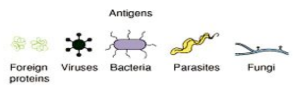
1

YOUR ACTIVE IMMUNE DEFENSES



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

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

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

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ADAPTIVE IMMUNE RESPONSE

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

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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

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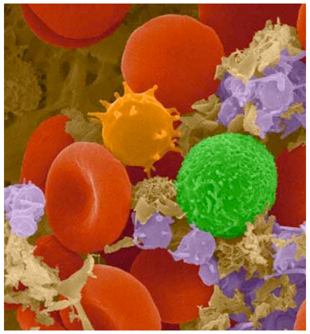
White Blood Cells (WBCs)

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
    - -macrophage (MØ)
    - -dendritic cells (DC)
    - -B cells
- B and T lymphocytes (B or T cells)
  - pathogen-specific
  - different types recognize different invaders and lead to their destruction

Human red and white blood cells



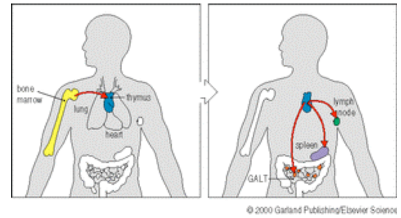
Human red blood cells (red), activated platelets (purple) and white blood cells - monocyte (green) and T lymphocyte (orange).

Colorized SEM (scanning electron micrograph)

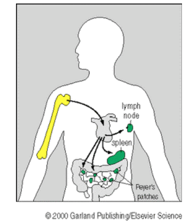
Magnification: 1200x (Based on an image size of 1 inch in the narrow dimension)

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

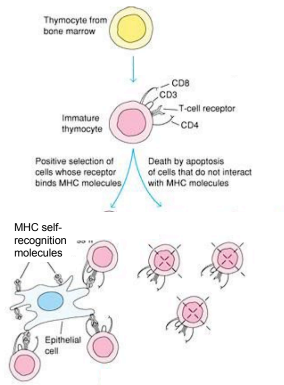
- there are millions of different T cells – the difference is in their receptors (surface markers)
- each T cell has a unique receptor that will recognize a different foreign substance
- mature in the thymus, where they learn to tell the difference between self and "non-self"
  - critical, because if 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

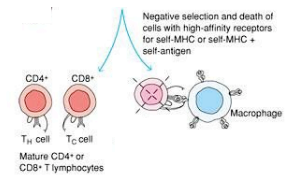
Steps in T cell development

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.

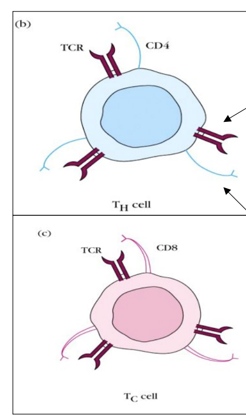


Types of T cells

Based on function, there are different types including:

- helper T cells (CD4+ or Th) – start the immune response
- cytotoxic T cells (CD8+ CTL or Tc) – kill the body's abnormal cells, like virus-infected cells and cancer cells

T Lymphocytes



- Formed in bone marrow; migrate to and mature in Thymus gland
- Exhibit unique T-cell Antigen receptors (**TCR**'s) on surface
- **TCR**'s can only recognize Ag with associated with MHC glycoproteins
  - **MHC I** – found on nearly all nucleated cells
  - **MHC II** – found only on APC's

Once T cell binds to Ag, it triggers cell division to form both memory T cells and effector T cells

There are 2 populations of T cells characterized by the type of **CD glycoprotein** found on surface:

T_H – exhibits **CD4**

T_C – exhibits **CD8**

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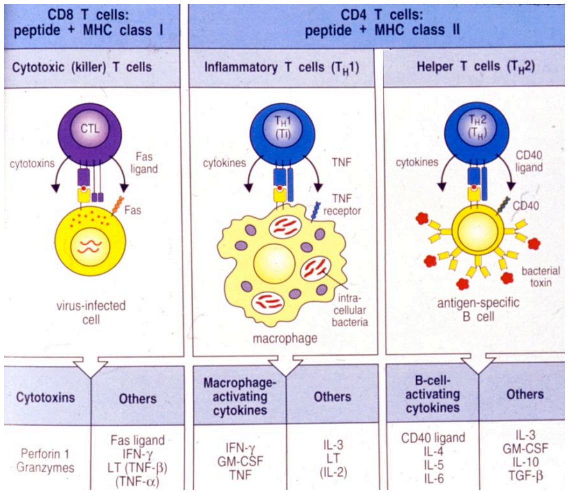

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The Antigen presentation scenario:

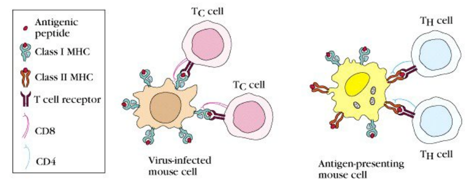

Fig 1-8 Kuby, 4e

Different patterns of cytokines determines types of Immune Response:

-if T_C cell recognizes an Ag/MHC I complex, it divides and differentiates to become CTL

if T_H cell recognizes Ag/MHC II complex, it divides and stimulates B cells, T_C cells, and MØ

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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

