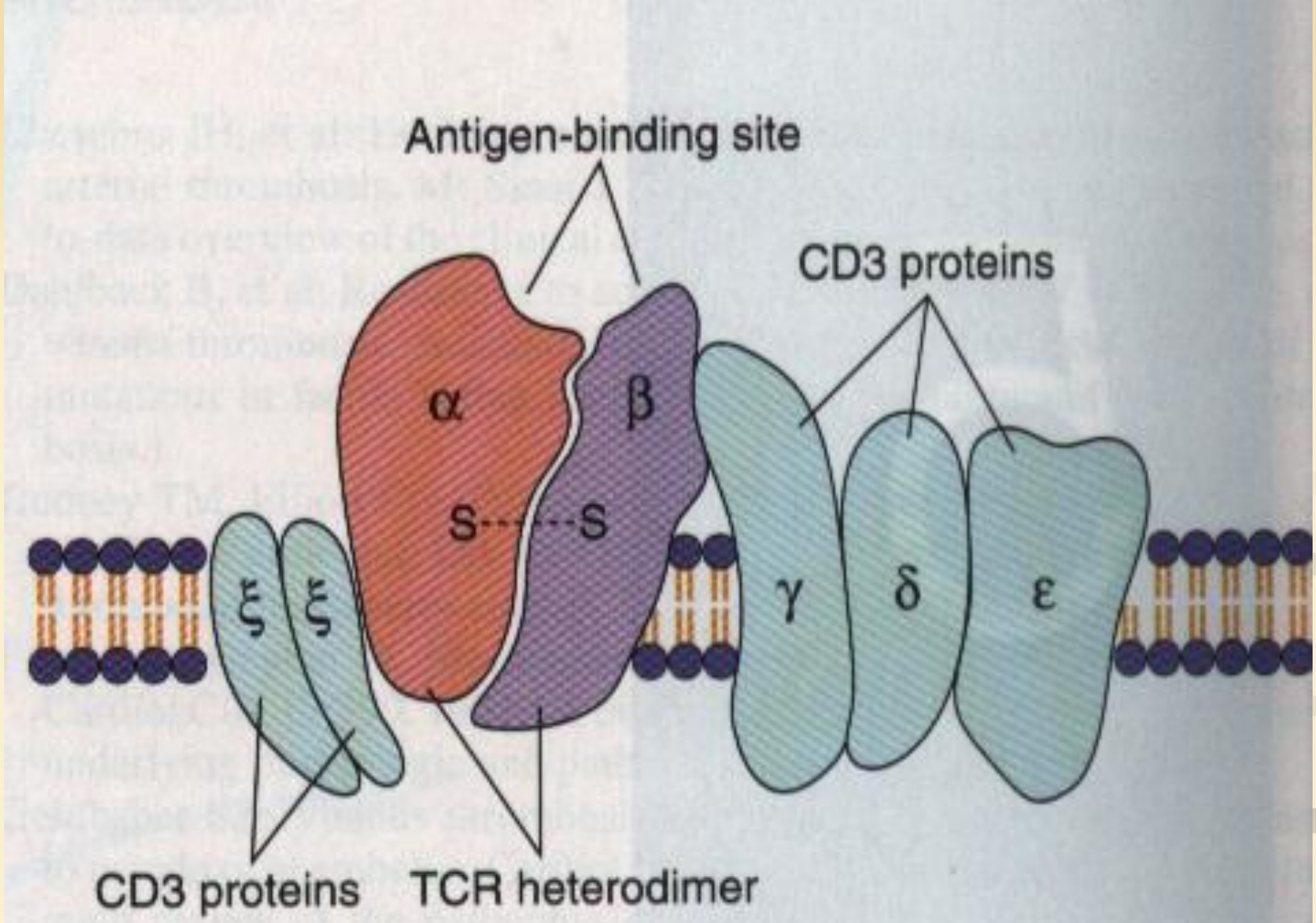

Antigen-binding site
CD3 proteins
α
β
S
S
ξ
ξ
γ
δ
ε
CD3 proteins
TCR heterodimer

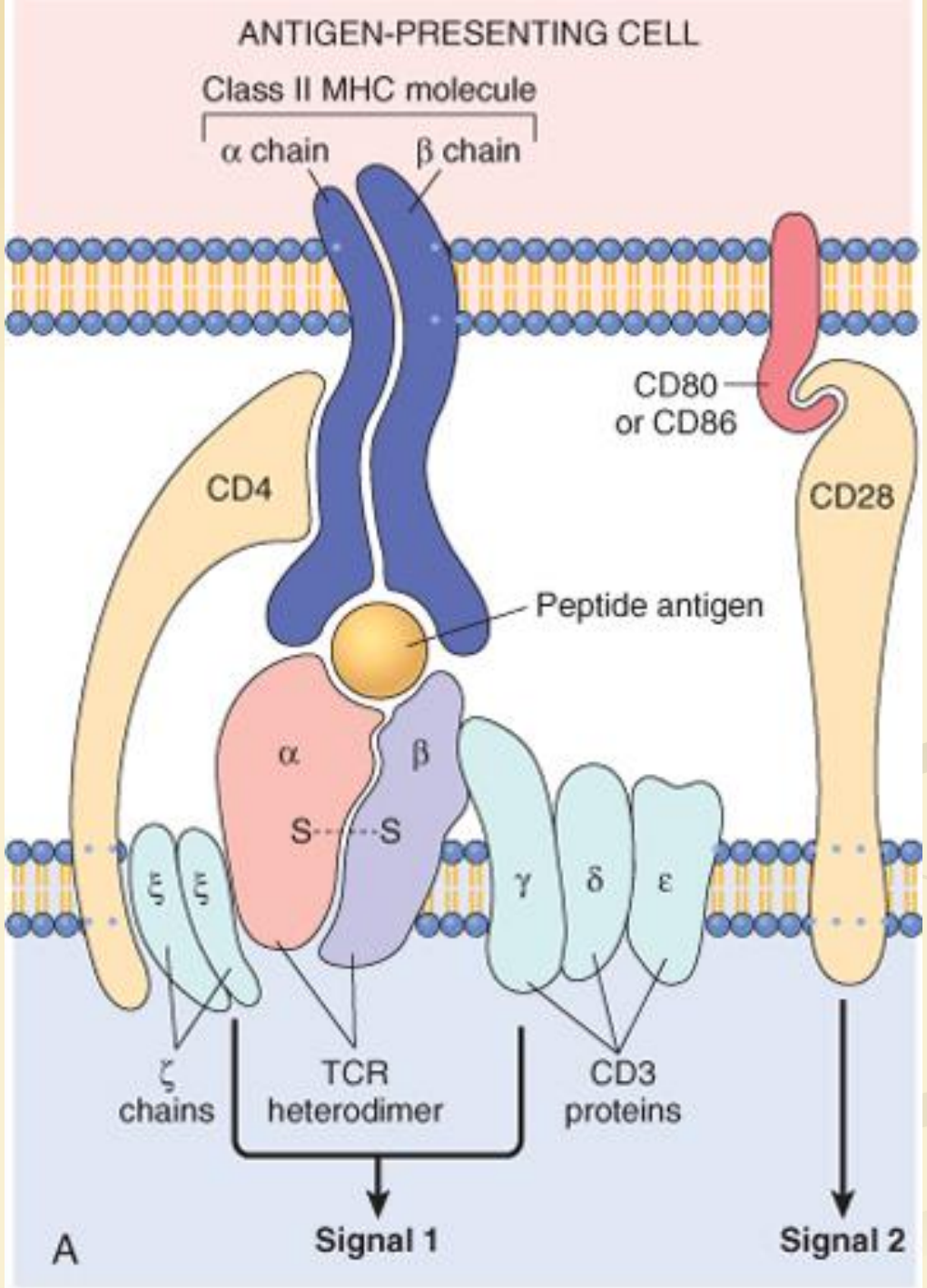
Figure 5–1

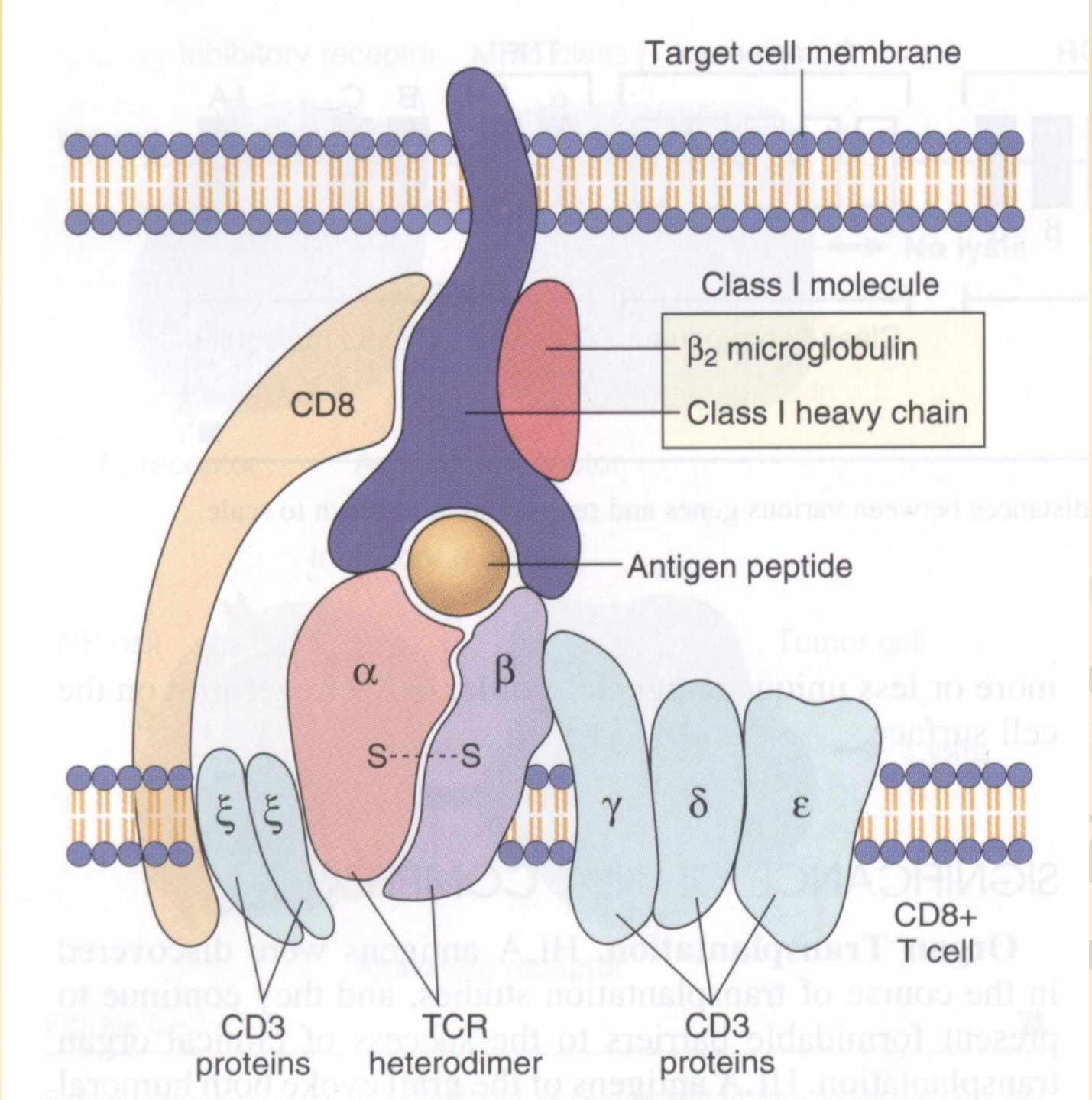
CD3, ζ chains, others

- TCRs are noncovalently linked to a cluster of five invariant polypeptide chains, **the γ, δ, and ε proteins of CD3** and **two ζ chains**
  - they do not themselves bind antigens
  - interact with the constant region of the TCR to transduce intracellular signals after TCR recognition of antigen.
- T cells express a number of **other** invariant function-associated molecules

other **invariant molecules**

- CD4 and CD8 are expressed on distinct T-cell subsets and serve as **coreceptors** for T-cell activation
  - CD4 molecules on T cells bind to invariant portions of class II MHC molecules on selected APCs
  - CD8 binds to class I MHC molecules


ANTIGEN-PRESENTING CELL
Class II MHC molecule
α chain
β chain
CD80
or CD86
CD4
CD28
Peptide antigen
α
β
S
S
ξ
ξ
γ
δ
ε
ζ
chains
TCR
heterodimer
CD3
proteins
A
Signal 1
Signal 2


Target cell membrane
Class I molecule
β_2 microglobulin
Class I heavy chain
CD8
Antigen peptide
α
β
S------S
ξ
ξ
γ
δ
ε
CD8+
T cell
CD3
proteins
TCR
heterodimer
CD3
proteins

CD4 and CD8 molecules

- CD4 is expressed on approximately 50-60% of mature T cells, whereas CD8 is expressed on about 40% of T cells

CD4+ and CD8+ cells

- CD4+ T cells are "helper" T cells
- CD8+ T cells are called "cytotoxic" T lymphocytes (CTLs)
- perform different but overlapping functions

CD4+ T cells functions

- they secrete soluble molecules (*cytokines*) that help B cells to produce antibodies (helper)
- also help macrophages to destroy phagocytosed microbes The central role of CD4+ helper cells in immunity is highlighted by the severe compromise that results from the destruction of this subset by human immunodeficiency virus (HIV) infection.

