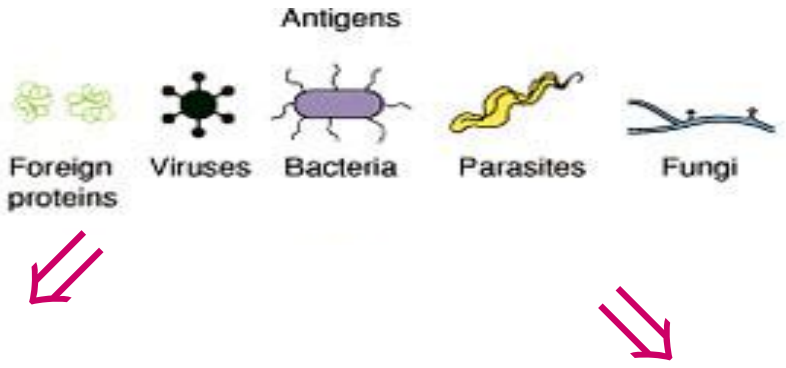
Dr Imad Aboukhamis Ph-D France

YOUR ACTIVE IMMUNE DEFENSES



Innate Immunity
- invariant (generalized)
- early, limited specificity
- the first line of defense

Adaptive Immunity
- variable (custom)
- later, highly specific
- "remembers" infection

1. Barriers - skin, tears
2. Phagocytes - neutrophils, macrophages
3. NK cells and mast cells
4. Complement and other proteins

ADAPTIVE IMMUNE RESPONSE

- a specific response
- results in acquired immunity
- long term immunity - "memory"
- involves two types of lymphocytes:
  - T cells
  - B cells

ADAPTIVE IMMUNE RESPONSE

- the specific response is customized for each pathogen
- responsible for acquired immunity
- involves antigen-presenting cells and two types of lymphocytes
- turns on when needed - inducible
- “remembers” the pathogens it has “seen” and goes into action faster the second time
- may confer lifelong immunity

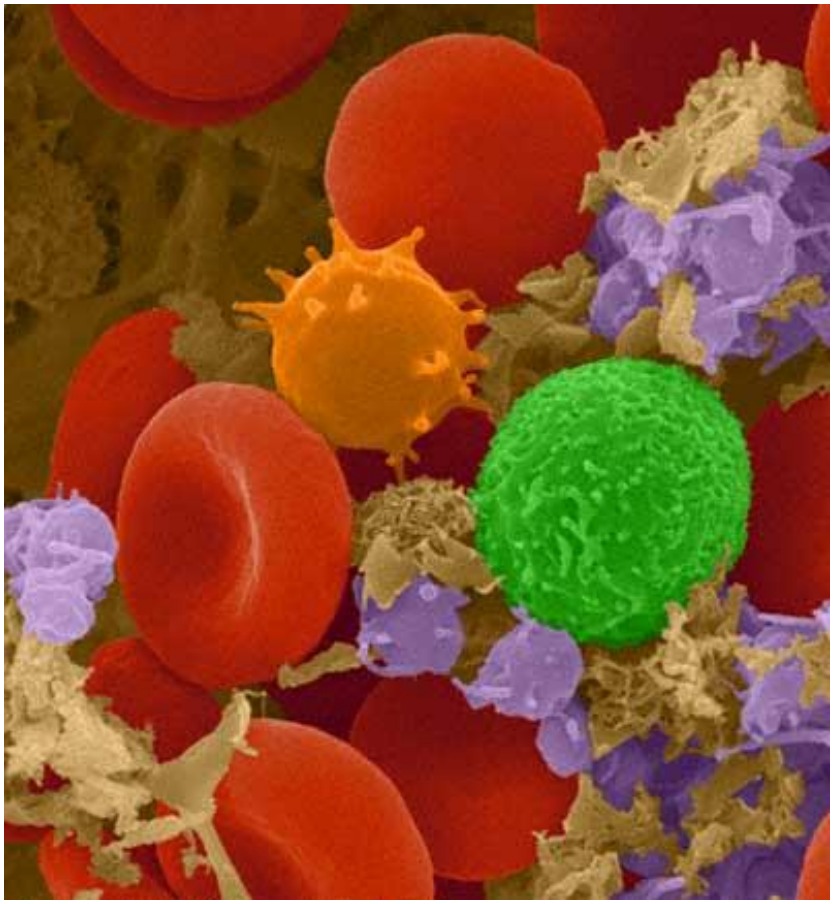
White Blood Cells (WBCs)

There are two main types of WBCs involved in the adaptive immune response:

- antigen-presenting cells (APCs)
  - not pathogen-specific
  - ingest foreign substances and break them down
  - e.g., macrophage

- lymphocytes
  - pathogen-specific
  - different types recognize different invaders and lead to their destruction

