Immunology 101 For The Practicing Oncologist

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The Origin of Immunology is Often Attributed to Edward Jenner

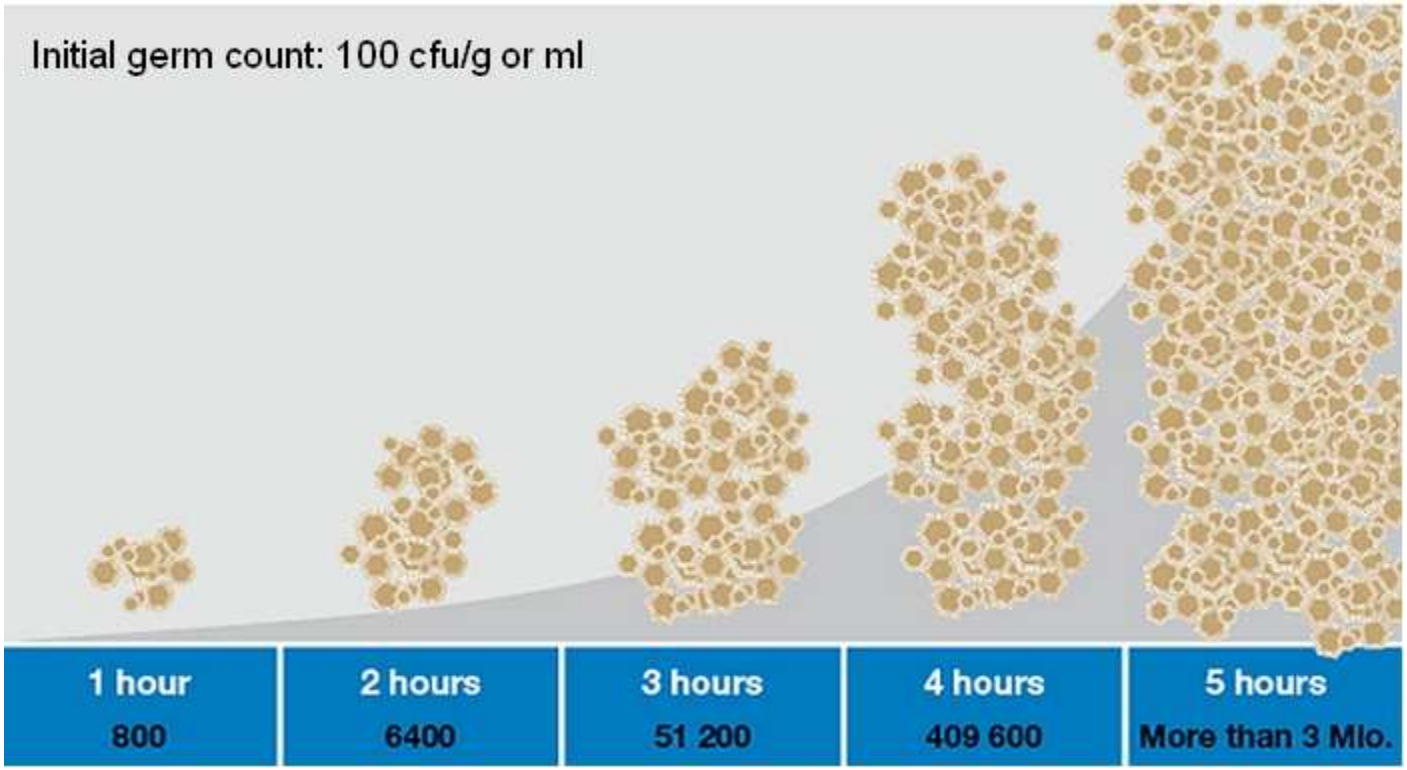
Smallpox: A Devastating Disease That Deformed and Killed For Centuries

Once afflicted with Cow Pox, Milk Maids never seemed to contract the more serious disease, smallpox.