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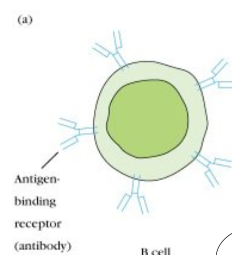
B Lymphocytes:



- Form and mature in bone marrow
- Exhibit antibody receptors on membrane
- Once naïve B cells bind Ag, they divide rapidly to produce:
  - Plasma cells (effector B cells)
  - Memory cells

Humoral Immunity →

Plasma cells are secretory; live only a few days (produce > 2,000 molecules of Ig/sec)

Memory cells have longer life span than naïve B cells

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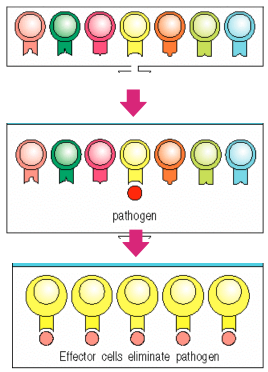
Selection of B cells by antigen (clonal selection)

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.



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B cells make 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
- Must be associated with Ig β (B29) and Ig α (mb-1) to form the functional B Cell Receptor molecule (BCR)

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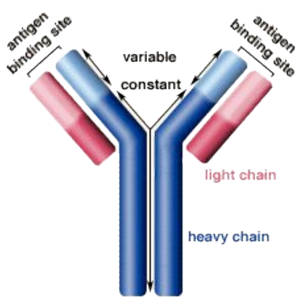
Antibody structure

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!

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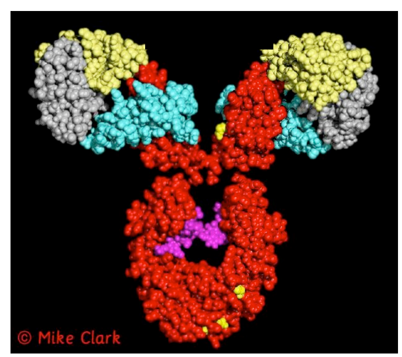
Antibody – another view



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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).

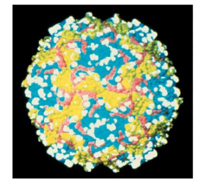
Four classes of secreted antibodies

- 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

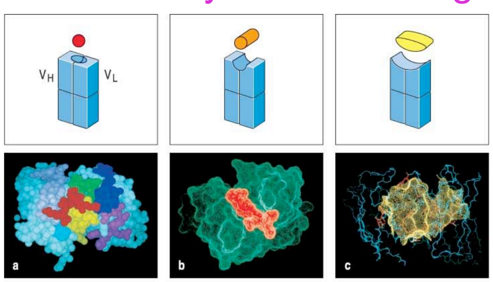


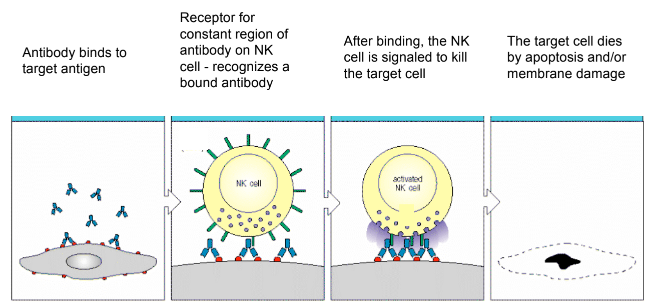
Fig 3.8 © 2001 Garland Science

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



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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?

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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

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Antibody Genes

Genes for antibodies aren't like most other genes
- they come in pieces that are assembled by cutting and pasting the DNA (this only happens in Ab and TCR genes)

- 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

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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!

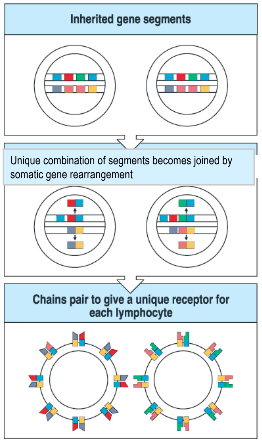
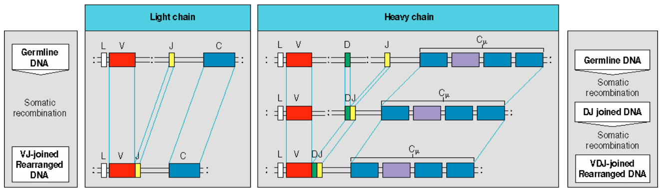


Fig 1.18 © 2001 Garland Science

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

Humoral vs Cell-mediated Immune Response:

Humoral: occurs when Ag becomes coated with Ab which brings about the elimination of the foreign body (B cell mediated)

-cross-link several Ag's to form clumps -> more easily phago'd
-bind complement proteins
-neutralize toxins, viruses, and bacteria from binding target cells

Cell-Mediated: occurs when effector T cells are activated (T cell mediated)

-activated T_H cells → activate phagocytic cells
activate B cells to produce Ab

-activated T_C cells → kill altered self cells (viral infected and tumor cells)

YOUR ACTIVE IMMUNE DEFENSES

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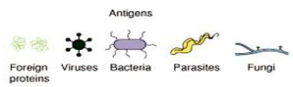

Innate Immunity
- invariant (generalized)
- early, limited specificity
- the first line of defense

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

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