Human red and white blood cells



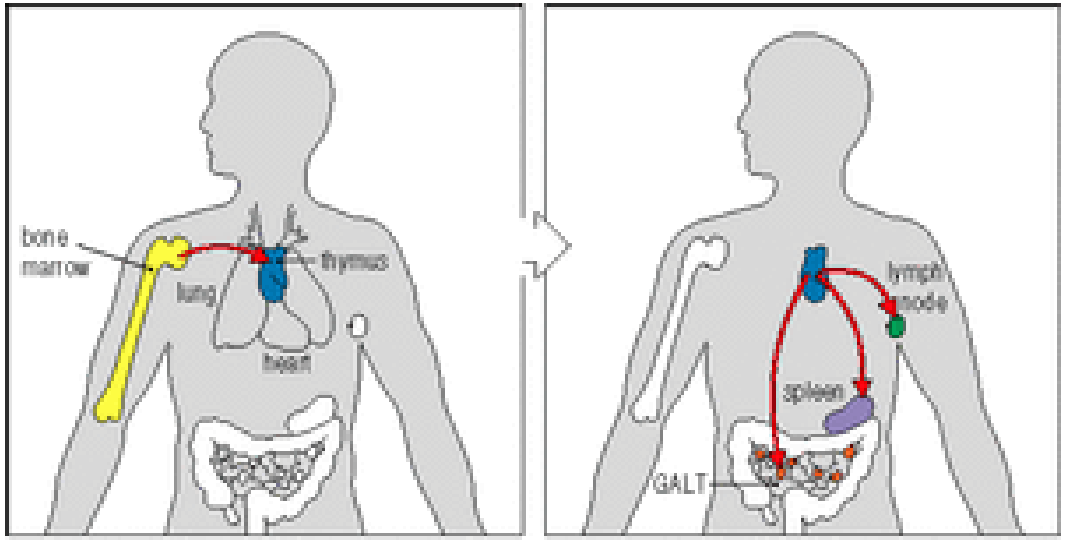
Human red blood cells (red), activated platelets (purple) and white blood cells - monocyte (green) and T lymphocyte (orange).

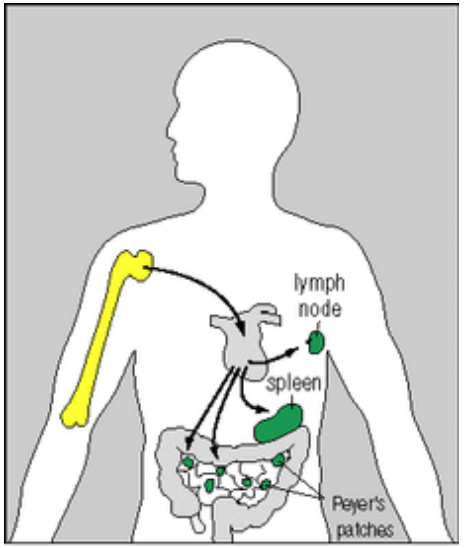
Colorized SEM (scanning electron micrograph)

Magnification: 1200x (Based on an image size of 1 inch in the narrow dimension)

Types of lymphocytes

There are two types of lymphocytes. Both form from bone marrow stem cells:





T cells mature in the thymus

B cells mature in the bone marrow

Both cell types enter the lymph nodes and spleen after they are mature. From there they can look for foreign invaders in the bloodstream.

T cells

- there are millions of different T cells – the difference is in their receptors (surface markers)

- each T cell has a unique receptor that will recognize a different foreign substance

- mature in the thymus, where they learn to tell the difference between self and “non-self”

  - critical, because if they did attack “self”, autoimmune disease could result

T cell training

- T cell precursors arrive in the thymus from the bone marrow

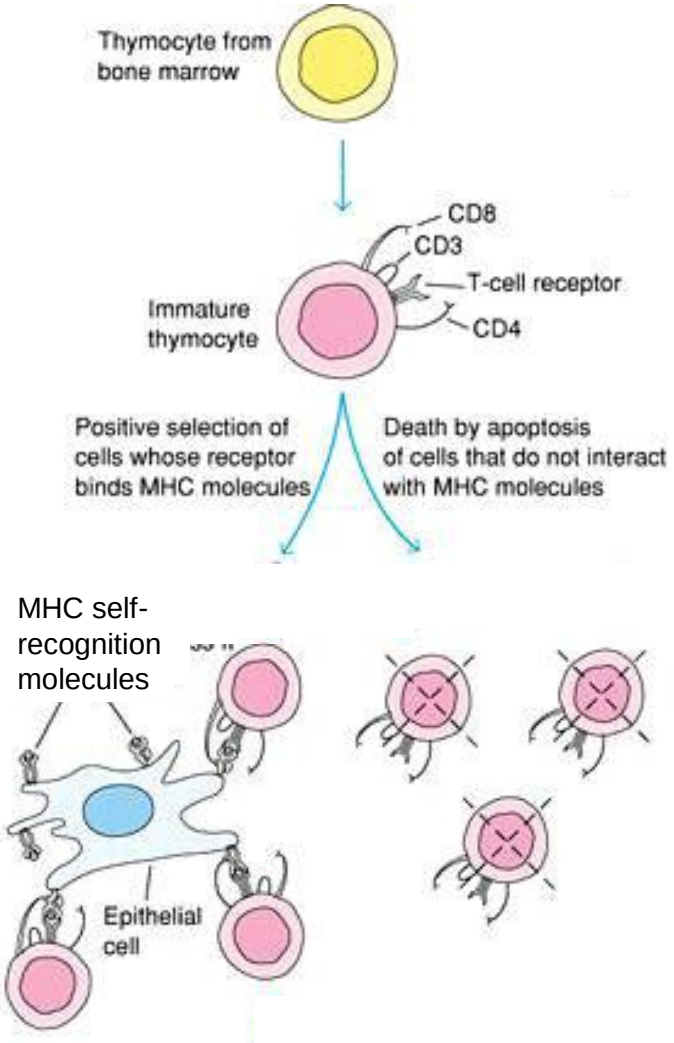
- there, they express specific T cell receptors and meet cells that “wear” bits of self proteins, called MHC (major histocompatibility complex), that are markers for the body’s own cells