CD8+ T cells functions

- can also secrete cytokines
- they play a more important role in directly killing virus-infected or tumor cells (CTLs)

CD28

- important invariant proteins on T cells
- functions as the **receptor** for:
  - molecules that are induced on APCs by microbes (costimulators), strengthen the bond between the T cells and APCs
  - various adhesion molecules, control the migration of the T cells to different tissues

γδ T cells

- TCRs are heterodimers of γ and δ chains
- are similar but not identical to the α and β chains
  - minority of peripheral blood T cells
  - many of the T cells associated with mucosal surfaces (e.g., lung and gastrointestinal tract)

γδ T cells

- do not express CD4 or CD8
- recognize nonprotein molecules (e.g., bacterial lipoglycans)
- their functional roles are not well understood

NKT cells

- small population of T cells expresses markers of T cells and NK cells
- recognize microbial glycolipids,
- their importance is also not established

γδ T cells and NKT cells

- The antigen receptors are much less diverse than the receptors of "conventional" T cells
- recognize conserved microbial structures

regulatory T lymphocytes

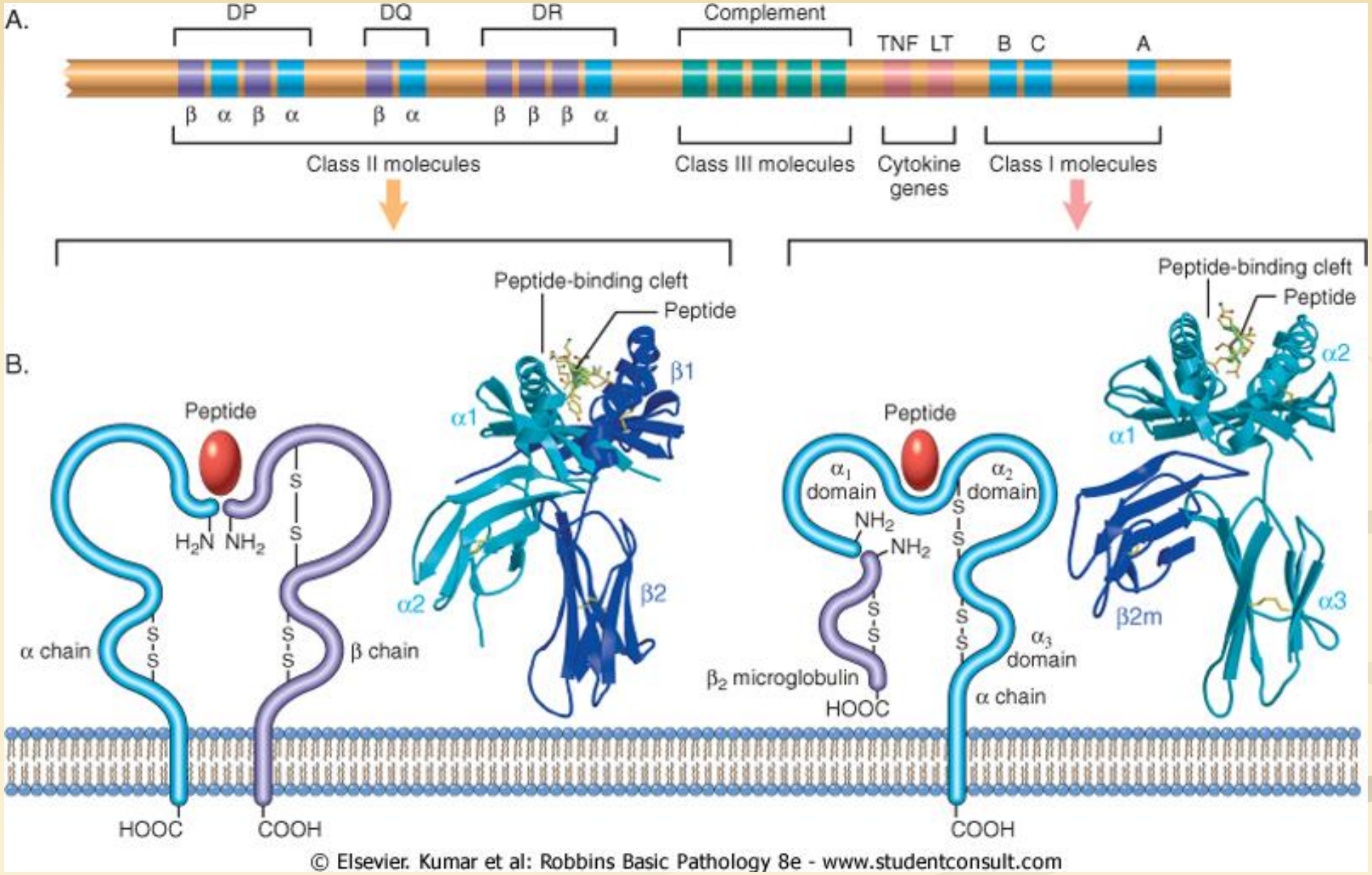
- Another population of T cells
- in context of tolerance of self antigens

populations of T cells

- CD4+ T cells (helper" T cells)
- CD8+ T cells (CTLs)
- γδ T cells
- NKT cells
- Regulatory T lymphocytes

review of the structure and function of MHC

- *or HLA* molecules
- fundamental to T-cell recognition of antigens
- variations in MHC molecules are associated with immunologic diseases
- Synthesized by a cluster of genes on ch.6



MHC is highly polymorphic

- a vast array of peptides can be displayed by MHC molecules for recognition by T cells
- this polymorphism also constitutes a formidable barrier to organ transplantation

MHC gene products fall into three categories:

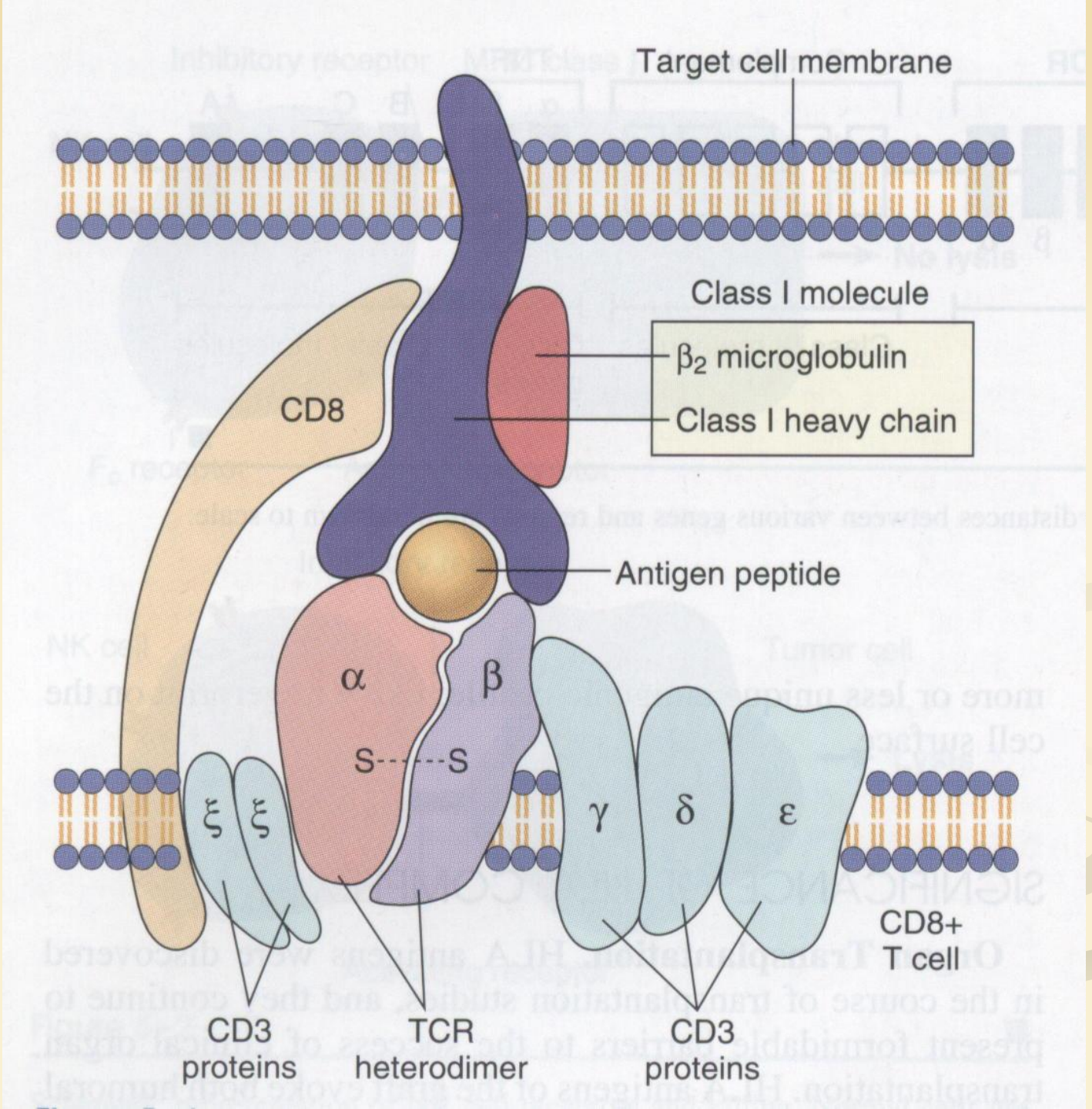
- On the basis of their chemical structure, tissue distribution, and function:

- Class I MHC molecules
- Class II MHC molecules
- Class III proteins

Class I MHC molecules

- three loci, HLA-A, B, & C
- Each is a heterodimer, consisting of a polymorphic 44-kD α chain, noncovalently associated with a 12-kD nonpolymorphic β2-microglobulin (gene on ch.15)
- The extracellular portion of the α chain contains a cleft where foreign peptides bind to MHC molecules for presentation to CD8+ T cells

- In general, class I MHC molecules bind to peptides derived from proteins synthesized within the cell (e.g., viral antigens)
- Because class I MHC molecules are present on all nucleated cells, all virus-infected cells can be detected and eliminated by CTLs


Target cell membrane
Class I molecule
β_2 microglobulin
Class I heavy chain
CD8
Antigen peptide
α
β
S------S
ξ
ξ
γ
δ
ε
CD8+
T cell
CD3
proteins
TCR
heterodimer
CD3
proteins

Class II MHC molecules

- are encoded by genes in the HLA-D region, which contains at least three subregions: DP, DQ, and DR
- heterodimers of noncovalently linked polymorphic α and β subunits
- the extracellular portion contains a cleft for the binding of antigenic peptides

Class II MHC molecules

- quite restricted tissue distribution

- they are expressed mainly on APCs (dendritic cells), and macrophages, and B cells

- bind to peptides derived from proteins synthesized outside the cell (e.g., extracellular bacteria)

- recognize the presence of extracellular pathogens

- orchestrate a protective response

Class III proteins

- Include:
  - some of the complement components (C2, C3)
  - genes encoding TNF and lymphotoxin (LT, or TNF-β) are also located within the MHC
- genetically linked to class I and II molecules
- not form a part of the peptide display system

different class I HLA molecules

- Every individual inherits one HLA allele from each parent

- expresses two different molecules for every locus.

- heterozygous individual can express six different class I HLA molecules

- three of maternal origin and three of paternal origin

different class II MHC molecules

- *a given individual expresses maternal and paternal alleles of the class II MHC loci*
- *some HLA-D α and β chains can mix and match with each other, each class II-expressing cell can have as many as 20 different class II MHC molecules*

the polymorphism of MHC genes

enable the population to display and respond to any conceivable microbial peptide

polymorphism of HLA

- Different MHC alleles bind to different peptide fragments
  - Allows to present a wide array of peptide antigens
- a virtually infinite number of combinations of molecules exist
  - each individual expresses a unique MHC antigenic profile on his or her cells.

in the context of transplantation

- HLA polymorphism
- HLA alleles differ to some extent from every other individual
- grafts from any person will evoke immune responses and be rejected, except for identical twins
- In fact, HLA molecules were discovered in the course of early attempts at tissue transplantation

Why often called "antigens"

- HLA molecules of the graft **evoke both humoral and cell-mediated responses**
- eventually leading to graft destruction

The role of the MHC in T-cell stimulation

- genetic control of immune responses
- The ability of any given MHC allele to bind the peptide antigens generated from a particular pathogen will determine **whether an individual's T cells can actually "see" and respond to that pathogen**

Two examples

- responsiveness to **ragweed pollen** cause allergic reaction, make individuals susceptible to this disease
- good responsiveness to a **viral antigen**, may be beneficial

B Lymphocytes

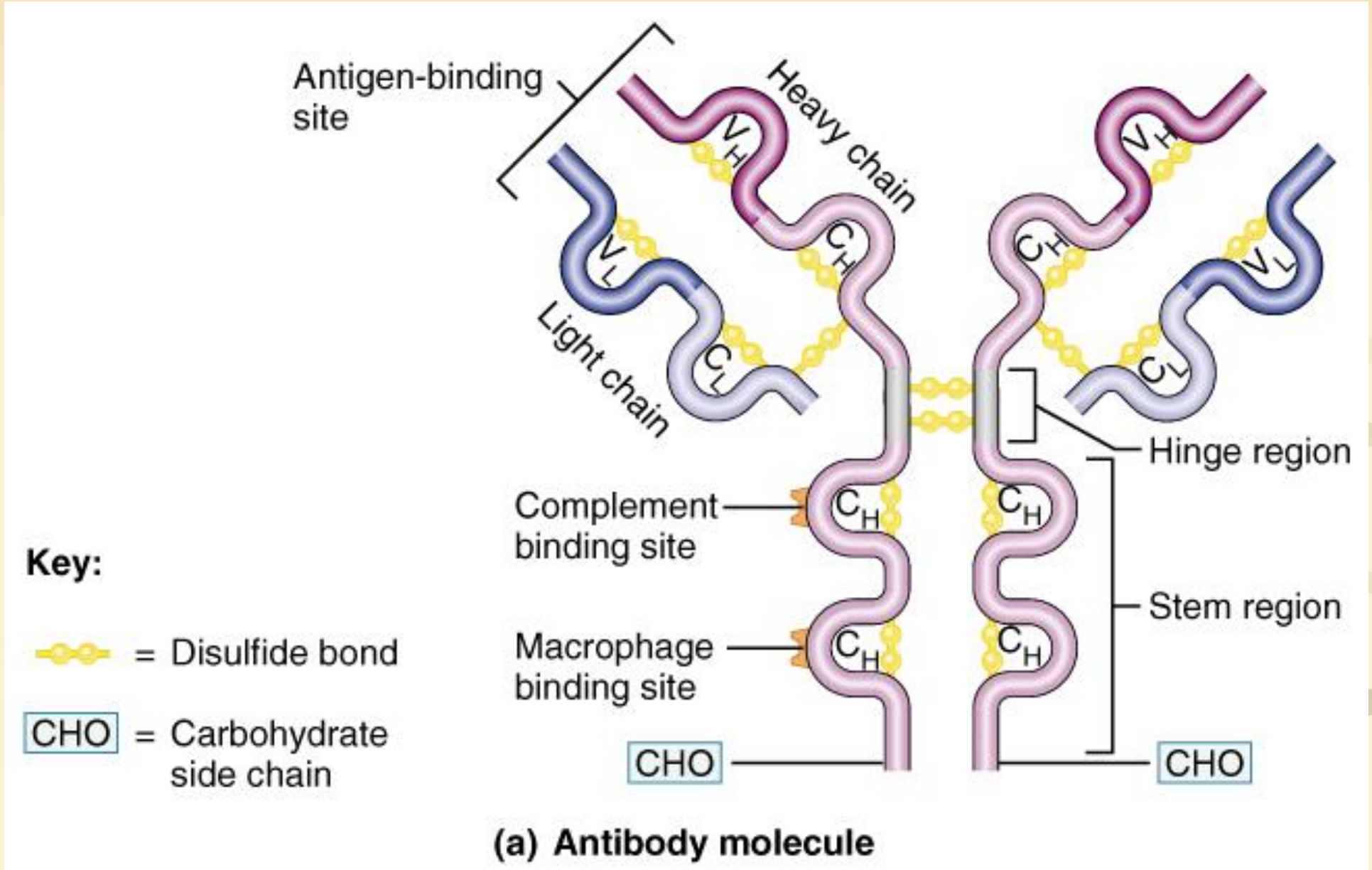
B Lymphocytes

- Bone marrow-derived lymphocytes
- 10% to 20% of the circulating peripheral lymphocyte population
- in bone marrow
- in the follicles of peripheral lymphoid tissues (lymph nodes, spleen, tonsils, and other mucosal tissues)

Function of B cells

- Stimulation of follicular B cells leads to the formation of a central zone of large, activated B cells, called a **germinal center**
- B cells are the only cell lineage that synthesize antibodies (Ig)