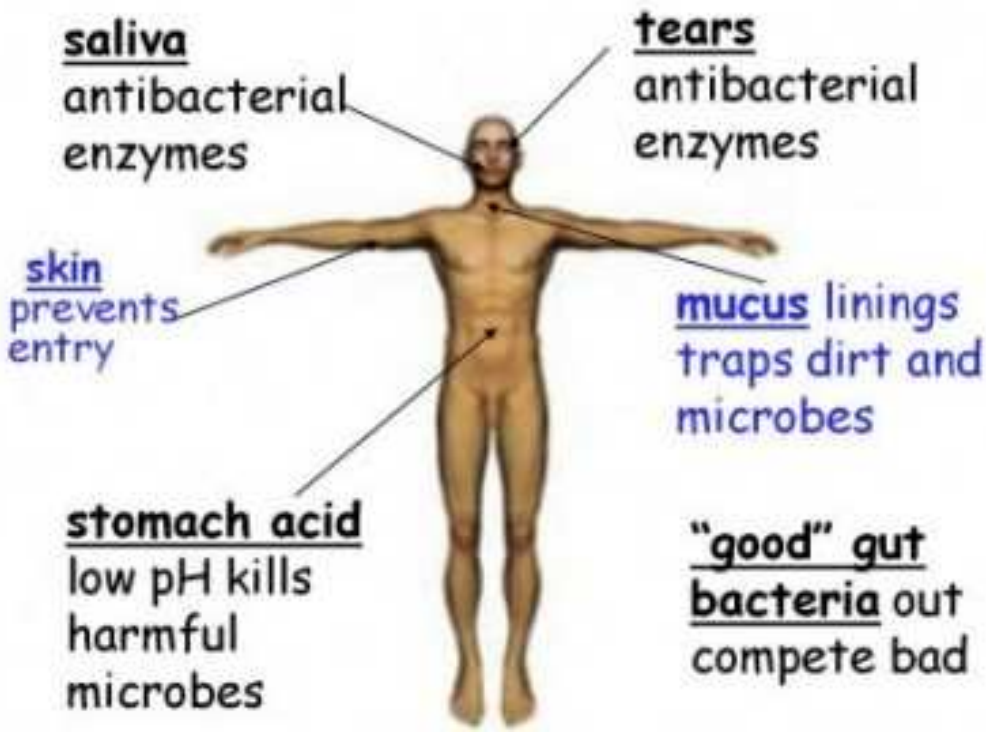
The Advantage Microbes Have In Causing Human Disease:

Microbes Can Reproduce And Evolve Very Rapidly,

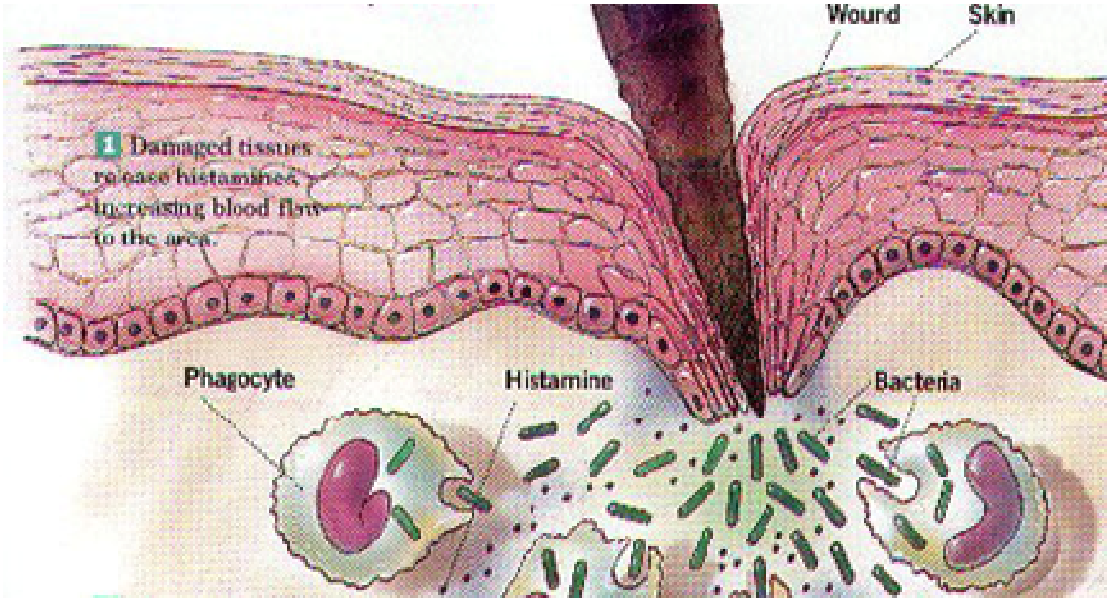
And Quickly Pit Enormous Numbers Against Their Host



First Lines of Defence

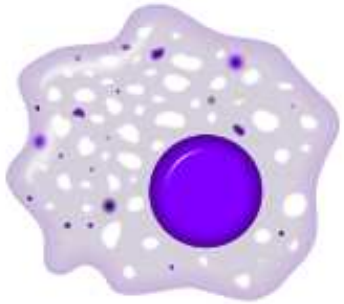


Invaders That Breach The Skin or Mucosa Are Greeted By Sentinel Cells Of The Innate Immune System