- there are two steps
  - first, T cells must recognize self-MHC, or they are destroyed
  - in a second step, T cells that bind too tightly to self-MHC are also destroyed

- remaining T cells go to the spleen and lymph nodes, and wait for antigens. If they recognize an antigen, some will “go into battle” and others become memory cells

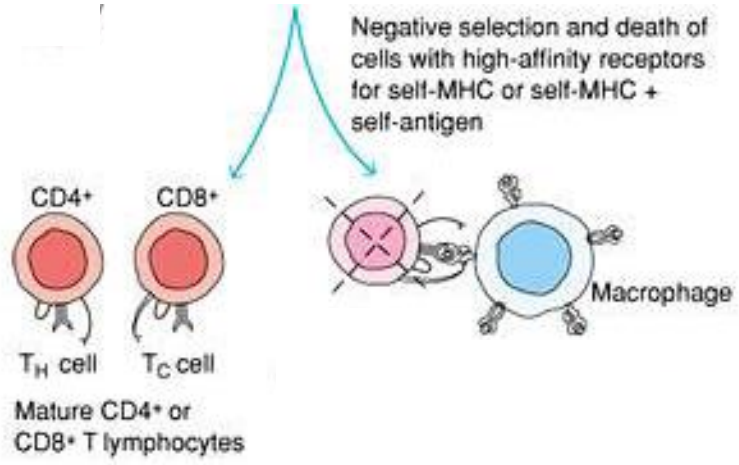
Steps in T cell development

Step 1. Positive selection
occurs in the thymic cortex



Steps in T cell development (cont'd)

Step 2. Negative selection occurs in the thymic medulla.

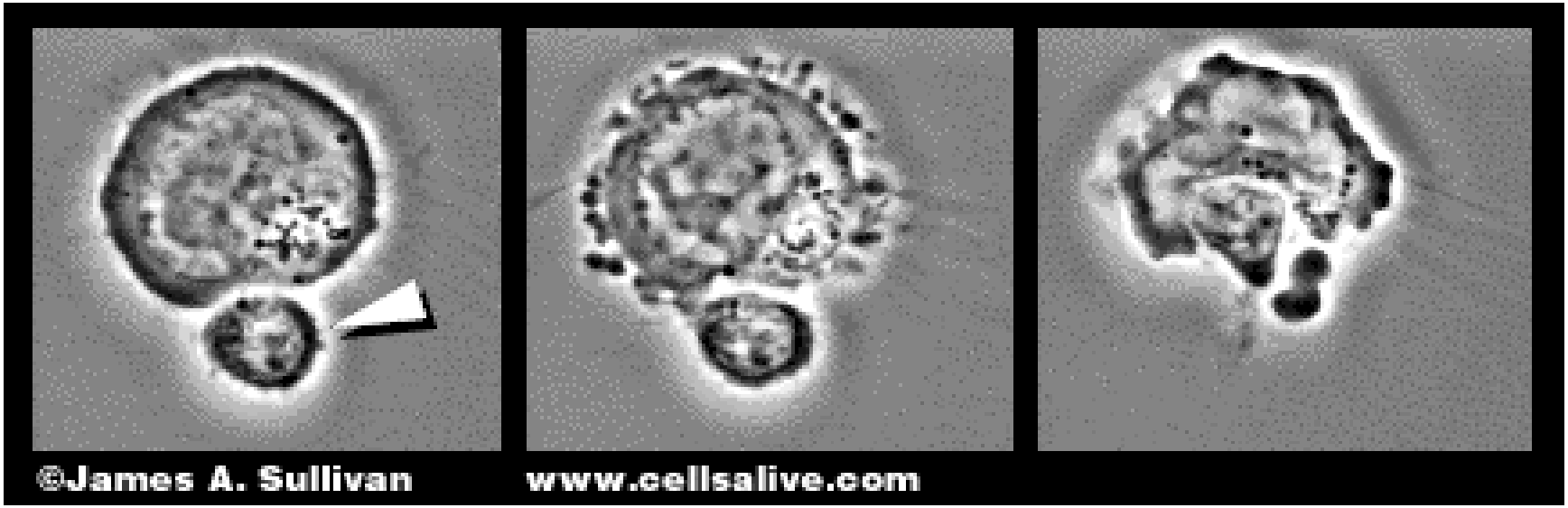


Types of T cells

Based on function, there are different types including:

- helper T cells – start the immune response
- cytotoxic T cells – kill the body's abnormal cells, like virus-infected cells and cancer cells
- suppressor T cells – suppress the activities of other T cells, helping to end the immune response

A Cytotoxic T Cell Attacking and Killing a Virus-Infected Target Cell



CELLS alive!