Basic Antibody Structure

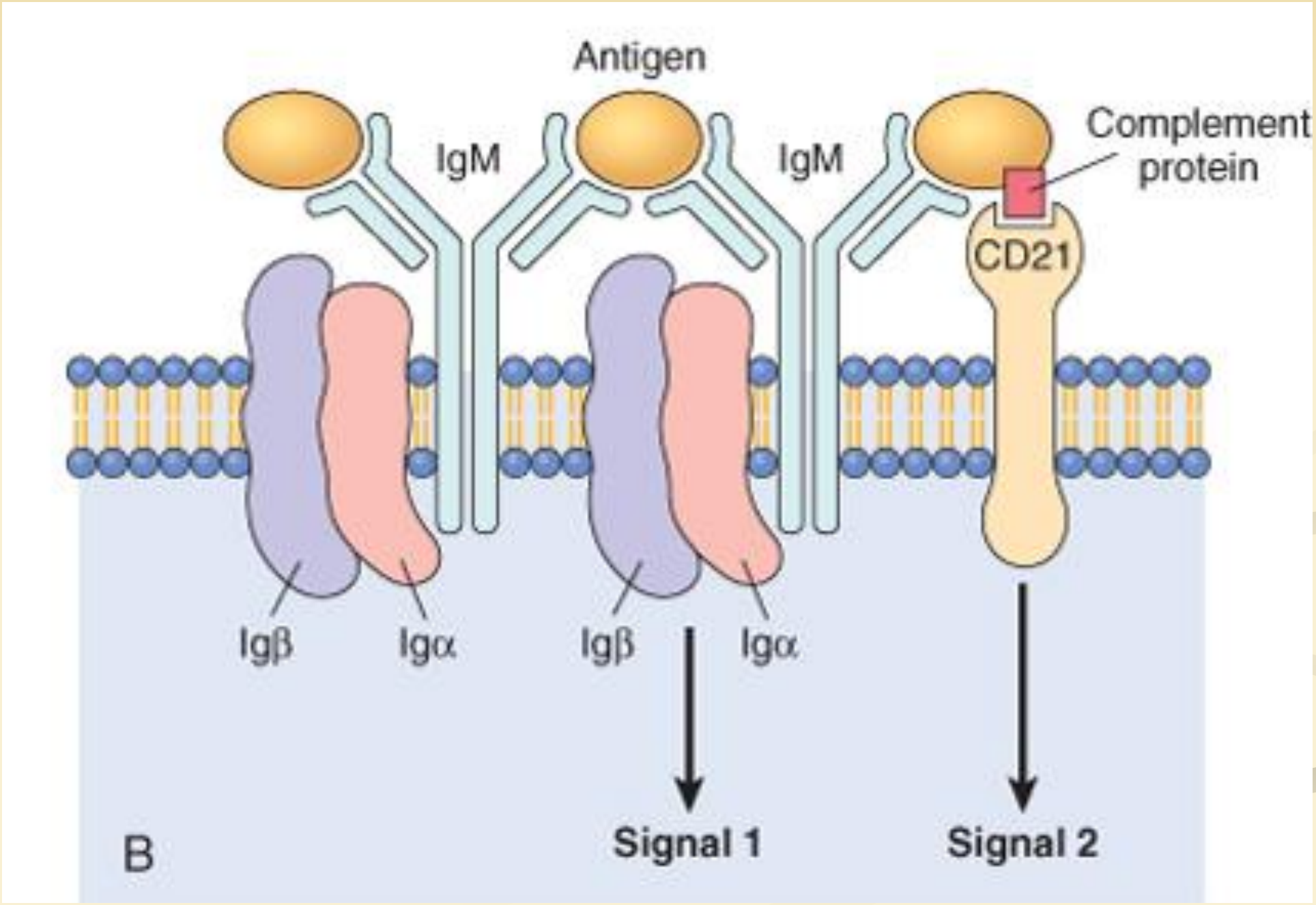


B-cell receptor (BCR) complex

- recognize antigen
- associated with signaling molecules
- can recognize and respond to many more chemical structures, proteins, lipids, polysaccharides, nucleic acids, and small chemicals
  - T cells can recognize only MHC-associated peptides
- recognize native conformational forms of these antigens

diversity of antibodies

- each antibody has a unique antigen specificity, as with TCRs
- The diversity of antibodies is generated during somatic **rearrangements of Ig genes**

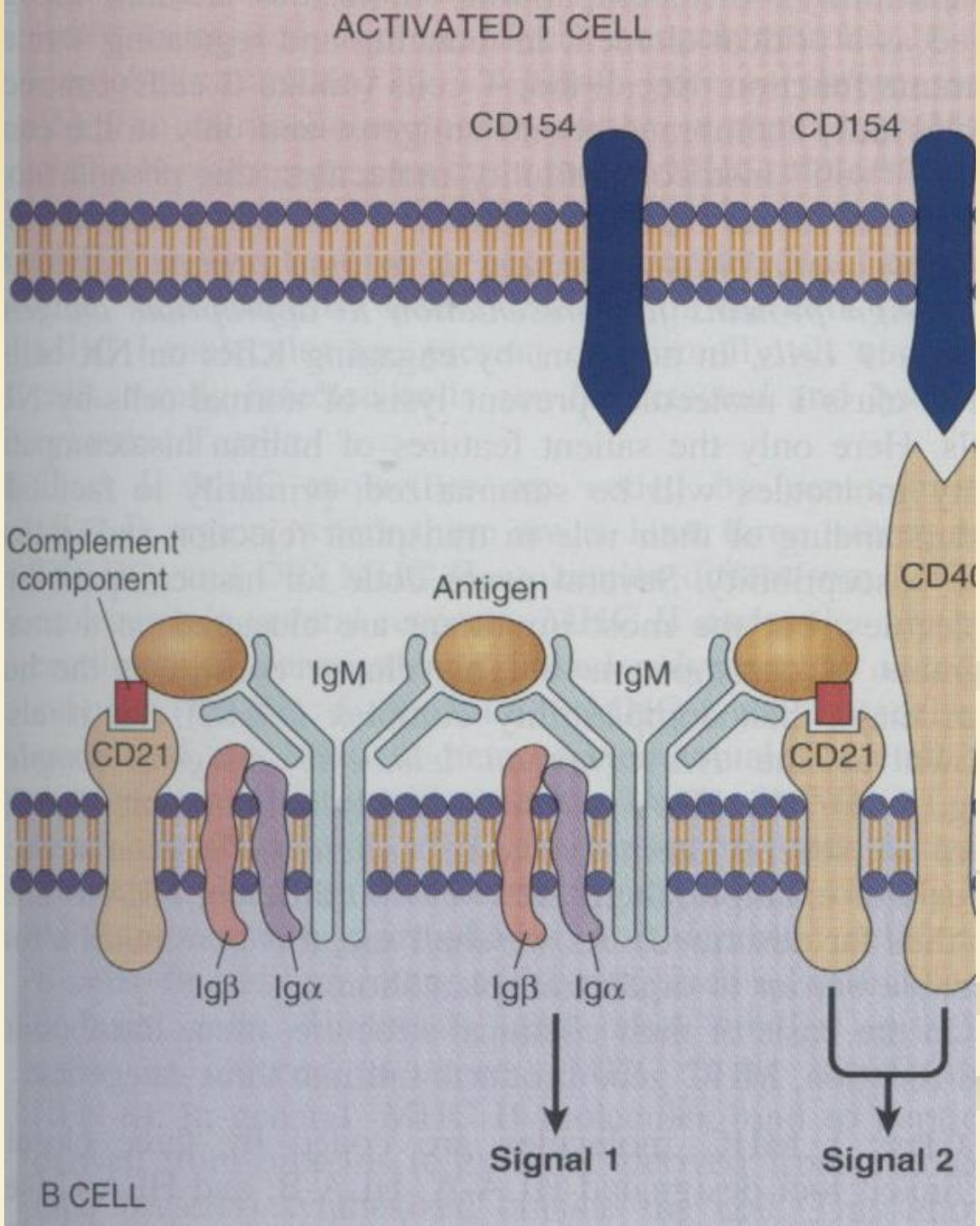

Antigen
IgM
IgM
Complement protein
CD21
Igβ
Igα
Igβ
Igα
Signal 1
Signal 2
B

Lymphocyte antigen receptors

- The B-cell receptor complex is composed of membrane IgM (or IgD)
- the associated signaling proteins Igα and Igβ
- CD21 is a receptor for a complement component that promotes B-cell activation

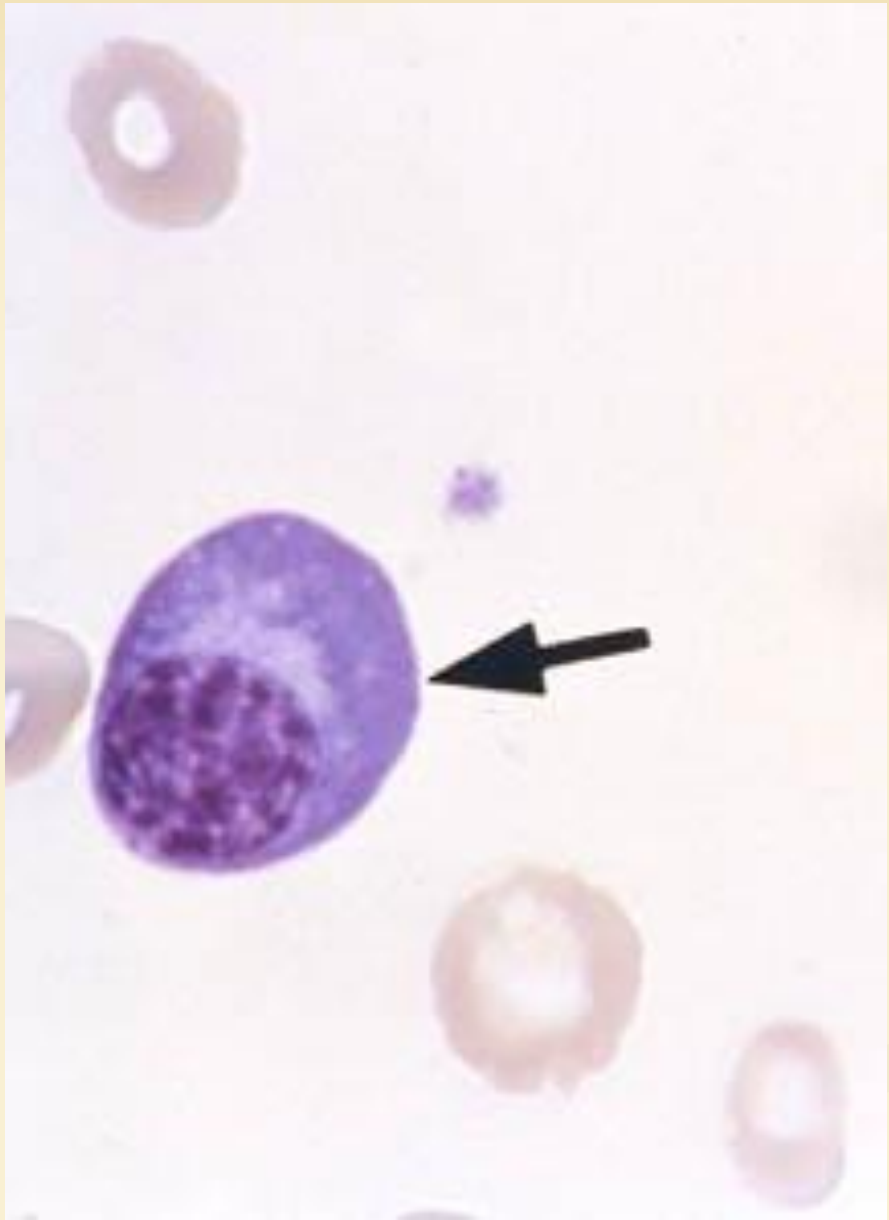
Other molecules on B cells

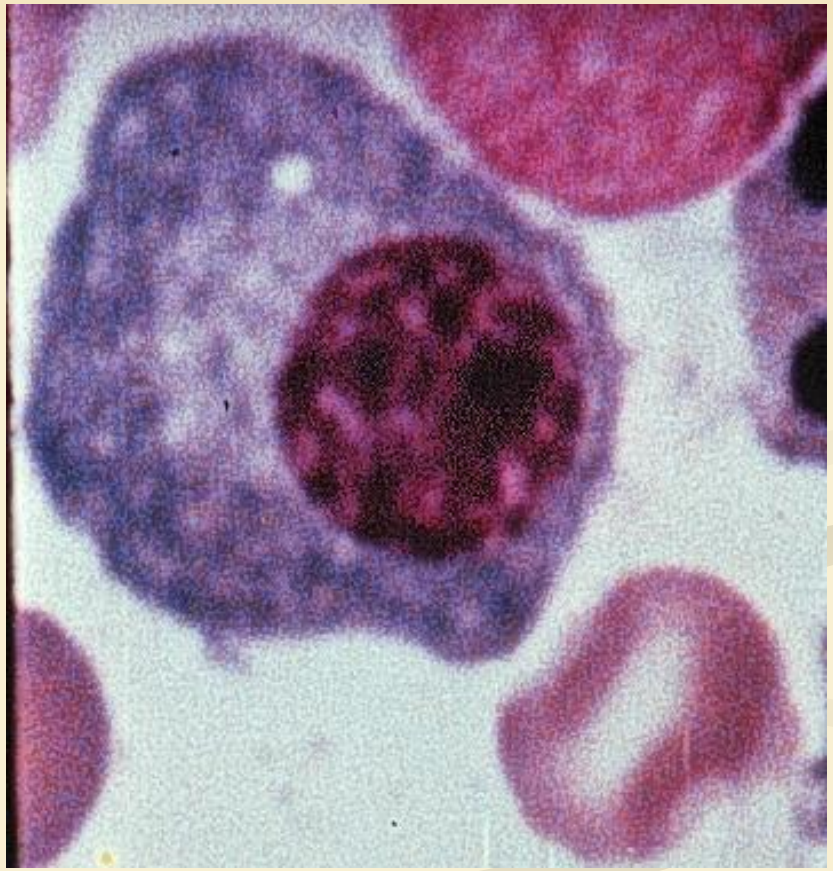
- several invariant molecules that are responsible for signal transduction and for activation of the cells
- **CD40 receptor**, which binds to its ligand expressed on helper T cells
- **CD21** (CR2), which recognizes a complement breakdown product that is frequently deposited on microbes