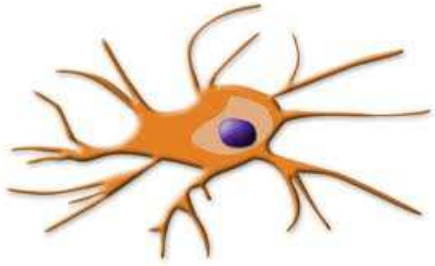


Very rapid responses

All multi-cellular organisms have it

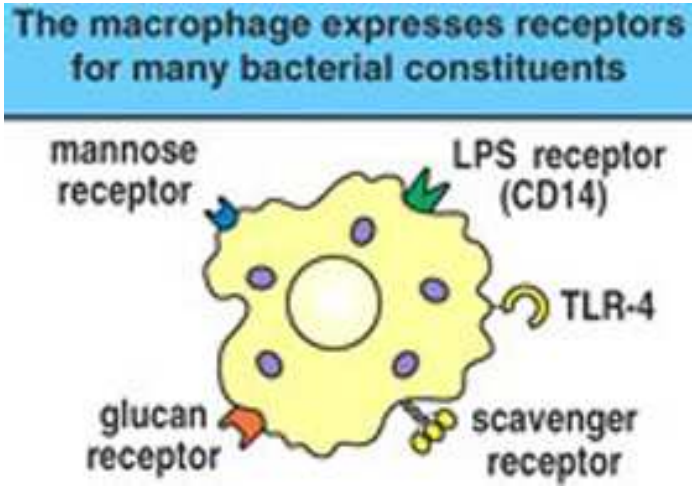


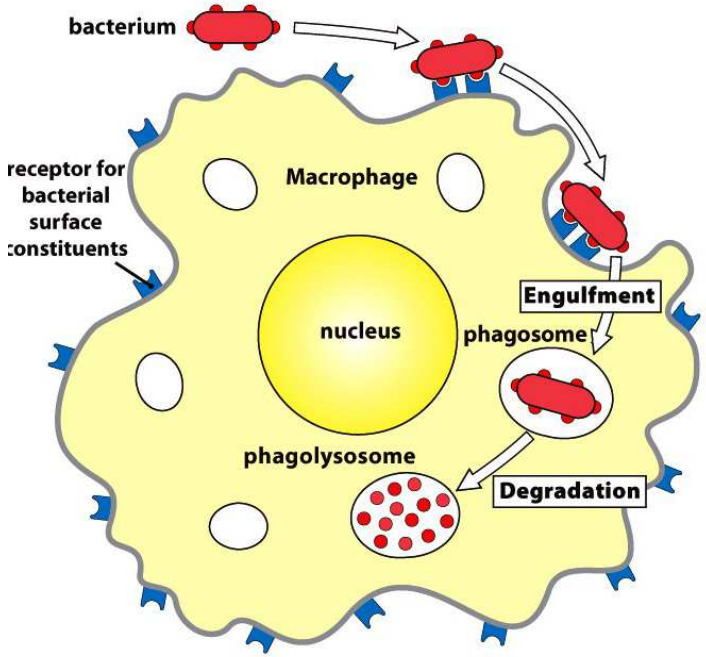
Macrophage



Dendritic Cell

Macrophages And DCs Internalize Pathogens Using Receptors That Recognize Molecules Commonly Expressed By Microbes





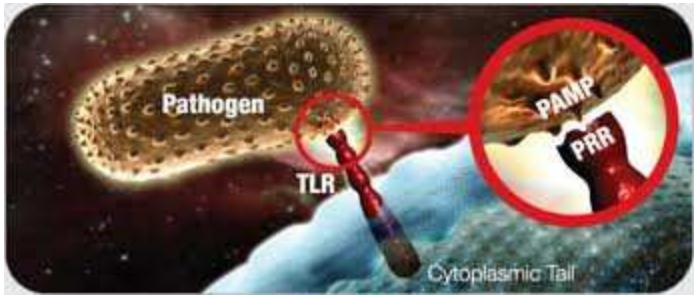
LPS- Gram Negative Organisms

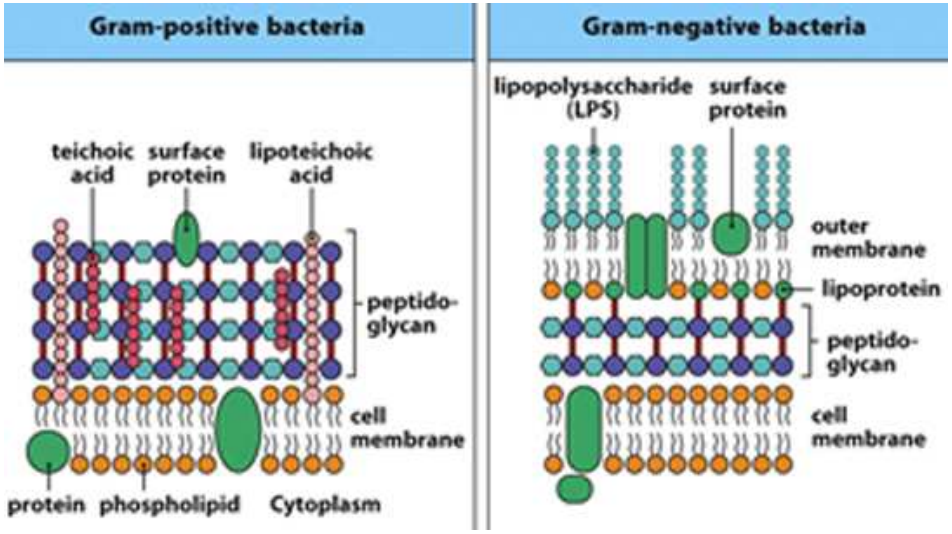
Unique conformations of mannose-viruses & bacteria