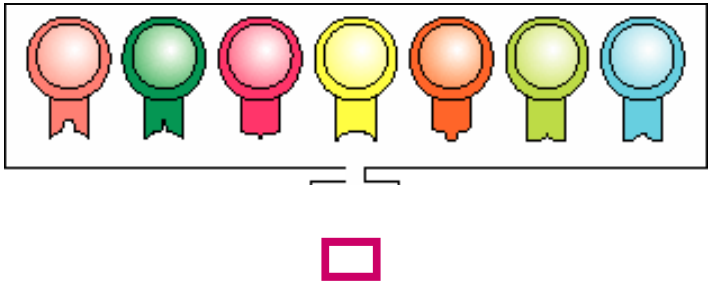
Here, the smaller cytotoxic T cell or T_c (arrow) is attacking and killing a much larger virus-infected cell. The T cell will survive while the infected cell is destroyed.

B cells

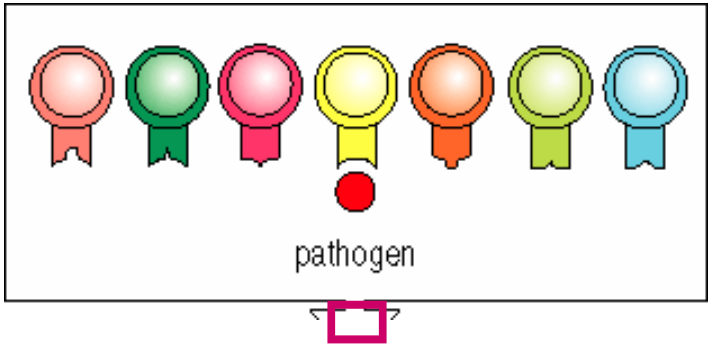
- produced and mature in bone marrow
- each B cell produces and wears a unique antibody on its surface
- clonal selection - when a B cell encounters a matching antigen, it begins to divide rapidly. Some then become plasma cells that all produce the same antibody, and then die. Others become memory cells.
- the specific antibody produced by a plasma cell is also secreted in soluble form and circulates in the blood

Selection of B cells by antigen (clonal selection)

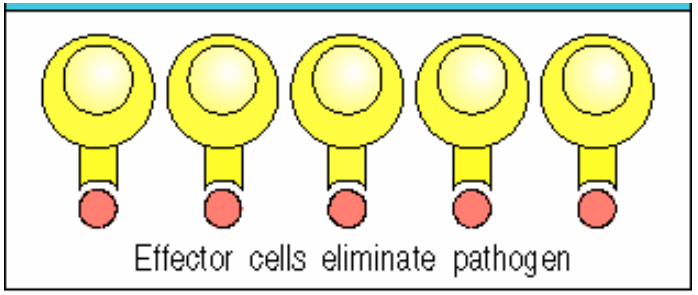
Different types of B cells have different receptor molecules.



When a pathogen (germ) “locks on” to a receptor, that type of B cell is selected.



The selected B cell divides rapidly to make lots of copies of itself. The copies make lots of antibodies against the pathogen.

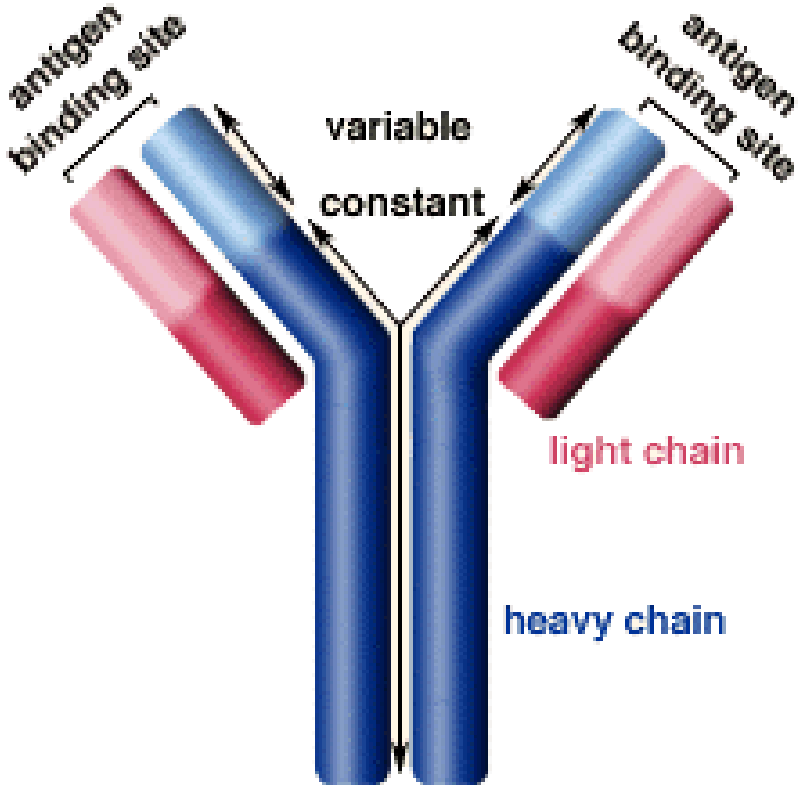


Antibodies

- specific – react with only one antigen
- Are Y-shaped proteins called immunoglobulins (Ig)
- each is made of two heavy and two light chains of amino acids, held together by disulfide bonds