ACTIVATED T CELL
CD154
CD154
Complement component
Antigen
IgM
IgM
CD21
CD21
Igβ
Igα
Igβ
Igα
Signal 1
Signal 2
B CELL

plasma cells

- B cells differentiate into them, after stimulation
- secrete large amounts of antibodies, the mediators of humoral immunity





five classes or isotypes of Igs

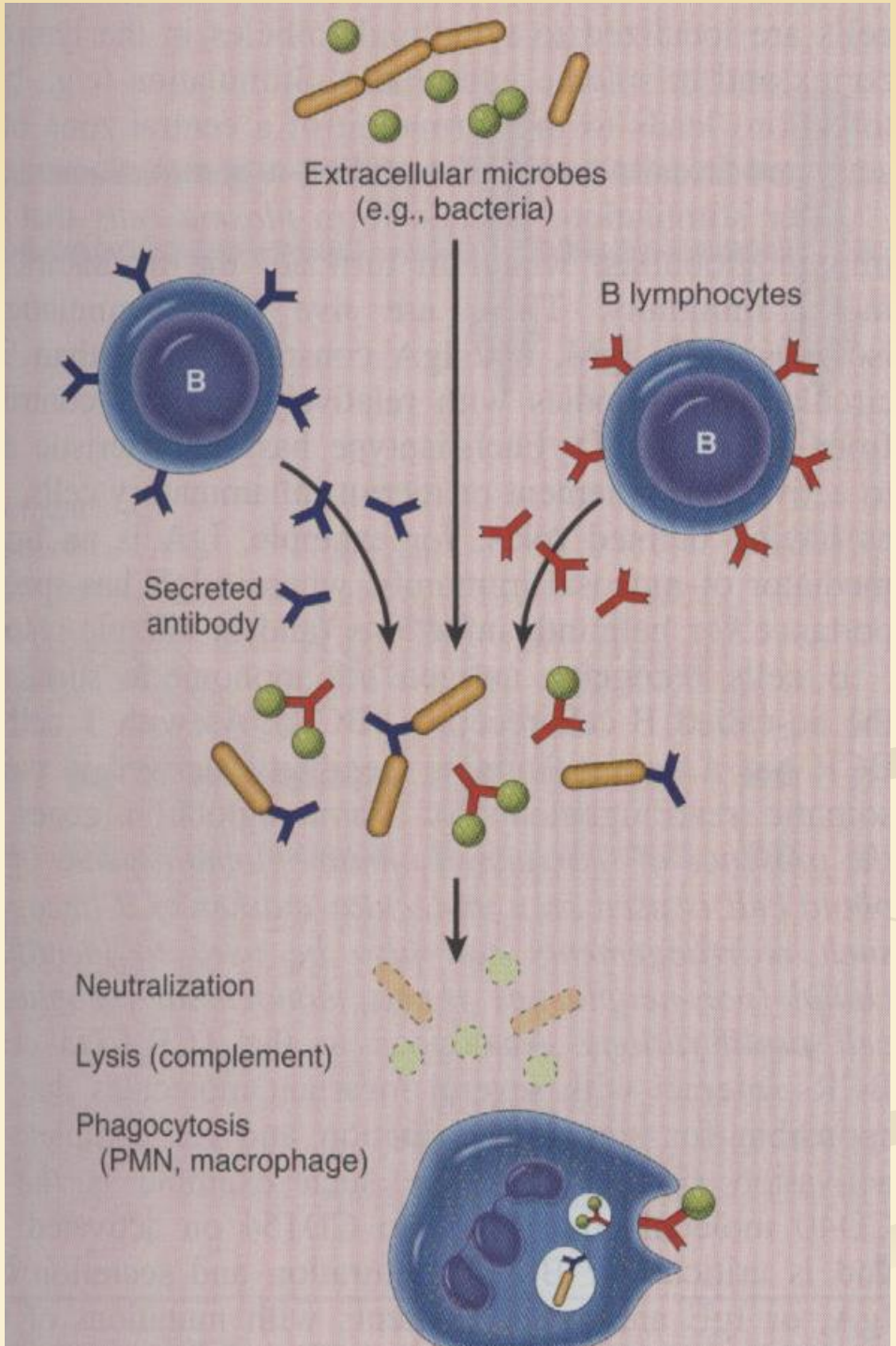
- **IgG, IgM,** and **IgA**, more than 95% of circulating Abs

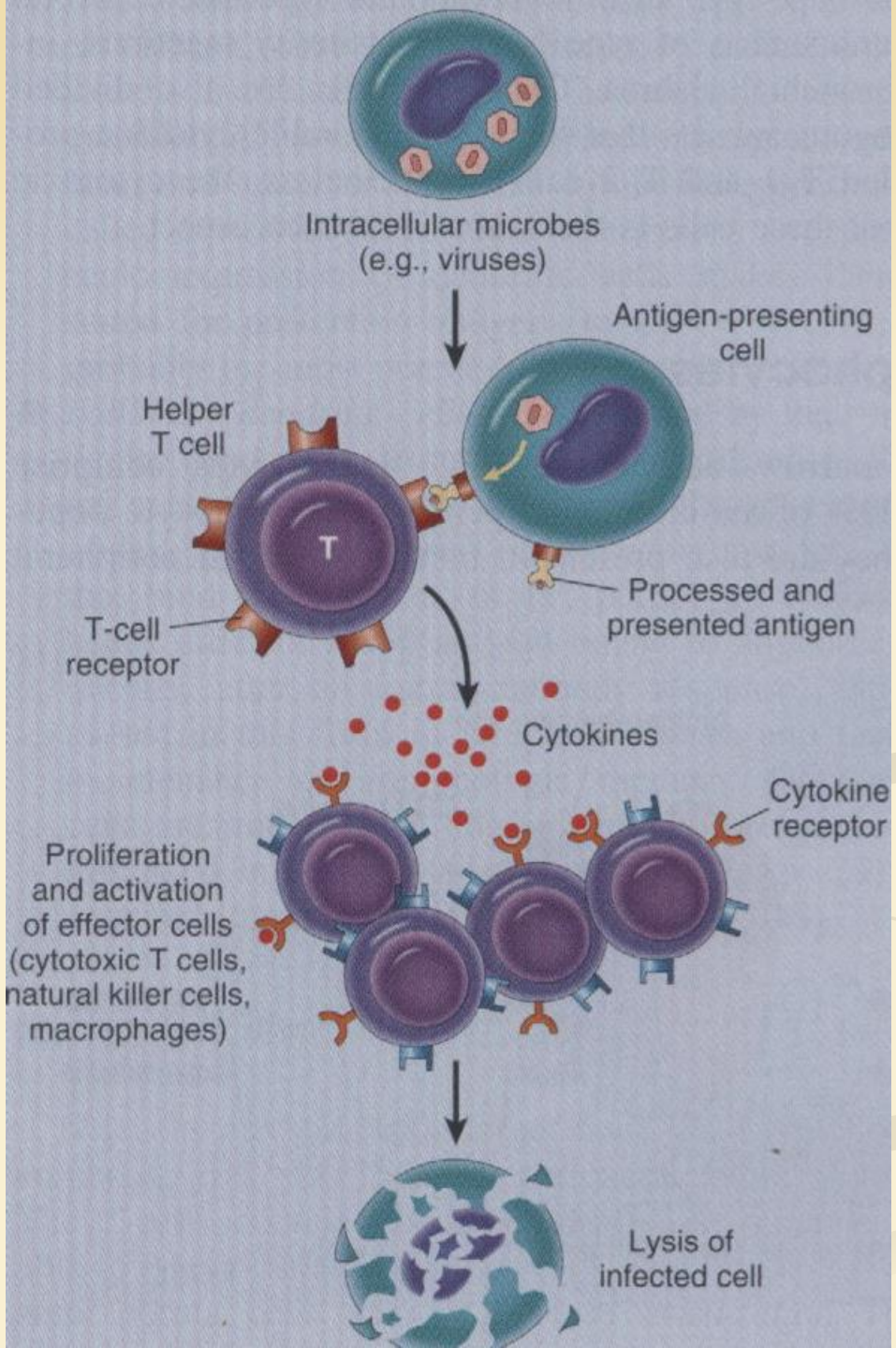
- IgA is the major isotype in mucosal secretions

- **IgE** is present in the circulation at very low concentrations and is also found attached to the surfaces of tissue mast cells,
- **IgD** is expressed on the surfaces of B cells but is not secreted

characteristic abilities of each Ig isotype

- activate complement
- recruit inflammatory cells
- plays a different role in
  - host defense
  - disease states


Extracellular microbes
(e.g., bacteria)
B lymphocytes
B
B
Secreted
antibody
Neutralization
Lysis (complement)
Phagocytosis
(PMN, macrophage)


Intracellular microbes
(e.g., viruses)
Antigen-presenting
cell
Helper
T cell
T
T-cell
receptor
Processed and
presented antigen
Cytokines
Cytokine
receptor
Proliferation
and activation
of effector cells
(cytotoxic T cells,
natural killer cells,
macrophages)
Lysis of
infected cell

Natural Killer Cells

Natural Killer Cells *(NK)*

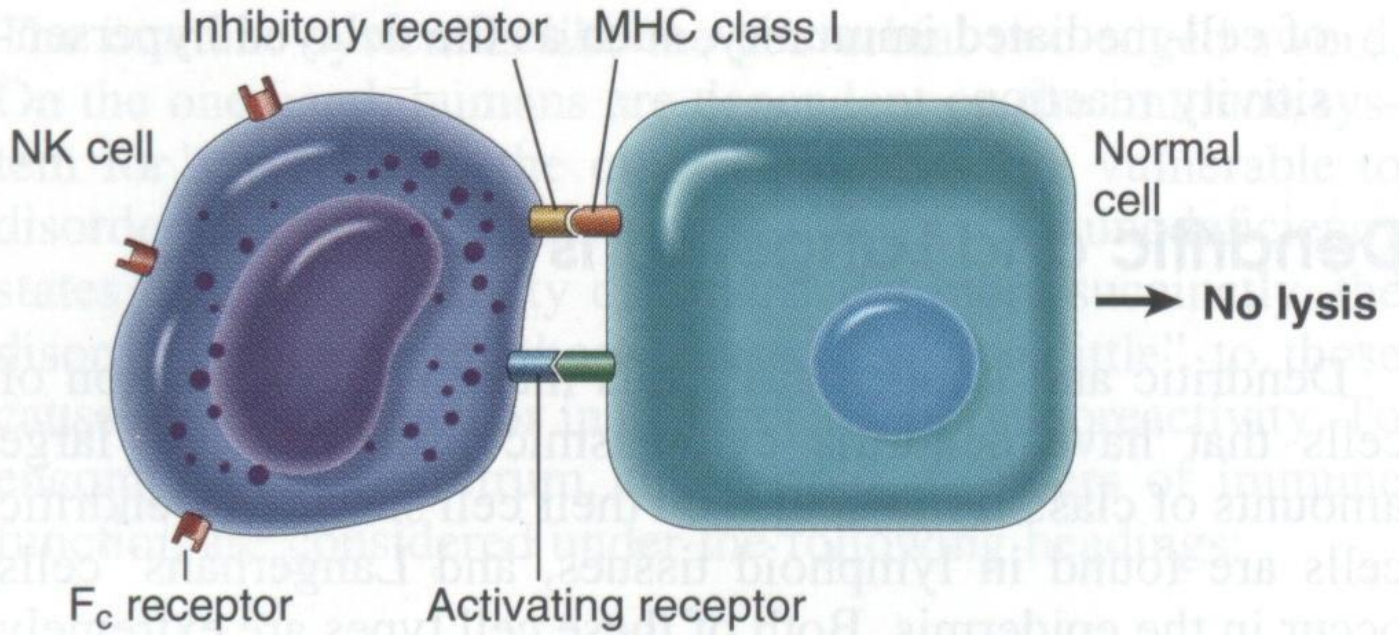
- are lymphocytes that arise from the common lymphoid progenitor
- are cells of **innate immunity**
- do not express highly variable and clonally distributed receptors for antigens

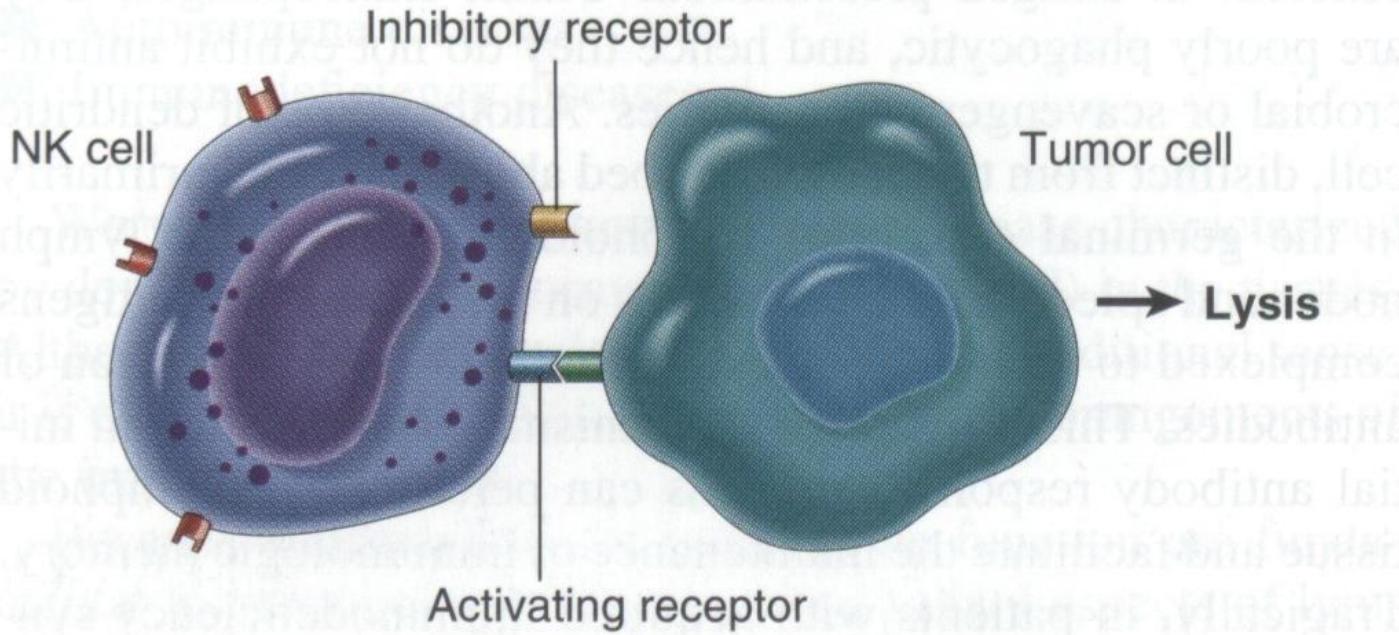
a unique specificity

- do not have specificities as diverse as do T or B cells
- use a limited set of activating receptors to recognize **stressed or infected cells or cells with DNA damage**
- **kill** these cells, thus eliminating irreparably damaged cells and potential reservoirs of infection

another unique specificity

- To avoid attacking normal host cells, NK cells express inhibitory receptors that recognize self class I MHC molecules, which are expressed on all healthy cells
- engagement of these inhibitory receptors typically overrides the activating receptors, prevents activation of the NK cells


Inhibitory receptor
MHC class I
NK cell
Normal cell
No lysis
F_c receptor
Activating receptor


Inhibitory receptor
NK cell
Tumor cell
Lysis
Activating receptor

Infections (especially viral infections) *and stress*

- loss of expression of class I MHC molecules
- the NK cells are released from inhibition
- able to respond to the activating ligands that were induced by the stress
- destroy the unhealthy host cells

Antigen-Presenting Cells

Antigen-Presenting Cells

- several cell types that are specialized to capture microbial antigens and display these to lymphocytes

- Foremost among are **dendritic cells** (DCs), the major cells for displaying protein antigens to naive T cells
- Several other cell types: **macrophages, B cells**

Dendritic Cells

- dendritic morphology (fine dendritic cytoplasmic processes)
- two functionally distinct types:

➢ **Interdigitating DCs, or more simply, DCs**

➢ **Follicular dendritic cells (FDCs)**

Interdigitating DCs
or more simply, DCs

- nonphagocytic cells, express high levels of class II MHC and T-cell costimulatory molecules
- **Immature DCs** reside in epithelia, where they are strategically located to capture entering microbes; Langerhans cell of the epidermis
- **Mature DCs** are present in the T-cell zones of lymphoid tissues, where they present antigens to T cells circulating through them

Interdigitating DCs

- also present in the **interstitium of many nonlymphoid organs** such as the heart and lungs
- can capture the antigens of microbes that have invaded the tissues

follicular dendritic cells (FDCs)

- in the **germinal centers of lymphoid follicles** in the spleen and lymph nodes
- bear receptors for:
  - the Fc tails of IgG
  - complement proteins

FDCs

- efficiently trap antigen bound to antibodies and complement
- display antigens to activated B lymphocytes in lymphoid follicles
- promote secondary antibody responses

Other APCs

- **Macrophages** ingest microbes and other particulate antigens and display peptides for recognition by T lymphocytes
  - T cells in turn activate the macrophages to kill the microbes, the central reaction of cell-mediated immunity
- **B cells** present peptides to helper T cells
  - receive signals that stimulate antibody responses to protein antigens

Effector Cells

Effector Cells

- Many different types of leukocytes perform the ultimate task of the adaptive immune response, which is to eliminate infections
- NK cells
- Antibody-secreting plasma cells
- T lymphocytes
- Macrophages

notes

- T lymphocytes secrete **cytokines** that recruit and activate other leukocytes, such as neutrophils and eosinophils
  - all these cell types function in defense against various pathogens
- **The same effector cells are responsible for tissue injury** in inflammatory diseases caused by abnormal immune responses

NK cells

- frontline effector cells
- ability to rapidly react against "stressed" cells

Plasma cells

- Antibody secretion
- effector cells of humoral immunity

T lymphocytes

- both CD4+ helper T cells and CD8+ CTLs
- effector cells of cell-mediated immunity
- often function in host defense together with other cells

Macrophages

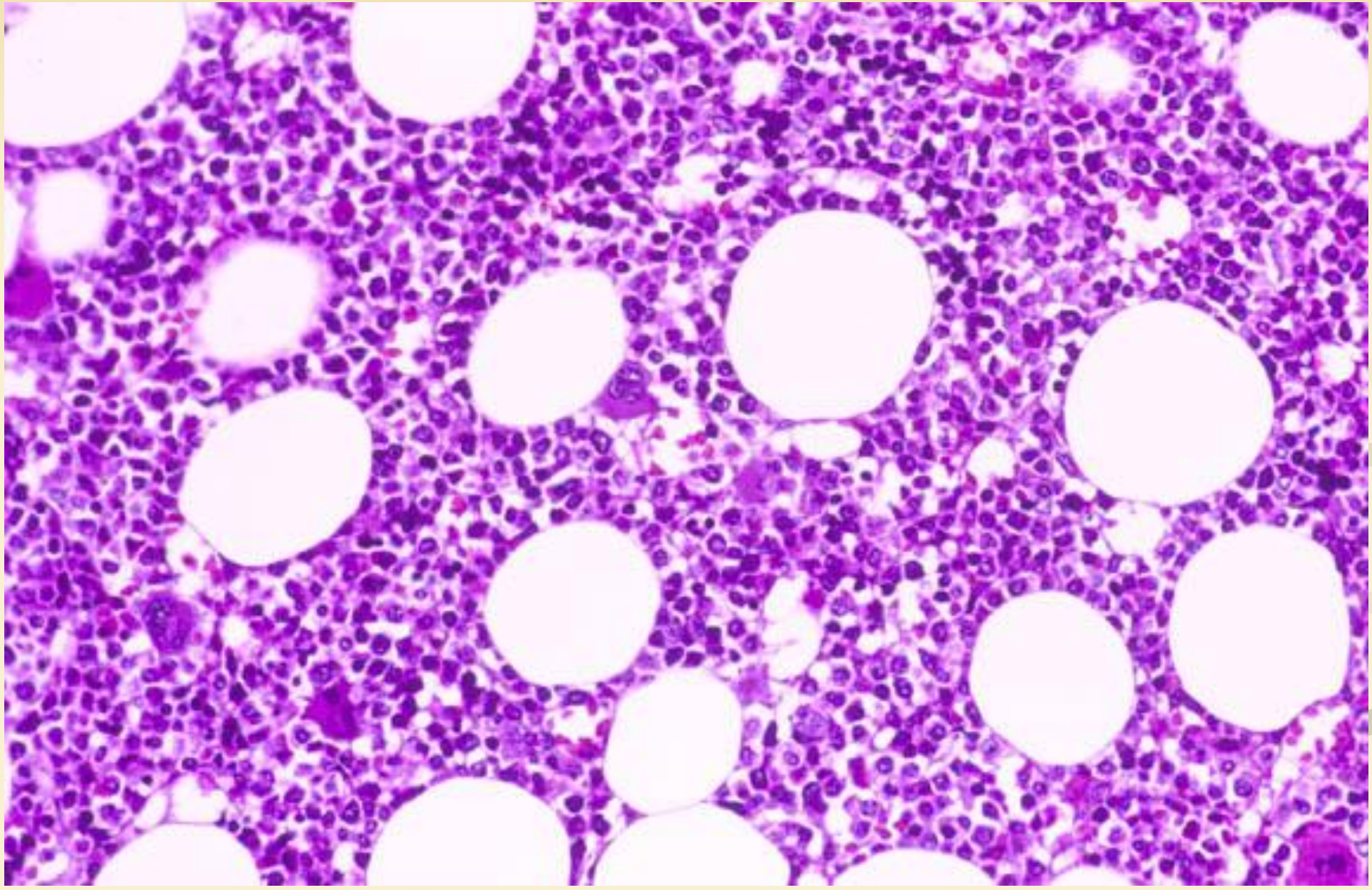
- bind microbes that are coated with antibodies or complement
- phagocytose and destroy microbes
- **effector cells of humoral immunity**
- respond to signals from helper T cells
- improve their ability to destroy phagocytosed microbes
- **effector cells of cellular immunity**

Lymphoid Tissues

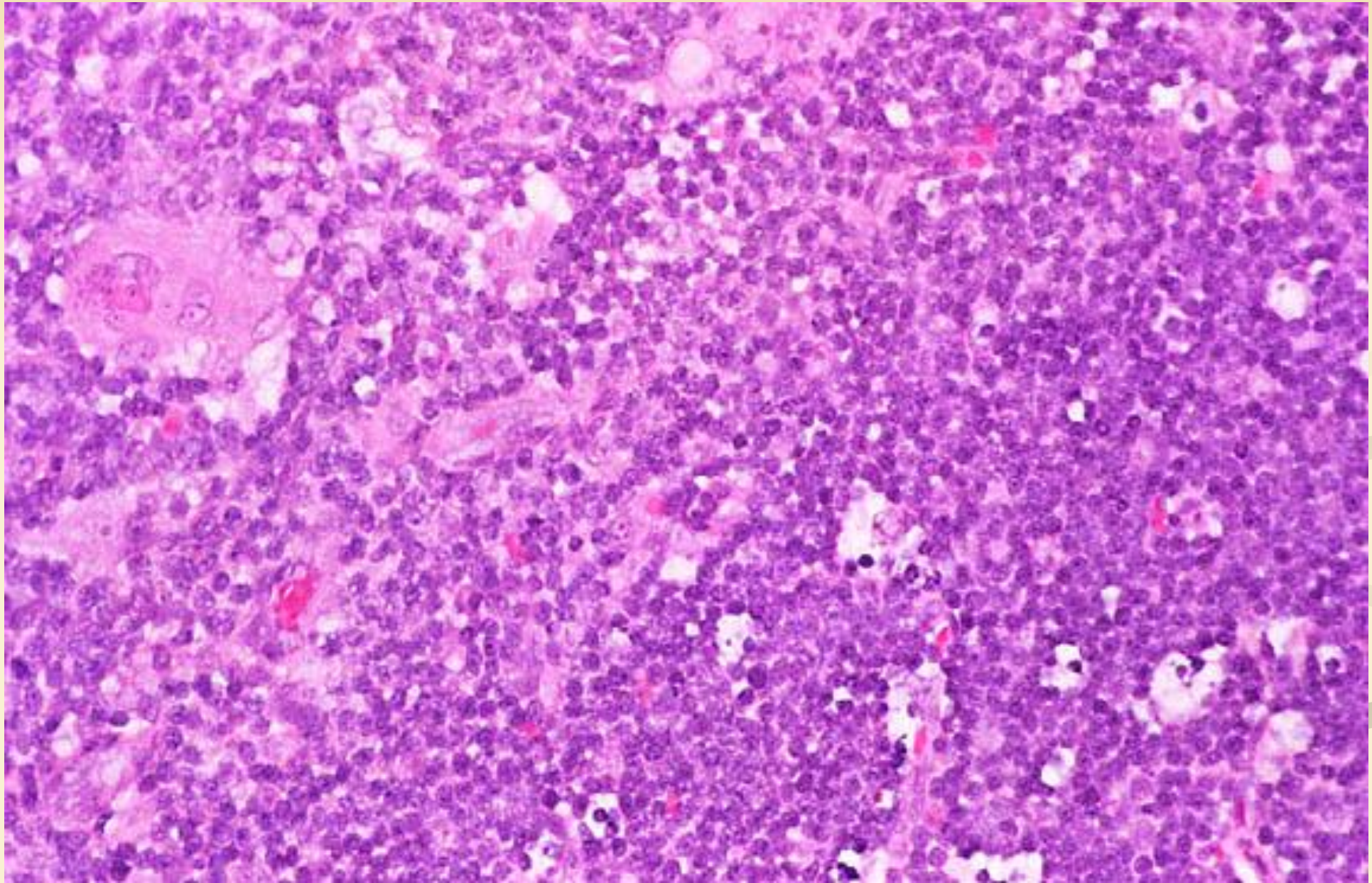
Lymphoid Tissues

- The lymphoid tissues of the body are divided into:
  - **generative (primary) organs**, where lymphocytes express antigen receptors and mature
  - **peripheral (secondary) lymphoid organs**, where adaptive immune responses develop