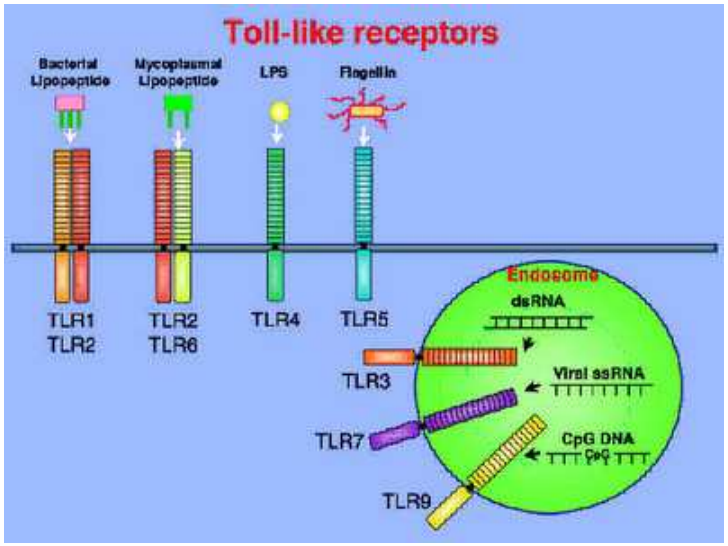
The Glucans of fungi

Cells of The Innate Immune Response Also Evolved To Express Signaling Molecules That Recognize And Are Activated by "PAMPS"