Antibody structure

Each is made of two identical heavy and two identical light amino acid chains, held together by disulfide bonds

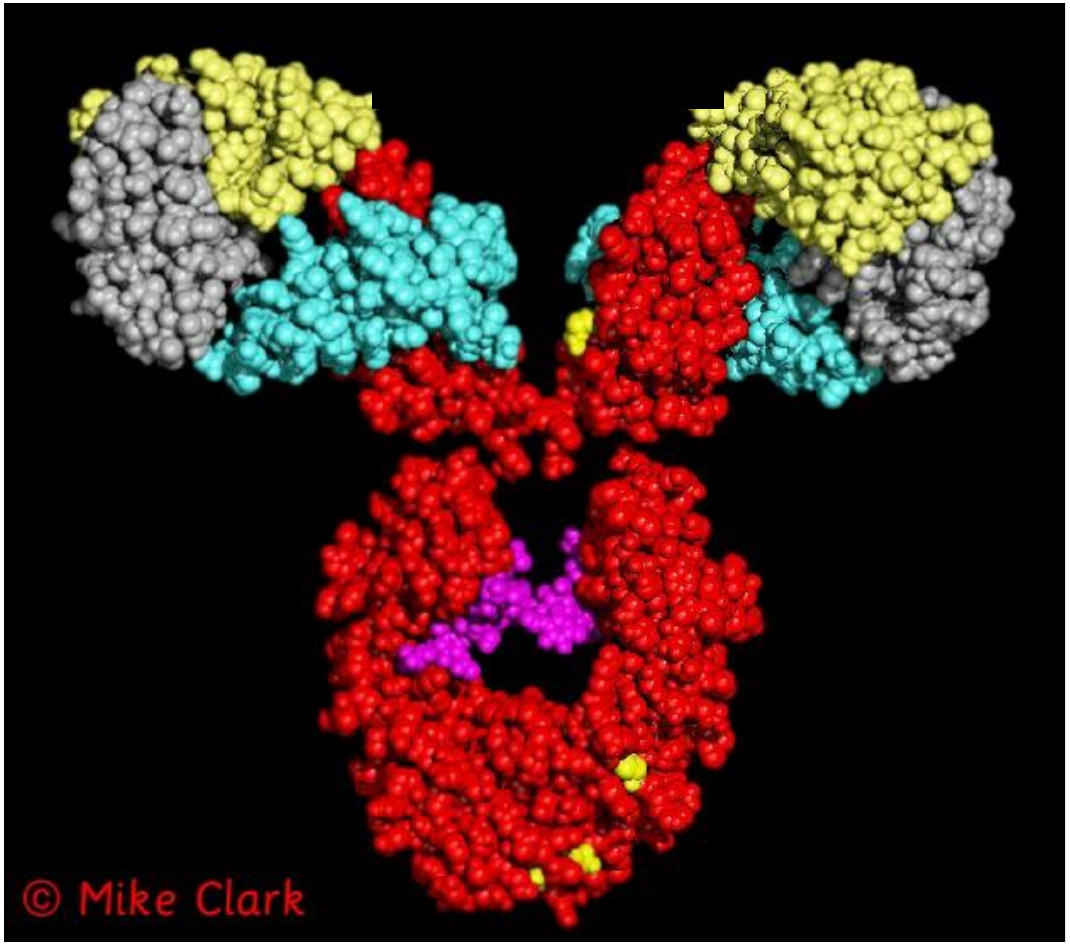


- parts of the antibody (Ab) are constant, i.e., the same for every antibody

- parts are variable - the arms of the "Y" have different amino acid sequences that cause specific binding to antigen

- the fact that there are many different variable regions results in antibodies that react with almost any antigen you could possibly encounter!

Antibody – another view



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- variable regions of the light chain (grey) and the heavy chain (yellow) form the antigen binding site

- light chain constant region is blue while heavy chain constant region is red. The two chains are joined by carbohydrate (purple).

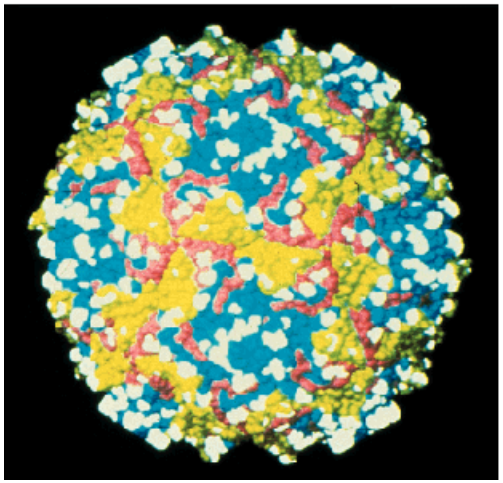
Four classes of secreted antibodies

- IgM – a pentamer – five Y-shaped immunoglobulins joined together – the “early” Ab, it is produced before any of the other types – it activates complement
- IgG – the most common form, and the major one for secondary responses
- IgA – mostly a dimer – two Y-shaped immunoglobulins secreted in saliva, colostrum, milk, semen, mucus
- IgE – binds to receptors found on mast cells – involved in allergy and parasitic infections