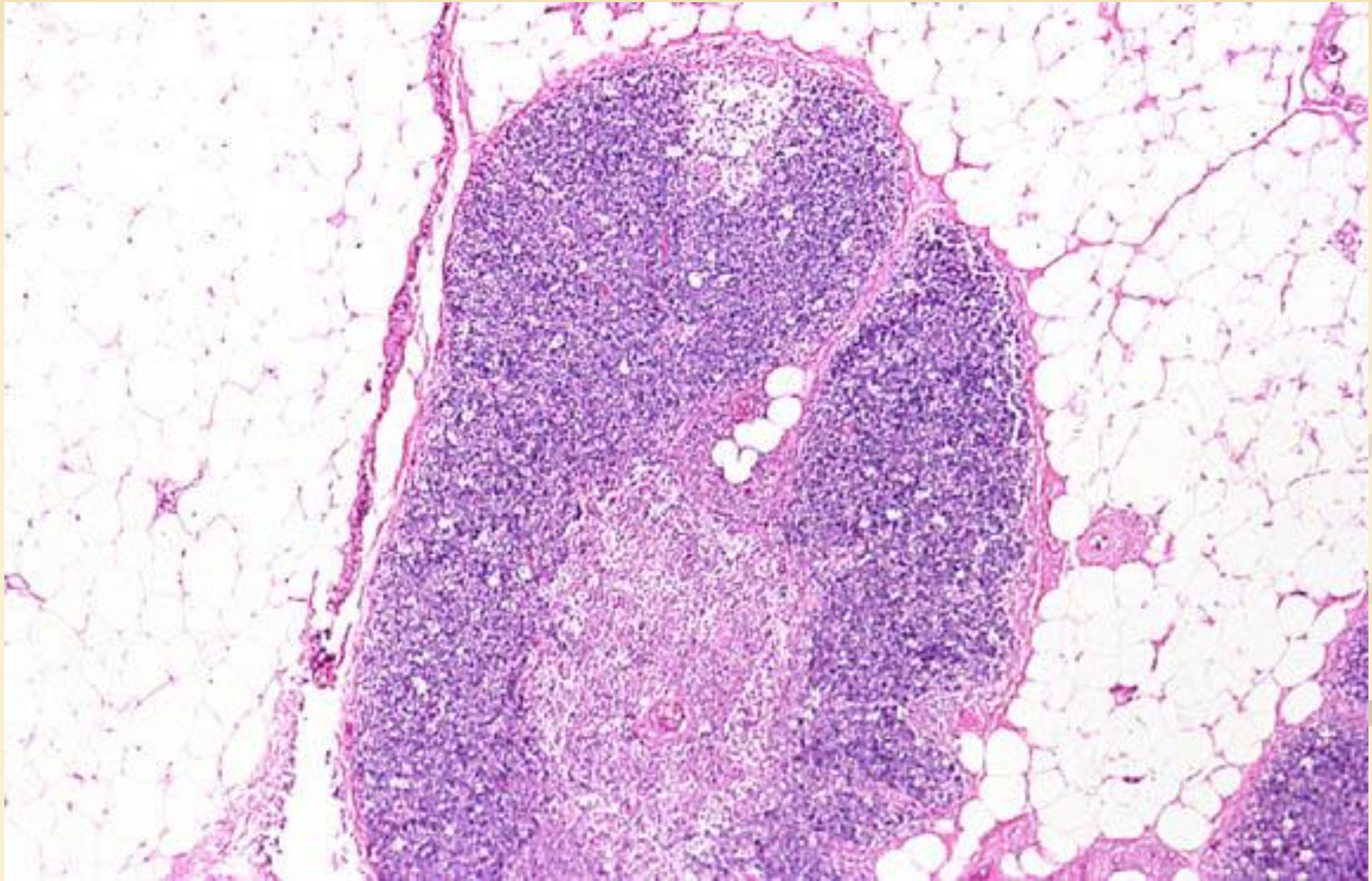
BM



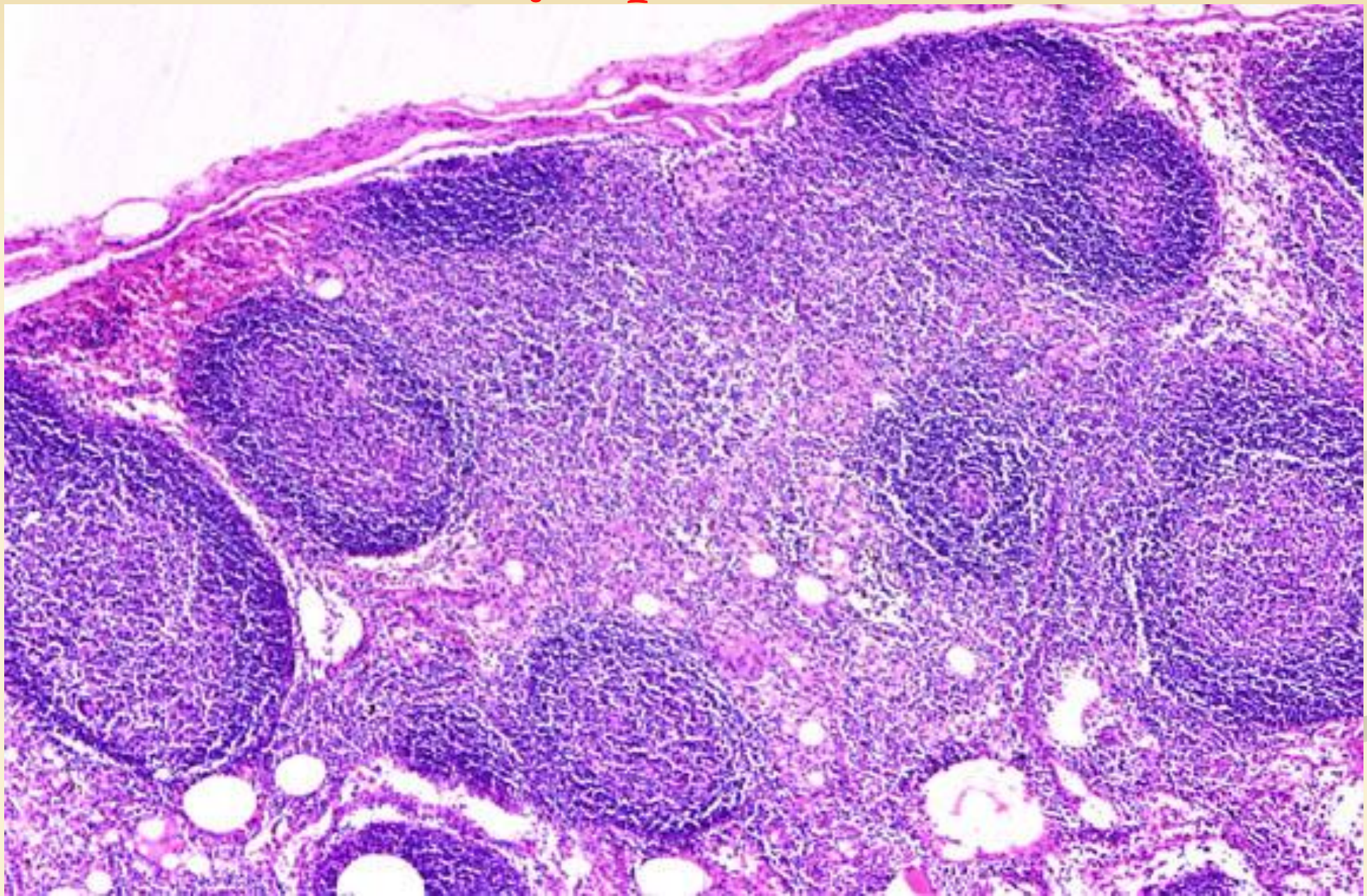
Thymus



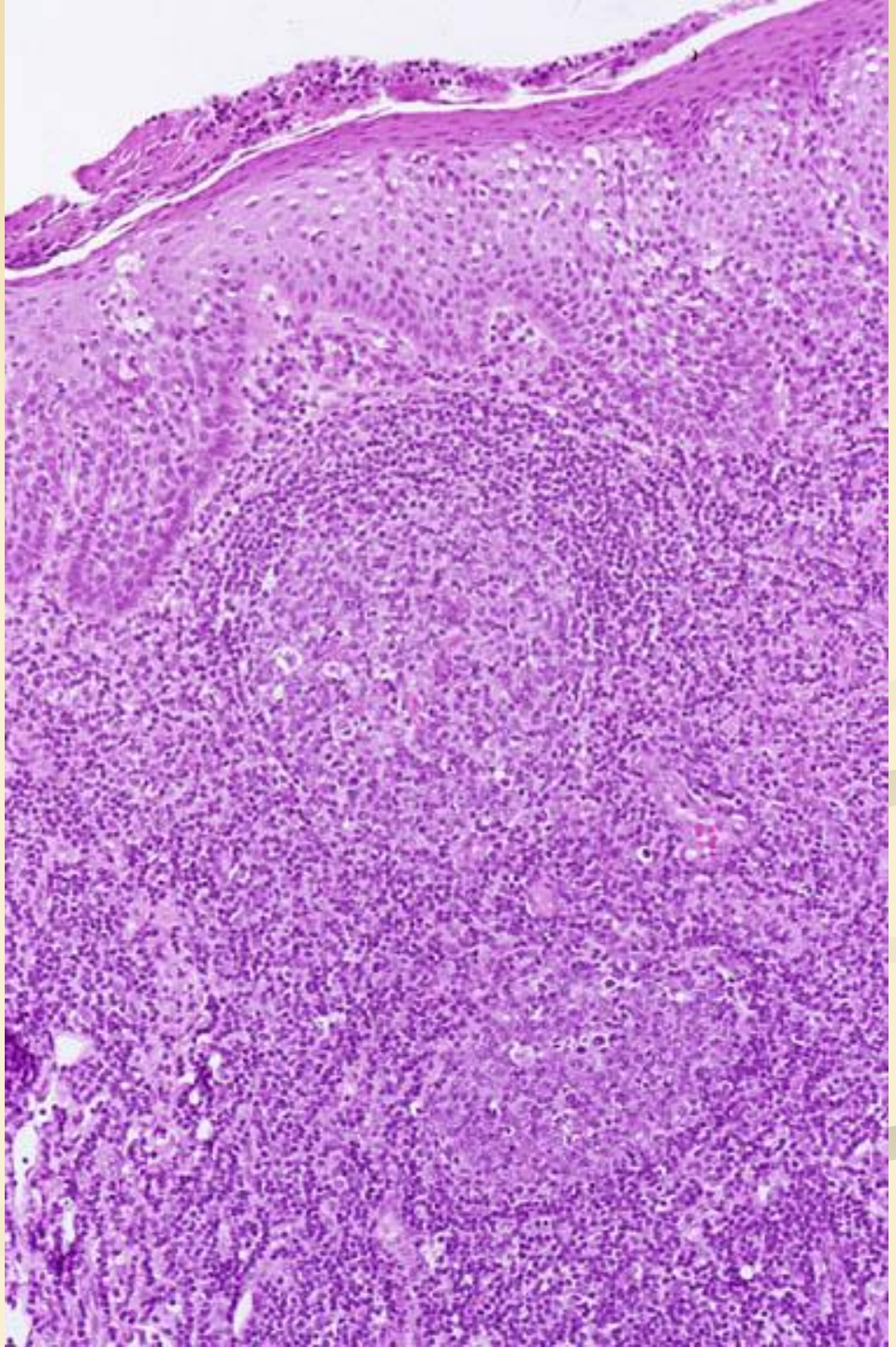
Thymus



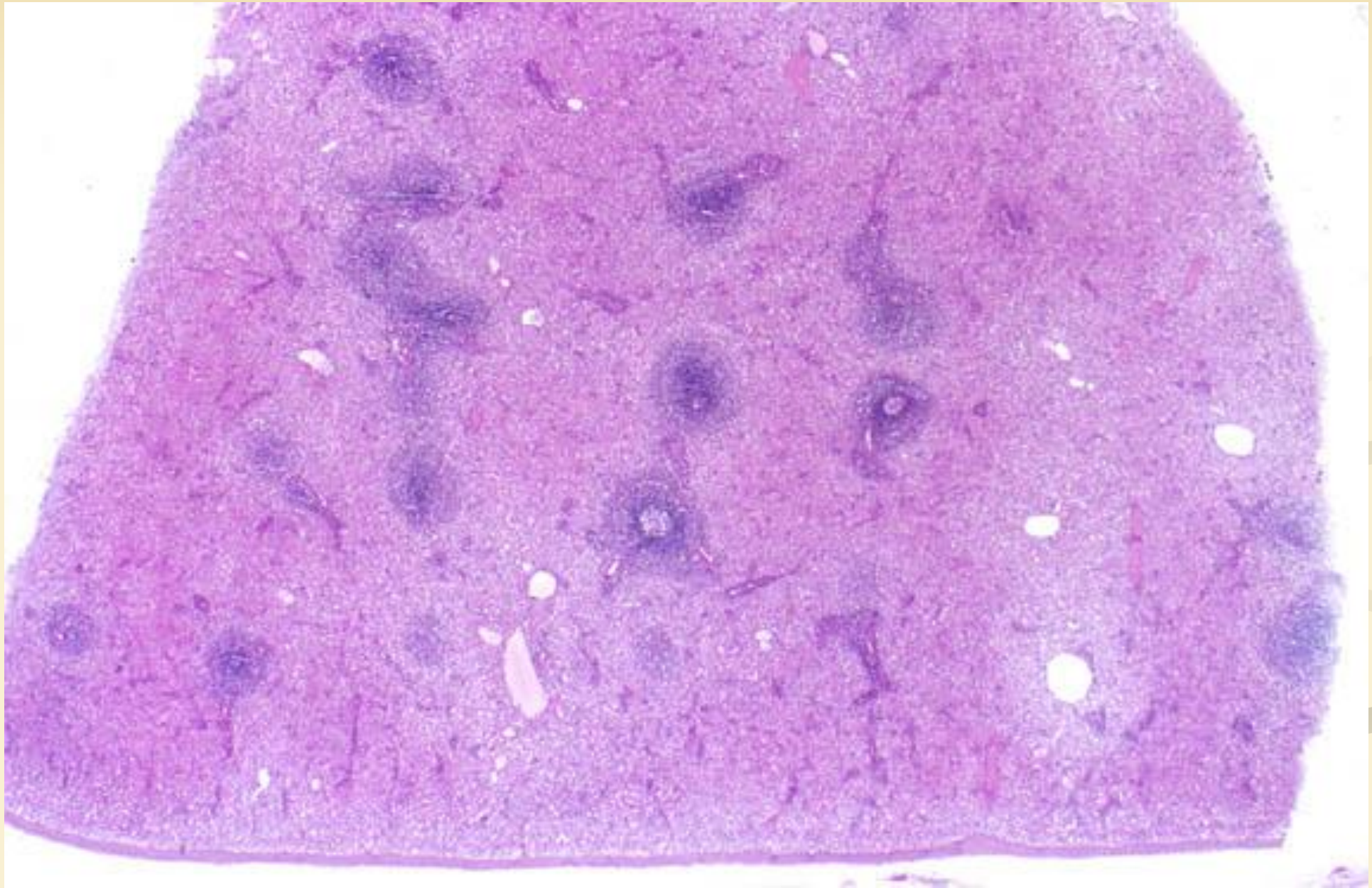
Lymph node



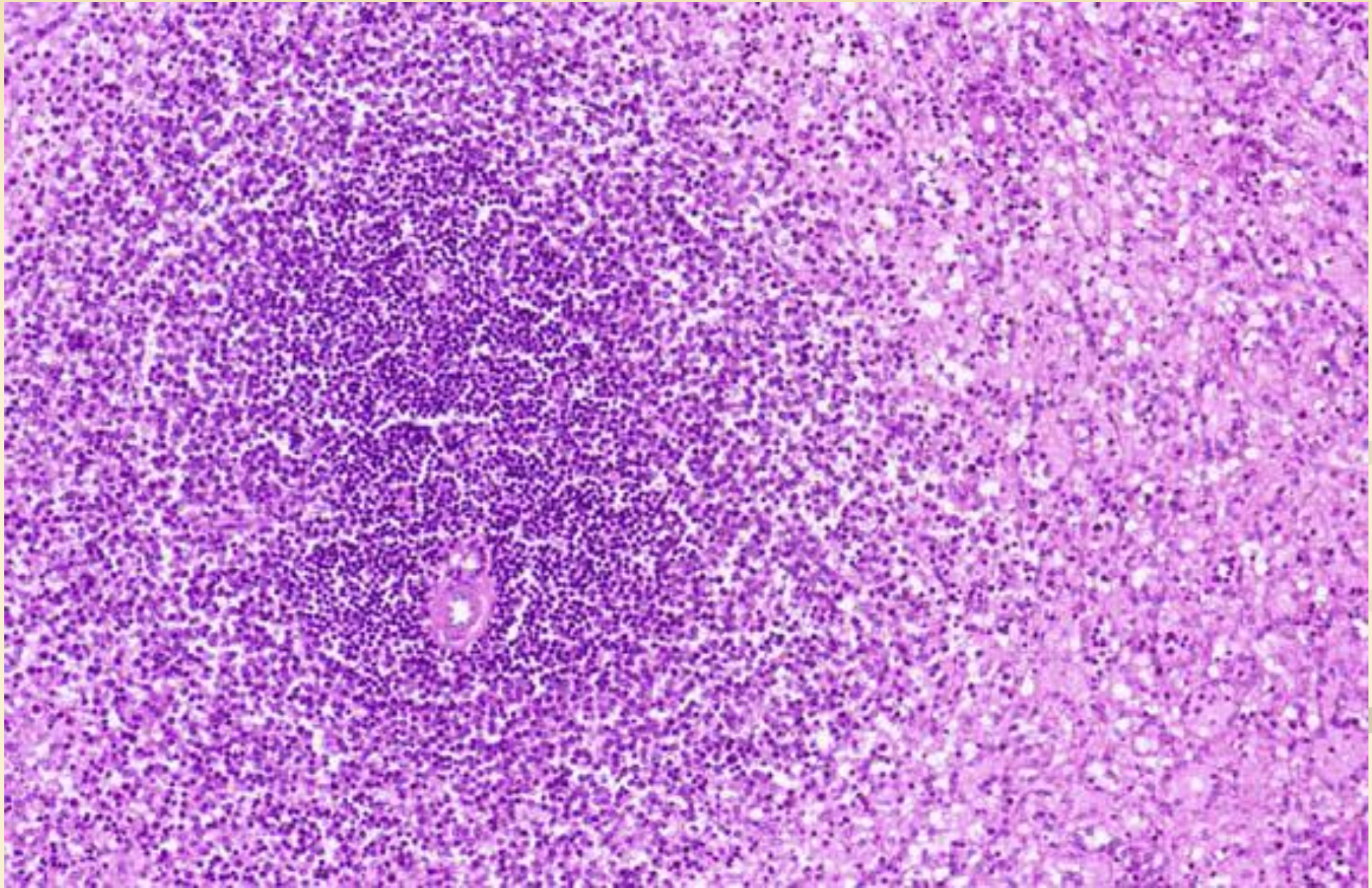
Tonsil



Spleen



Spleen



lymphoid tissues

- The **generative organs** are the thymus and bone marrow
- The **peripheral organs** are the lymph nodes, spleen, and mucosal and cutaneous lymphoid tissues