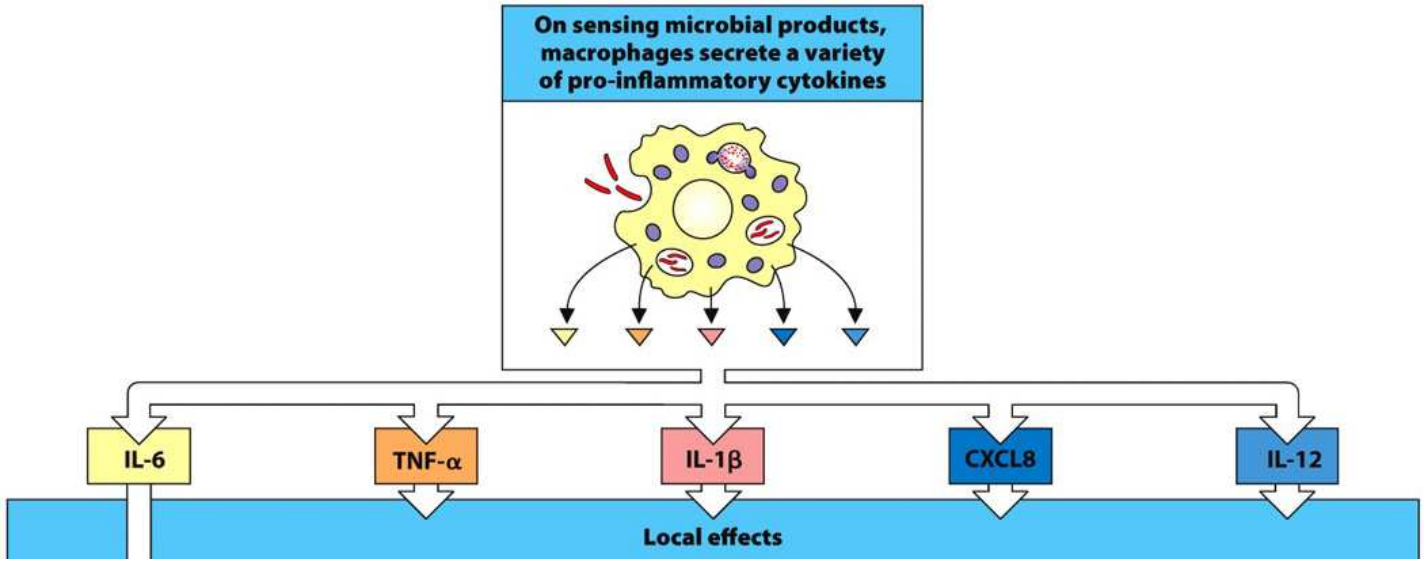
Pathogen Associated Molecular Patterns



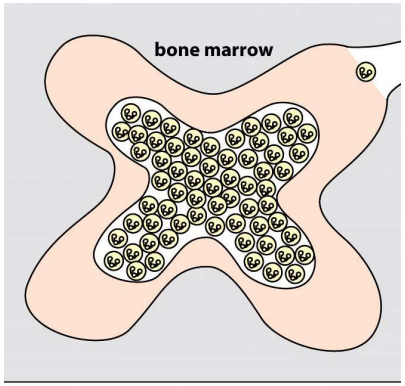




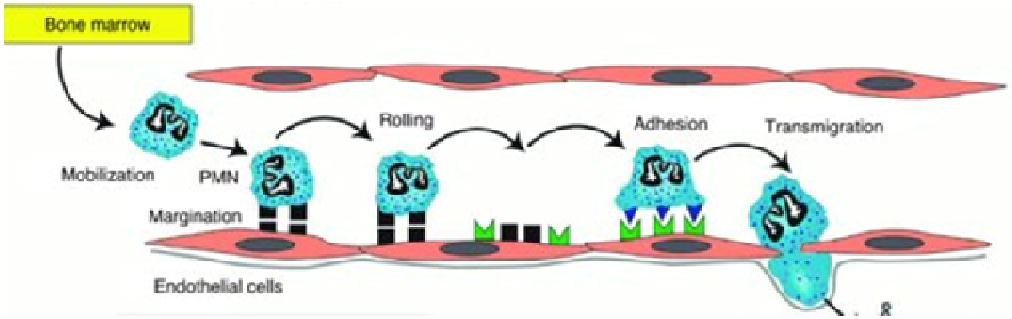
PAMP-Stimulated Cells Synthesize Cytokines That Induce Neutrophil Production and Chemokines That Elicit Them to Sites of Infection



Hematopoietic growth factors, chemokines, acute phase proteins, vascular dilation, permeability, coagulation

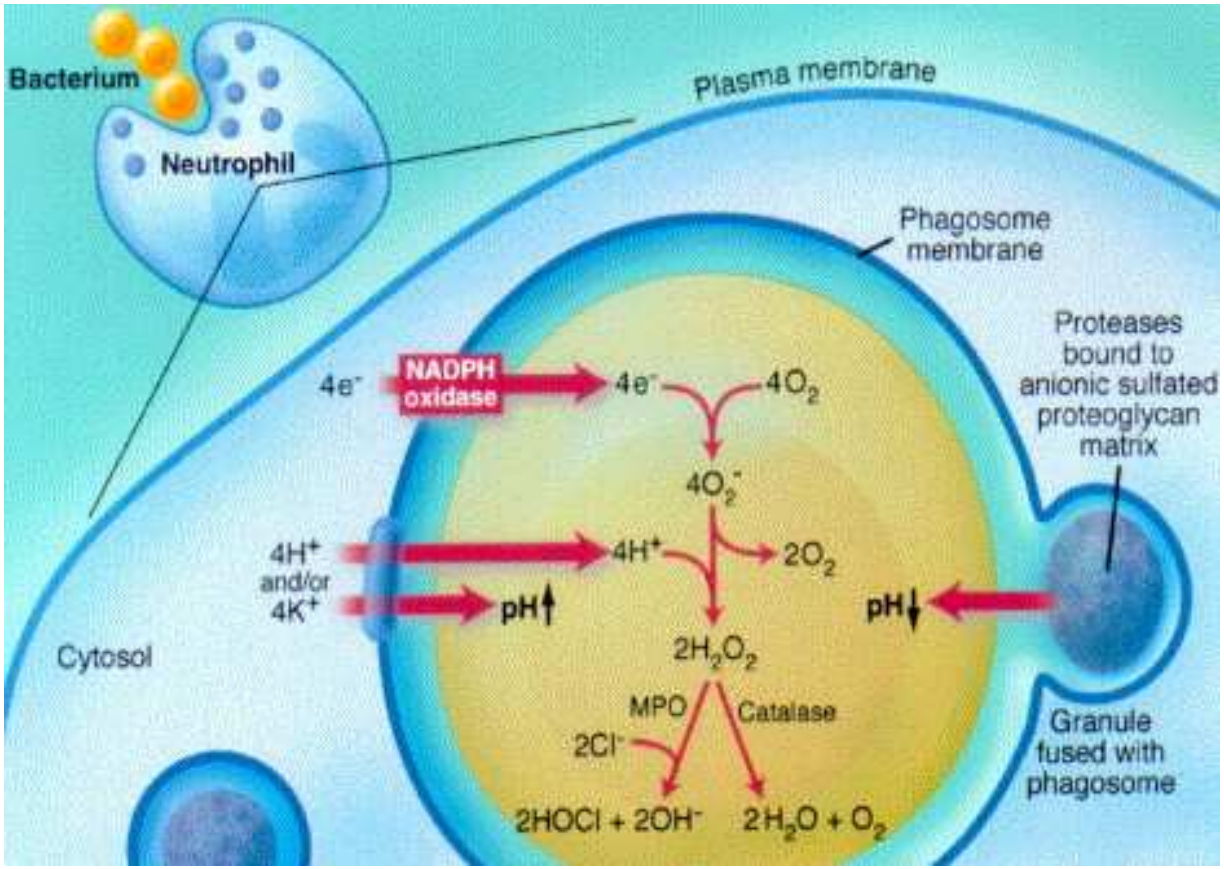


igure 1.16 The Immune System, 3ed. (© Garland Science 2009)



Elicited inflammatory cells kill pathogens at the site of infection multiple ways