Antigens

Antigen (Ag) – the molecule an antibody (Ab) binds to

- usually a foreign substance
- each antigen has different sites that antibodies can bind to, so that one antigen can be bound by several different antibodies



- examples in the case of allergy could be pollen, cat dander, or a chemical in soap

How Antibody Binds to Antigen

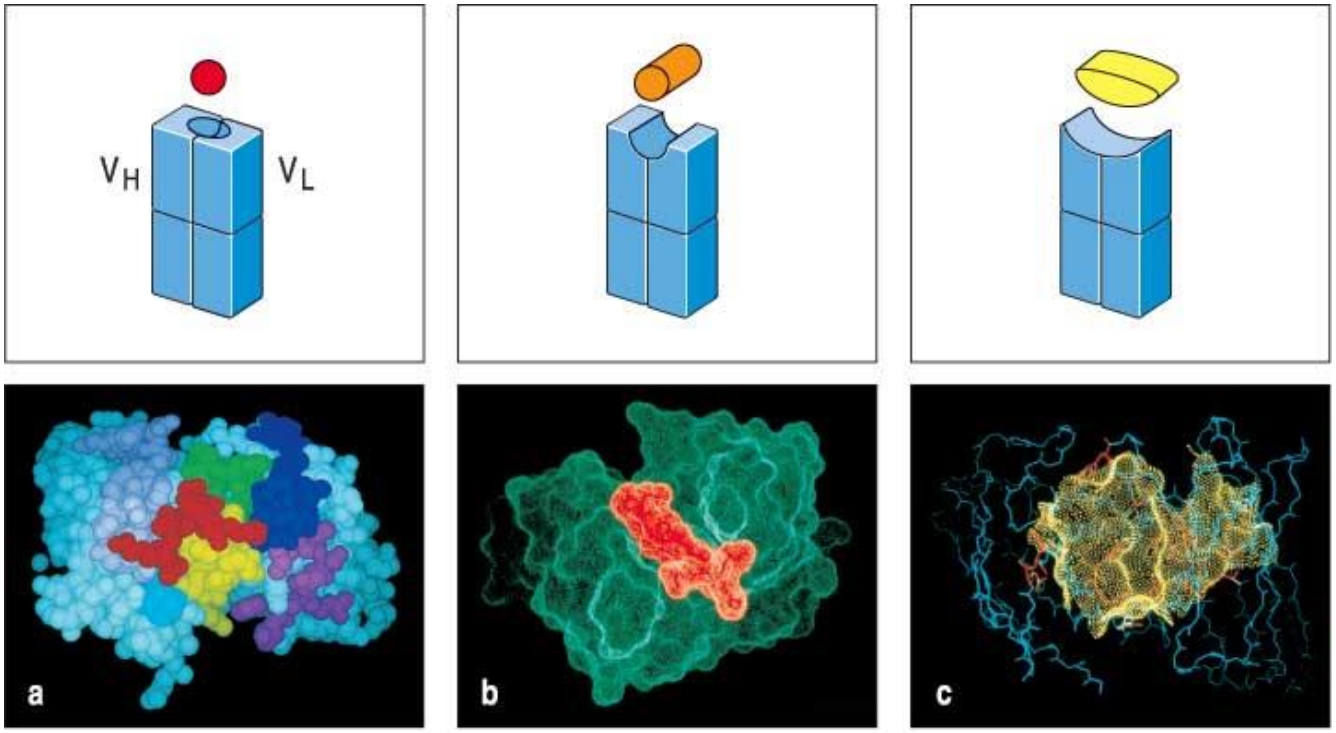


Fig 3.8 © 2001 Garland Science

The top part of this figure shows how different shaped antigens can fit into the binding site of antibodies: left, pocket; center, groove; right, extended surface. The panels below show space-filling or computer-generated models indicating where contact between the peptide antigen and antibody occurs.