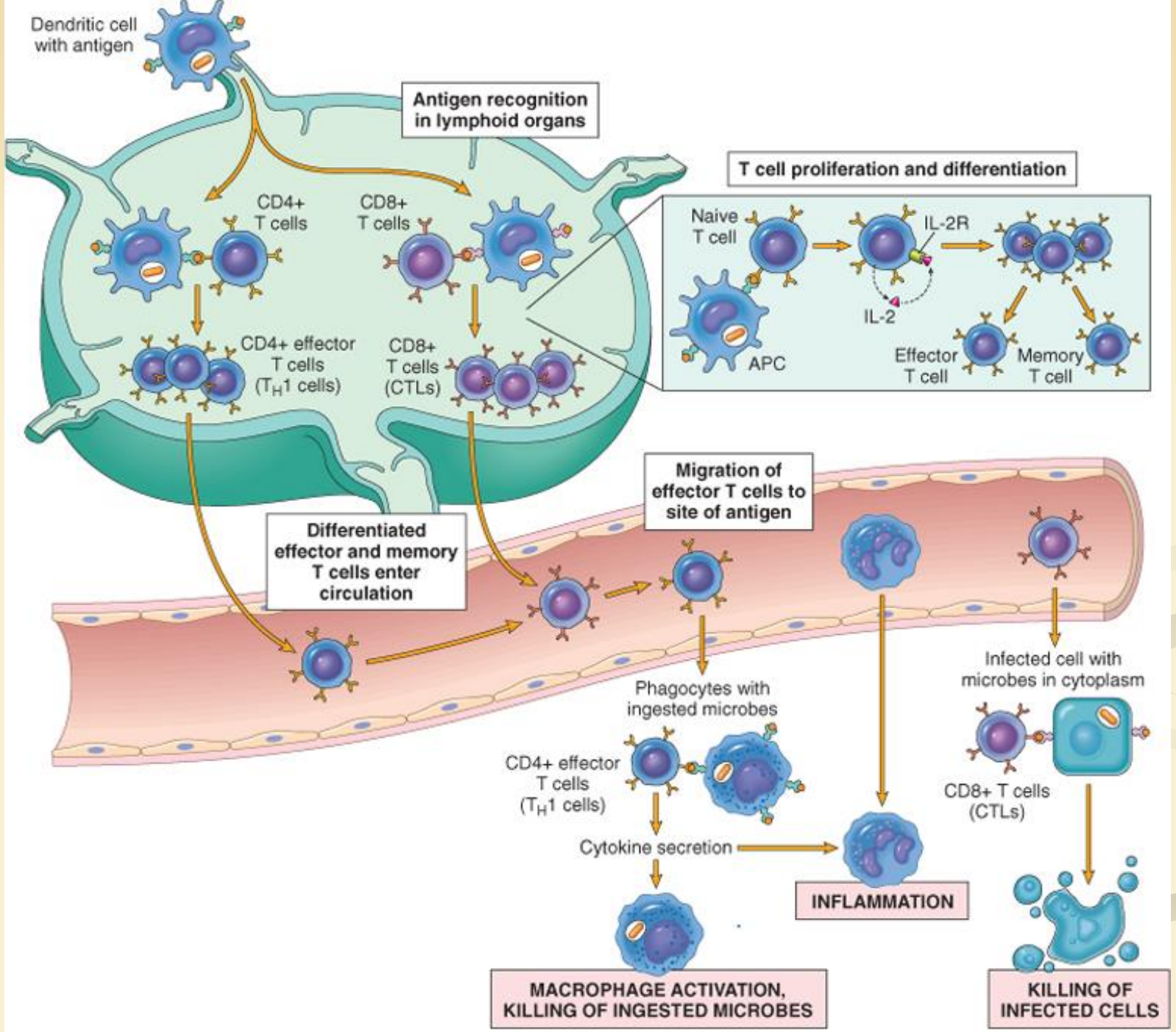
notes

- Mature lymphocytes **recirculate** through the peripheral organs, searching for microbial antigens to which they can recognize and respond

The Capture and Display of Antigens

The Capture and Display of Antigens

- Microbes and their protein antigens, are captured by **DCs** that are resident in these epithelia
- the cell-bound antigens are transported to draining lymph nodes



different MHC molecules and different subsets of T cells

1. Antigens from the extracellular environment
2. Antigens in the cytoplasm

Antigens from the extracellular environment

- processed in endosomal and lysosomal vesicles
- displayed bound to class **II MHC** molecules
- **CD4+** helper T cells recognize peptides, which are usually derived from ingested proteins

antigens in the cytoplasm

- displayed by class **I MHC** molecules
- recognized by **CD8+** cytotoxic T cells

Antigen recognition

- two classes of **T cells**
- CD4+ and CD8+ T cells combat microbes that are located in different cellular compartments
- Protein antigens, polysaccharides and other antigens, are recognized by **B lymphocytes** in the lymphoid follicles of the peripheral lymphoid organs

innate immune response

- the microbe elicits innate response
  - At the same time as the antigens of a microbe are recognized by B and T lymphocytes

The innate immune response activates APCs to:

- express costimulatory molecules
- secrete cytokines that stimulate the proliferation and differentiation of T lymphocytes

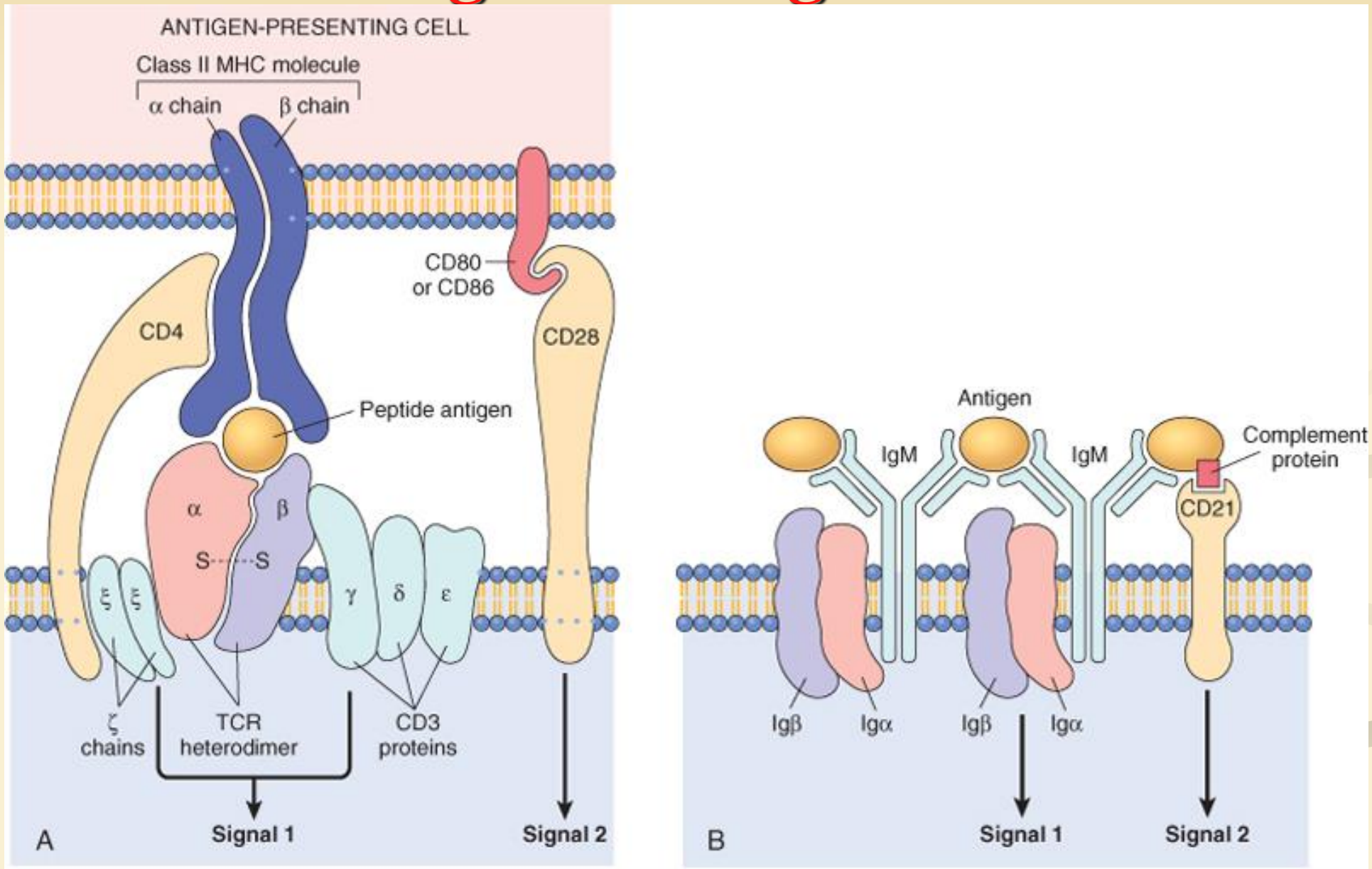
The principal costimulators for T cells

- the B7 molecules (CD80 and CD86)
  - expressed on professional APCs
  - recognized by the CD28 receptor on naive T cells

complement

- Activate by the innate immune response to some microbes and polysaccharides
- generating products that enhance the proliferation and differentiation of B lymphocytes

signal 1 & signal 2



antigen-specific lymphocytes

Antigen recognition and costimulation together trigger **the functional responses of the antigen-specific lymphocytes**

adaptive immune responses

- Cell-Mediated Immunity:
  - ✓ Activation of T Lymphocytes and Elimination of Cell-Associated Microbes
- Humoral Immunity:
  - ✓ Activation of B Lymphocytes and Elimination of Extracellular Microbes

Cell-Mediated Immunity:

Cell-Mediated Immunity:

- Activation of naive T Lymphocytes
- Elimination of Cell-Associated Microbes

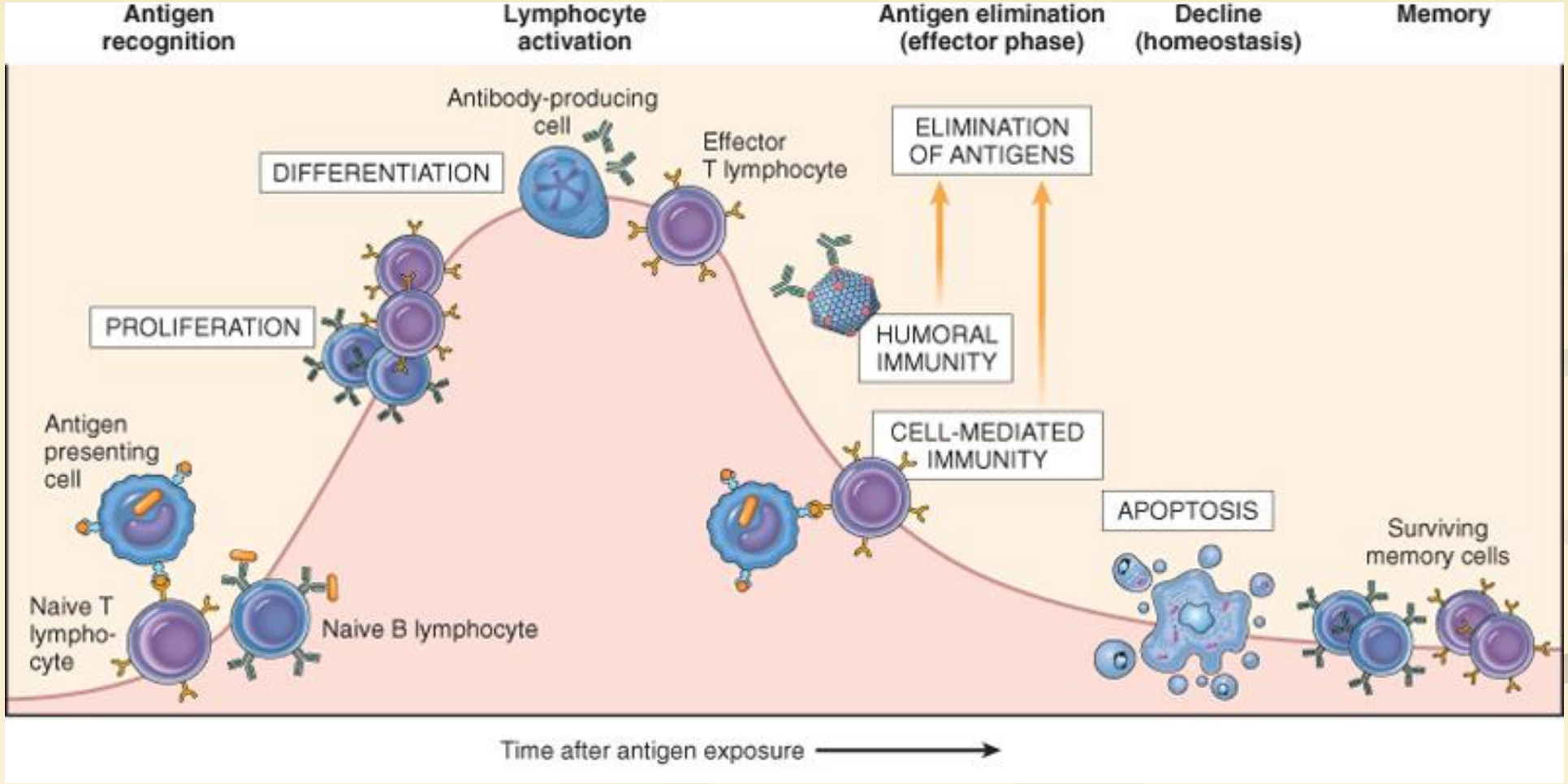
Naitve T lymphocytes are activated

- by antigen and costimulators
- in peripheral lymphoid organs
- proliferate and differentiate into effector cells
- migrate to any site where the antigen (microbe) is present

cytokines

- Activated T lymphocytes secrete
- function as:
  - growth and differentiation factors for lymphocytes and other cells
  - Mediate communications between leukocytes
- Have important roles in immune responses and inflammation

Adaptive immune responses consist of sequential phases:

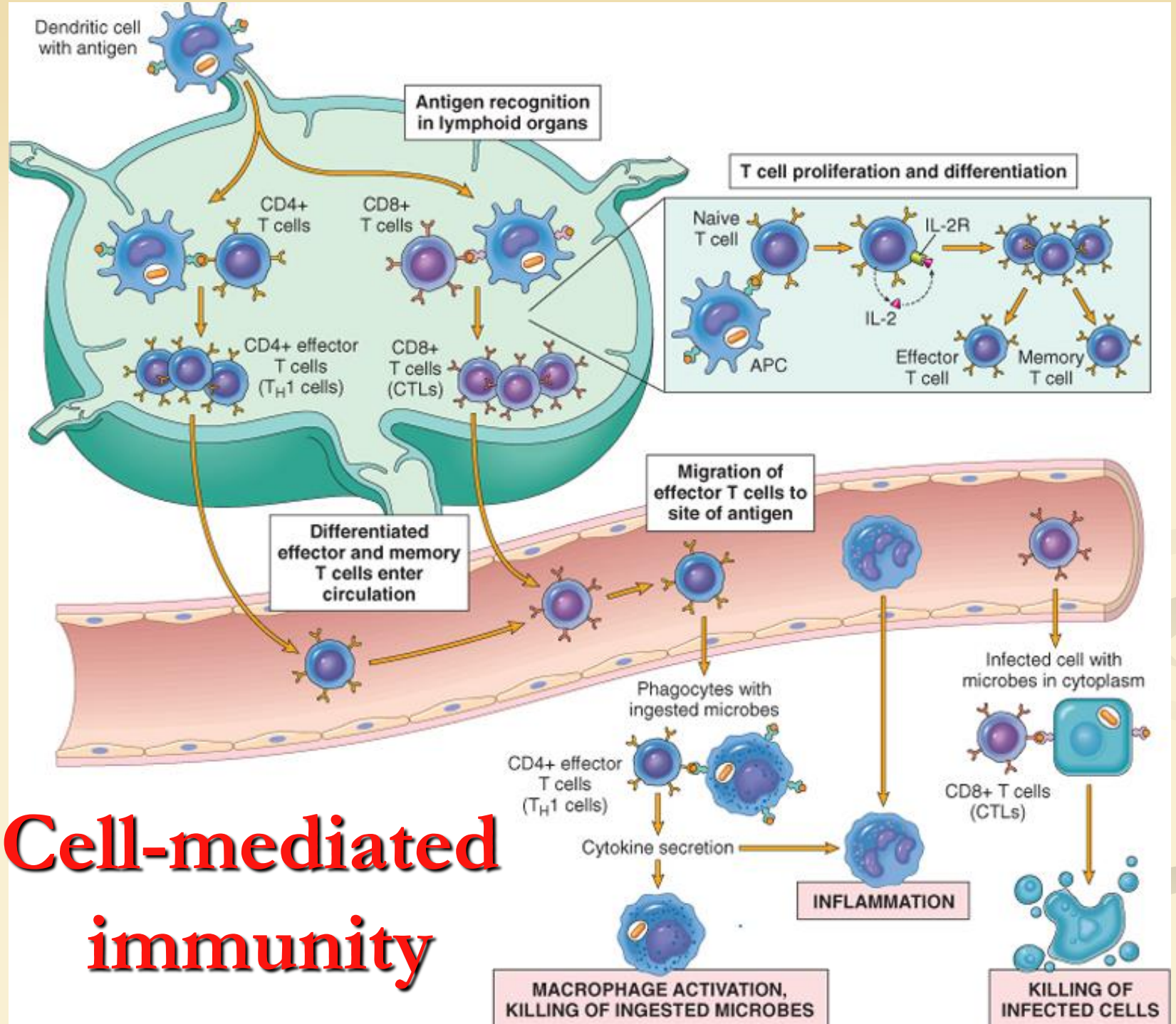


Adaptive immune responses consist of sequential phases:

- recognition of antigen by specific lymphocytes
- activation of lymphocytes (consisting of their proliferation and differentiation into effector cells)
- the effector phase (elimination of antigen)

In both humoral immunity and cell-mediated immunity

- The response declines as antigen is eliminated
- most of the antigen-stimulated lymphocytes die by apoptosis
- The antigen-specific cells that survive are responsible for **memory**
- The duration of each phase may vary in different immune responses



Cell-mediated immunity

Cell-mediated immunity

- peptide antigens displayed on dendritic cells in lymph nodes
- Naive T cells recognize
- cytokine IL-2
- The T cells are activated to
- proliferate and differentiate into effector and memory cells
- migrate to sites of infection

Cell-mediated immunity

- TH1 recognize the antigens
  - activate the phagocytes to kill the microbes
  - induce inflammation
- CTLs kill infected cells harboring microbes
- TH2, defense against helminths
- Some activated T cells differentiate into long-lived memory cells

Cytokines: Messenger Molecules of the Immune System

Cytokines

- polypeptide products of many cell types
- principally activated lymphocytes and macrophages
- function as mediators of:
  - Inflammation
  - adaptive immunity

cytokines

- diverse actions and functions
- share some common features
- synthesized and secreted in response to external stimuli
  - microbial products
  - antigen recognition
  - other cytokines

Secretion of cytokines

- Transient
- controlled by transcription and post-translational mechanisms

actions of cytokines

- Autocrine
- Paracrine
- Endocrine, less commonly

The effects of cytokines

- *pleiotropic* (one cytokine has effects on many cell types)
- *redundant* (the same activity may be induced by many proteins)

classes of cytokines

- Cytokines involved in innate immunity and inflammation
- Cytokines that regulate lymphocyte responses and effector functions in adaptive immunity
- Cytokines that stimulate hematopoiesis

Cytokines involved in innate immunity and inflammation

- the earliest host response to microbes and dead cells
- TNF and IL-1, chemokines, IL-12, and IFN-γ
- Major sources: activated macrophages, DCs, endothelial cells, lymphocytes, mast cells, and other cell types

Cytokines that regulate lymphocyte responses and effector functions in adaptive immunity

- **IL-2 and IL-4**, proliferation and differentiation of lymphocytes
- activation of various effector cells
  - **IFN-γ**, which activates macrophages
  - **IL-5**, which activates eosinophils
- Sources: stimulated CD4+ helper T lymphocytes
- induction of adaptive cell-mediated immune responses

Cytokines that stimulate hematopoiesis (colony-stimulating factors)

- increase the output of leukocytes from the bone marrow
- replenish leukocytes that are consumed

Effector Functions of T Lymphocytes

CD4+ helper T Lymphocytes

- ***One of the earliest responses:***

1. secretion of the IL-2
2. expression of high-affinity receptors for IL-2

CD4+ helper T Lymphocytes differentiate into effector cells:

- TH1
- TH2
- TH17

TH1 cells

- produce the cytokine IFN-γ
  - activates macrophages
  - stimulates B cells to produce antibodies
  - activate complement and coat microbes for phagocytosis

TH2 cells produce

- **IL-4,** stimulates B cells to differentiate into IgE-secreting plasma cells
- **IL-5,** activates eosinophils
- **IL-13,** activates mucosal epithelial cells to secrete mucus and expel microbes

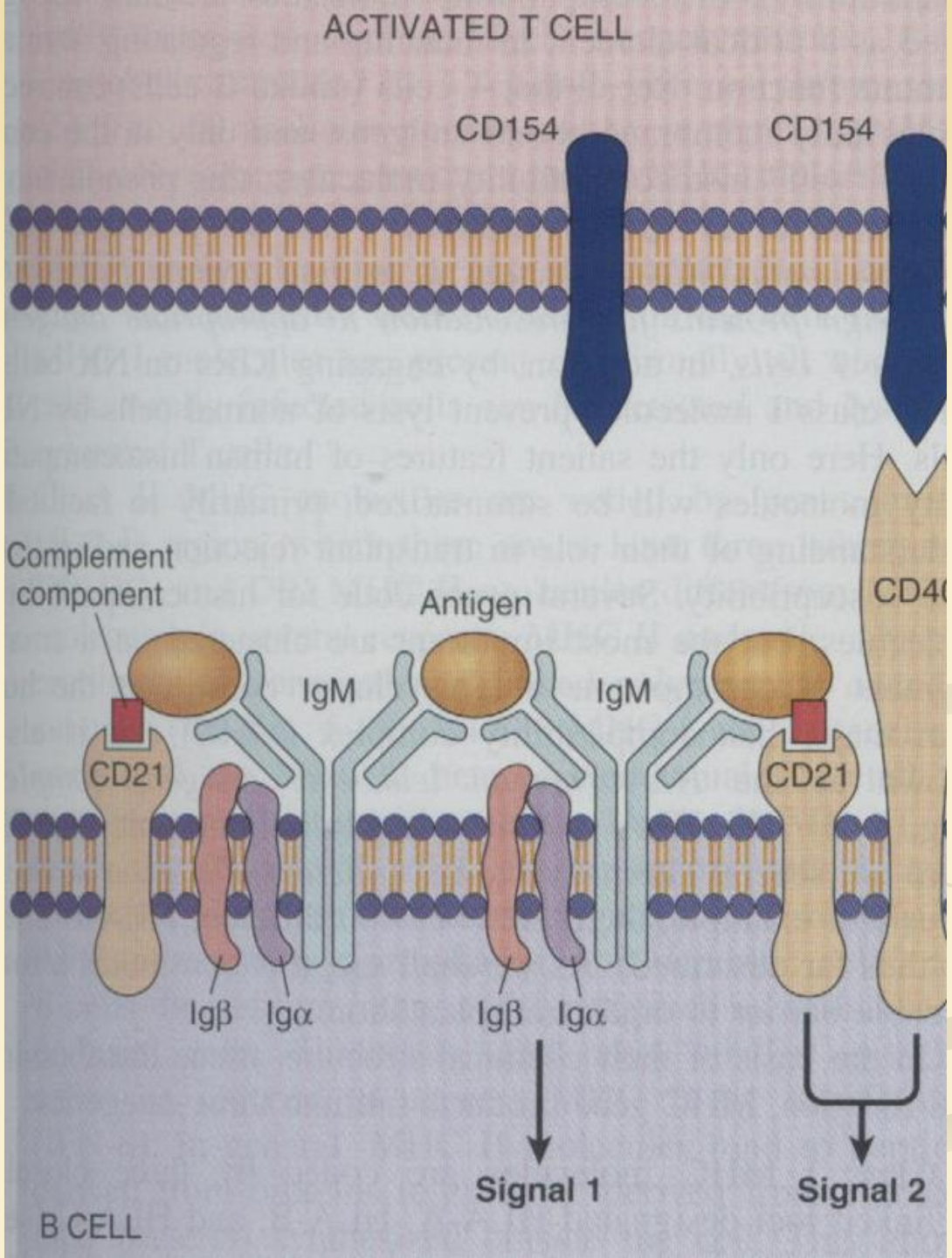
TH17 cells

- produces IL-17, promotes inflammation
  - play an important role in some T cell-mediated inflammatory disorders
- migrate to sites of infection
- When again encounter cell-associated microbes, activated to eliminate the microbes

The key mediator of the functions of helper T cells is CD40 ligand

CD40 ligand (CD40L)

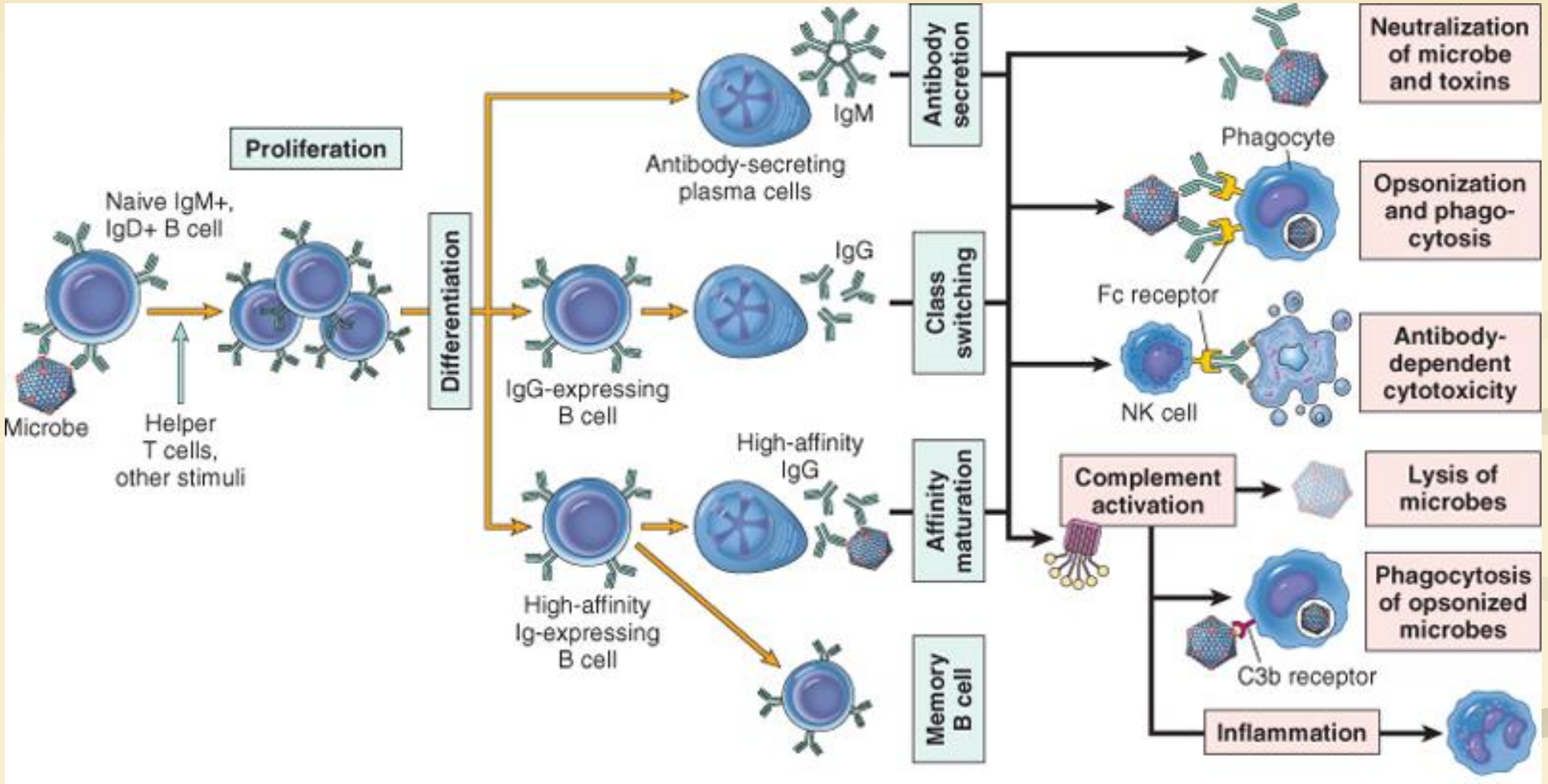
- binds to:
  - its receptor, CD40, on B cells and macrophages
  - various cytokines


ACTIVATED T CELL
CD154
CD154
Complement component
Antigen
IgM
IgM
CD21
CD21
Igβ
Igα
Igβ
Igα
Signal 1
Signal 2
B CELL

The humoral immune response combats microbes in numerous ways

- "neutralizing" the microbes
- IgG coat ("opsonize") microbes
- IgG and IgM activate the complement system
- IgA is secreted in mucosal tissues
- IgG is actively transported across the placenta
- IgE kill the parasites

Humoral immunity



- Antibodies bind to microbes, prevent them from infecting cells, neutralizing the microbes
- IgG antibodies coat (opsonize) microbes, phagocytes (neutrophils and macrophages) express FcR for IgG
- IgG and IgM activate the complement system by the classical pathway; phagocytosis and destruction of microbes
- Most opsonizing and complement-fixing IgG antibodies are stimulated by TH1 helper cells

- IgA is secreted in mucosal tissues, neutralizes microbes in the lumens of the respiratory and GI tracts
- IgG is actively transported across the placenta, protects the newborn
- IgE coats helminthic parasites, and functions with mast cells and eosinophils to kill the parasites
- TH2 cells secrete cytokines, stimulate the production of IgE, activate eosinophils, and orchestrated the response to helminths

Half life

- Most circulating antibodies have half-lives of about 3 weeks
- Some plasma cells migrate to the bone marrow, live for years, continuing to produce low levels of antibodies

Decline of Immune Responses and Immunologic Memory

Decline of Immune Responses and Immunologic Memory

- The majority of effector lymphocytes induced by an infectious pathogen die by apoptosis after the microbe is eliminated
- returning the immune system to its basal resting state
  - This return to a stable or steady state is called **homeostasis**

Cause of homeostasis

- The microbes provide essential stimuli for lymphocyte survival and activation
- The effector cells are short-lived

- as the stimuli are eliminated, the activated lymphocytes are no longer kept alive

long-lived memory cells

- Generated in the initial activation of lymphocytes
- survive for **years** after the infection
- an expanded pool of antigen-specific lymphocytes (more numerous than the naive cells specific for any antigen that are present before encounter with that antigen)
- **respond faster and more effectively** against the antigen than do naive cells
- an important goal of vaccination