PAMP-Stimulated Phagocytes Undergo An Oxidative Burst, Which Generates Toxic Reactive Oxygen Species



Superoxide

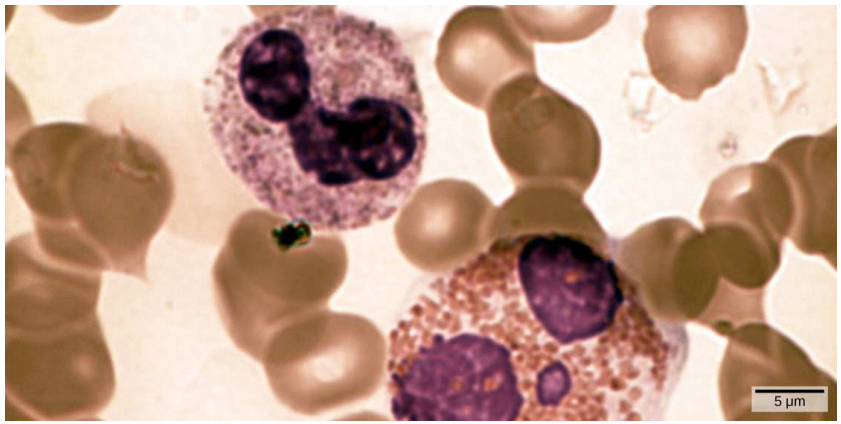
Hydrogen peroxide

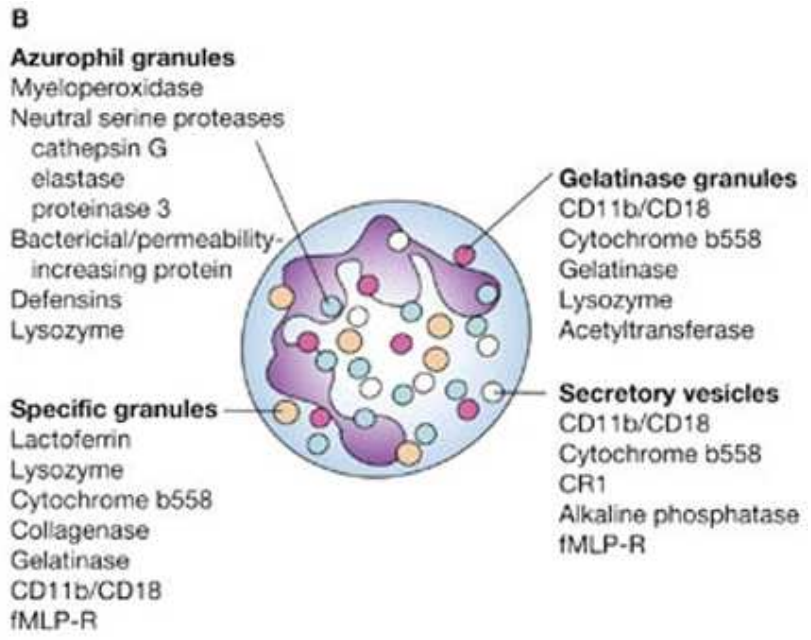
Hypochlorite ion

All kill cells by damaging macromolecules and cell structure.

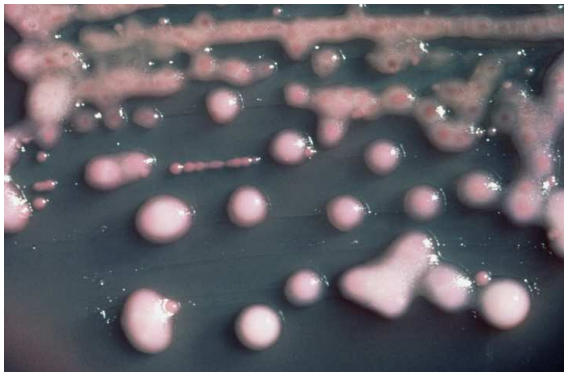
Elicited Neutrophils Also Kill Microbes By Non-Oxidative Mechanisms

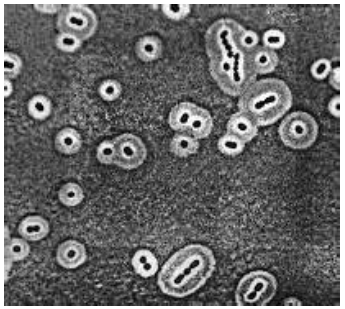
Neutrophils contain multiple types of granules, each with their own set of microbicidal enzymes and molecules