How an Antibody Works

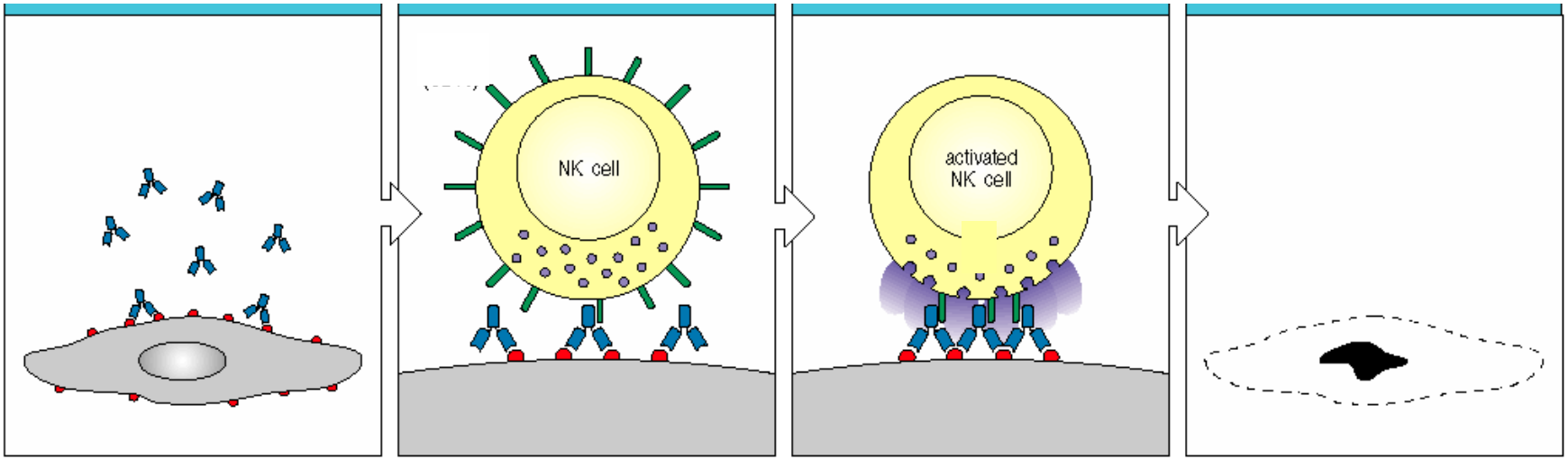
When an Ab finds its Ag on an invader, it will bind there and act as a “trash tag”, marking it for destruction by “killer” cells, macrophages or complement

Antibody binds to target antigen

Receptor for constant region of antibody on NK cell recognizes a bound antibody

After binding, the NK cell is signaled to kill the target cell

The target cell dies by apoptosis and/or membrane damage



The Number Dilemma

- You have about a trillion different antibodies able to react with millions of different types of Ag

- but you only have about 30,000-60,000 genes which code for all the proteins you need in your entire body, most of which are not Ab

- so there cannot be one gene for one antibody to code for these – we wouldn't have enough antibodies!

So how can your body produce Ab to so many antigens, even those it's never seen?

Antibody Variability

There are several reasons why there are an enormous number of different antibodies:

- different combinations of heavy and light chains which are encoded by different genes
- recombination
- others

Antibody Genes

Genes for antibodies aren't like most other genes - they come in pieces ("gene-lets"):

- variable segments (V) – many different versions
- diversity segments (D) – several different versions
- joining segments (J) – a few different versions
- constant segments (C) – a few different versions that are nearly identical

A unique recombination occurs in each B cell

- each B cell combines these gene segments to make an Ab chain like shuffling a deck of cards
  - V, D, and J for the heavy chain, V and J for the light chain
- since there are multiple types of each gene segment, there are many thousands of possible V-D-J combinations so that each B cell gets a unique combination of segments!

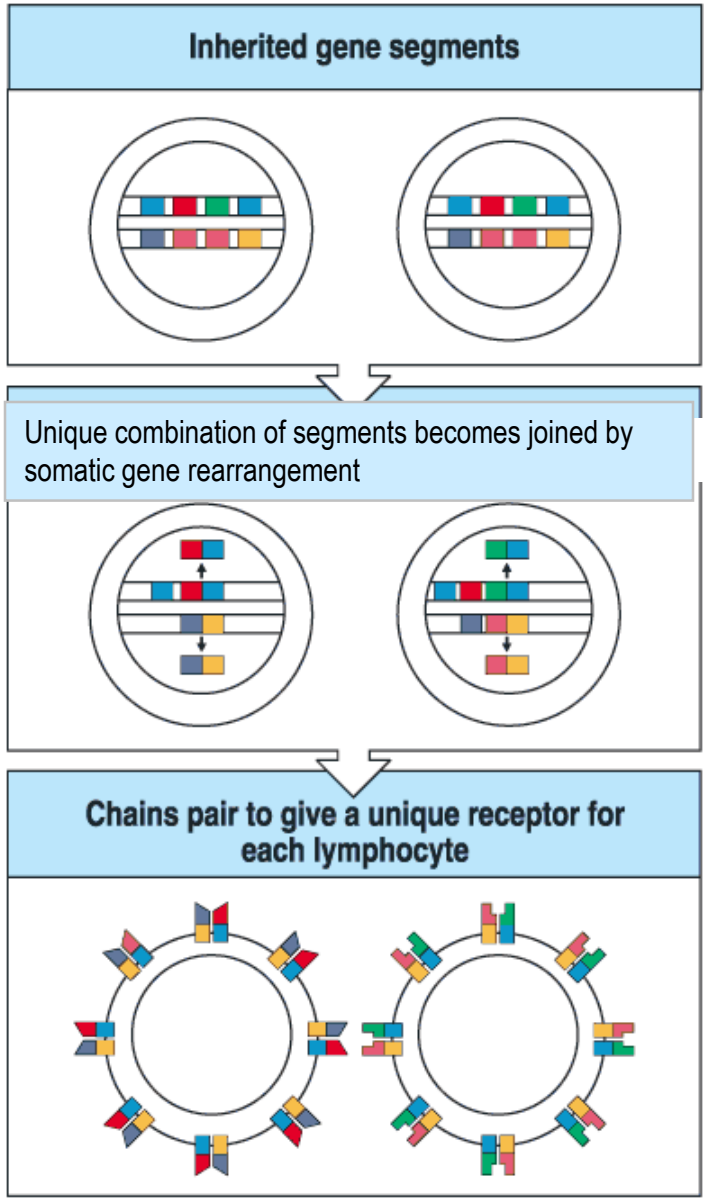
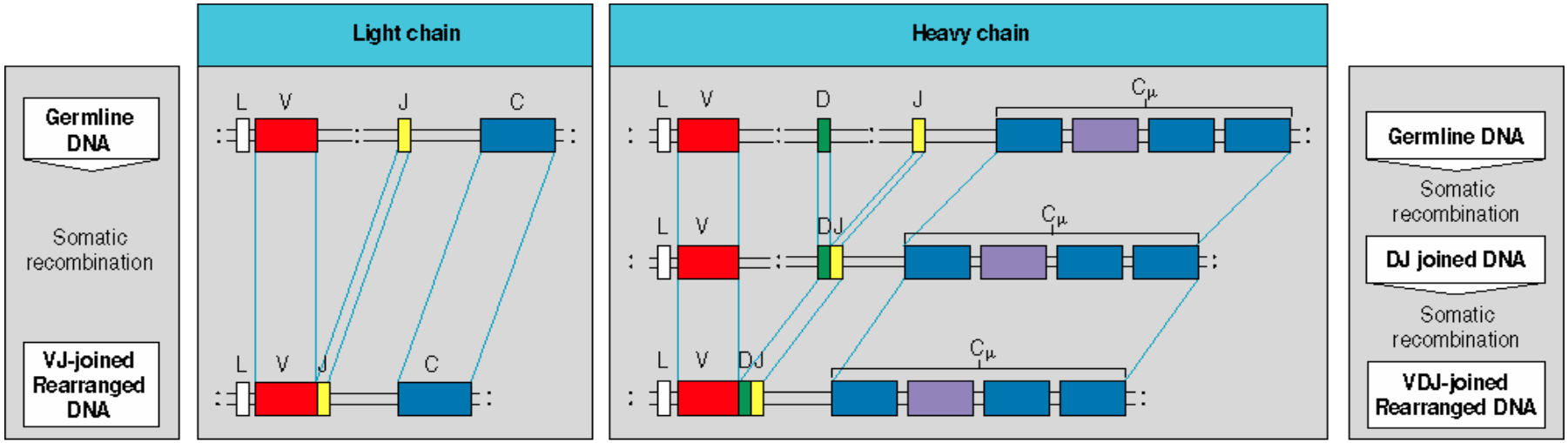


Fig 1.18 © 2001 Garland Science

A unique recombination occurs in each B cell



- each B cell combines these gene segments to make an Ab chain like shuffling a deck of cards

  - V, D, and J are joined to C for the heavy chain, V and J are joined to C for the light chain

Since there are multiple types of each gene segment, there are many thousands of possible V-D-J combinations so that each B cell gets a unique combination of segments! Additional diversity occurs because there are two types of light chains.

Number of functional gene segments in human immunoglobulin loci

Segment	Light chains		Heavy chain
	κ	λ	H
Variable (V)	40	30	65
Diversity (D)	0	0	27
Joining (J)	5	4	6

Fig 4.3 © 2001 Garland Science

Other sources of variability

- when V, D, and J pieces are joined, they may not always be joined perfectly – if some base-pairs are lost or added, the Ab will end up with a different amino acid sequence

- variable region genes mutate at a higher rate than other genes in your body

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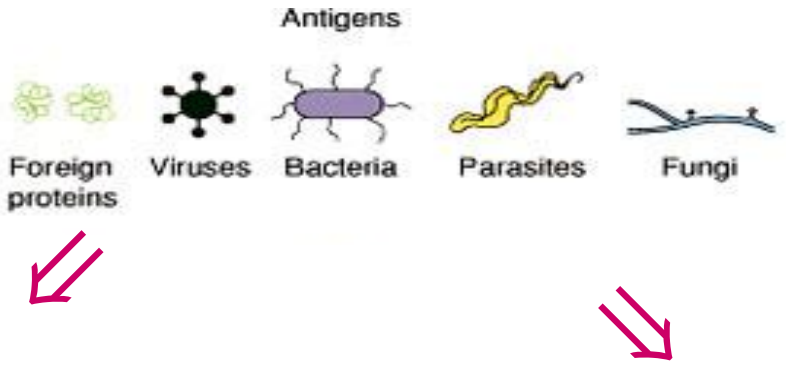

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- the first line of defense

1. Barriers - skin, tears
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Adaptive Immunity
- variable (custom)
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- "remembers" infection

1. APCs present Ag to T cells
2. Activated T cells provide help to B cells and kill abnormal and infected cells
3. B cells - produce antibody specific for antigen