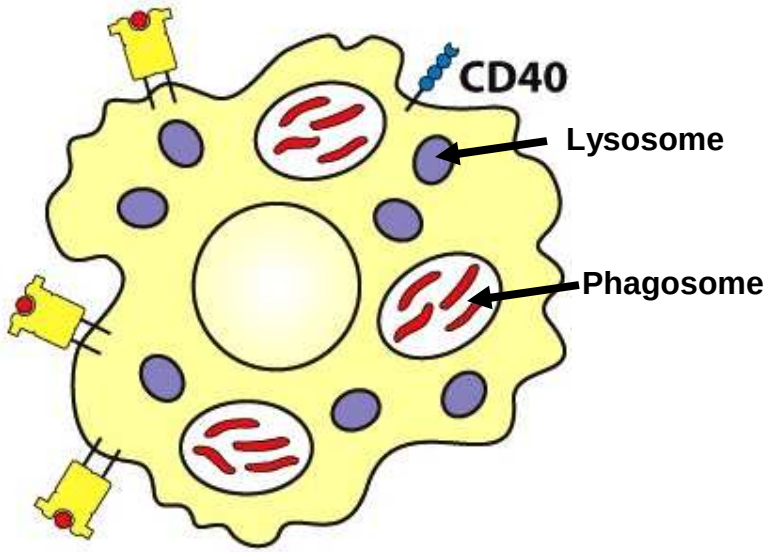




Sometimes An Innate Response Just Isn't Enough: Microbial Numbers Are Too Great, Or The Bugs Have Learned New Tricks





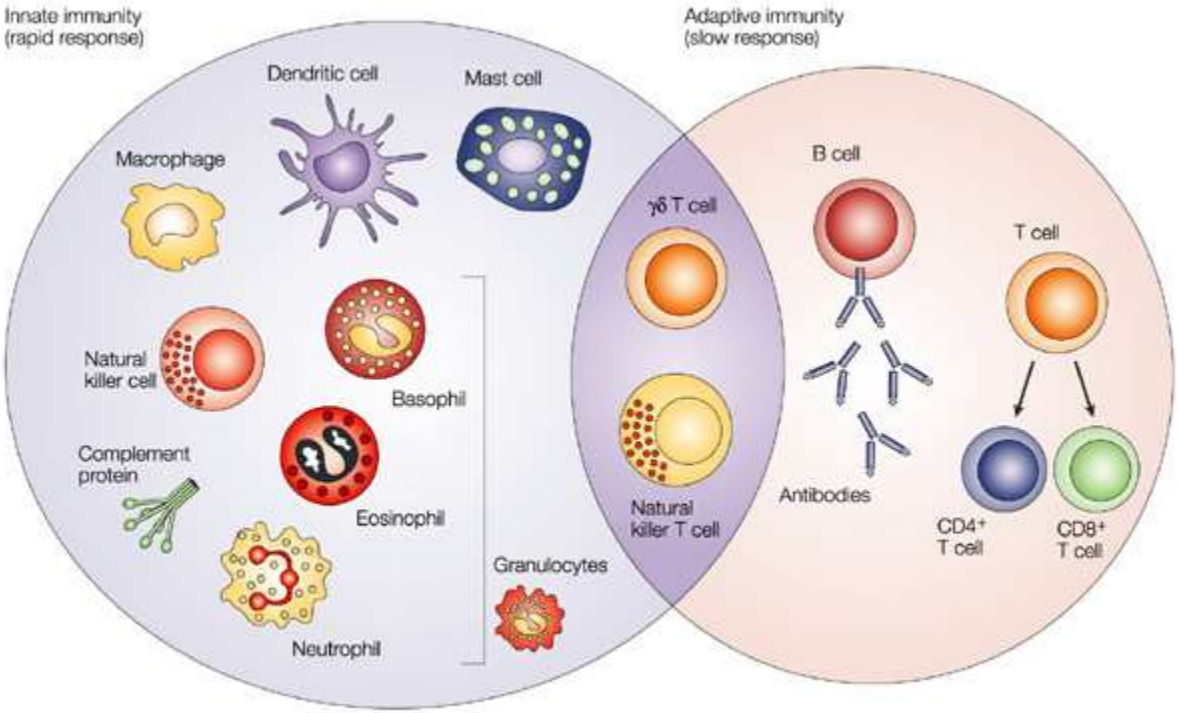


Some bacteria build a carbohydrate capsule that surrounds and masks the cell wall

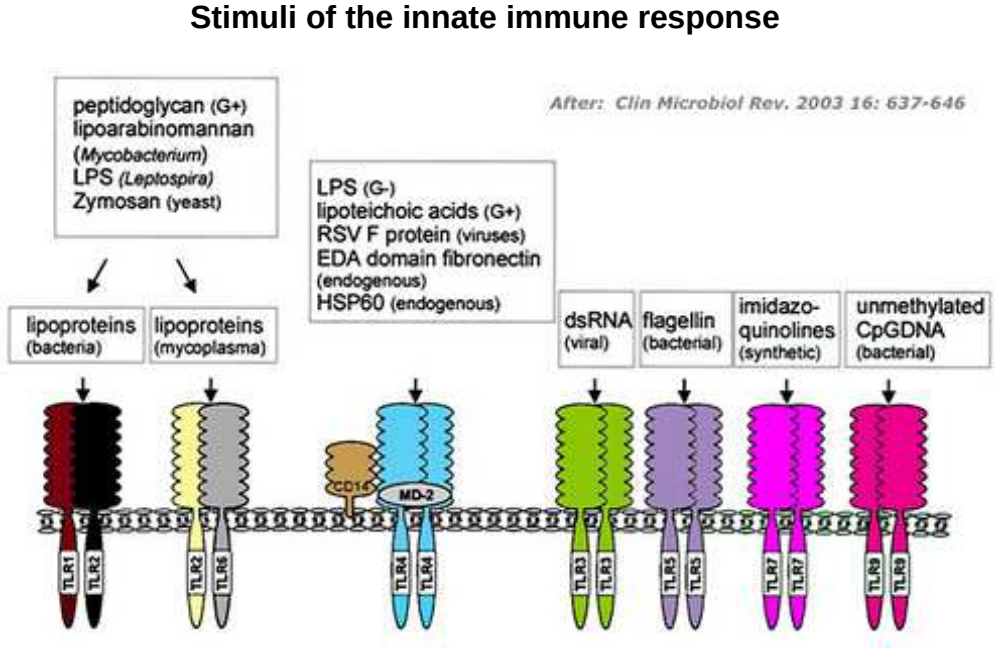
Some Intracellular organisms prevent the fusion of phagosomes and lysosomes

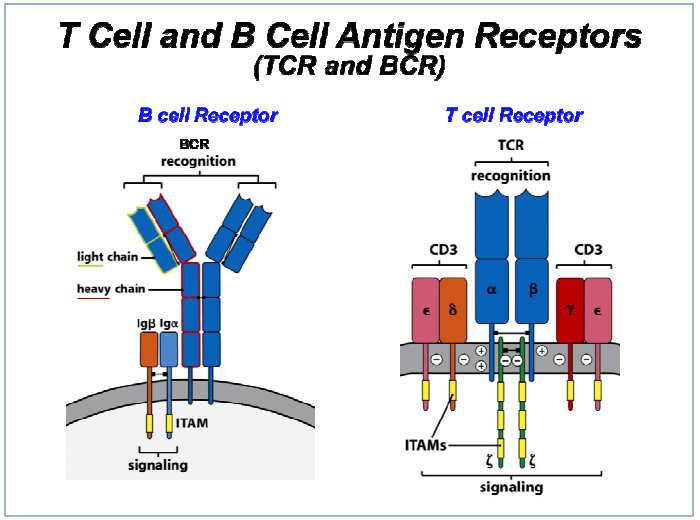
Vertebrates Have A Third Level Of Defense That Can Adapt To Protect A Host Against Almost Any Invader

The Adaptive Immune Response



Unlike the Innate Response, The Adaptive Response Is Directed Against Epitopes Unique To The Infectious Agent



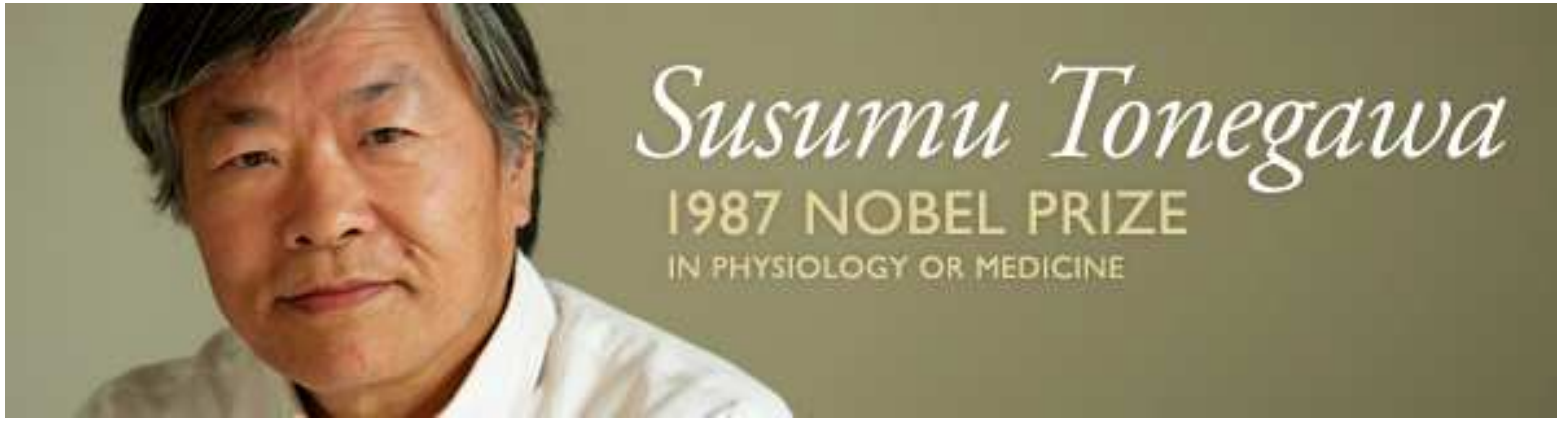


Adaptive response requires very specific receptors on B and T cells capable of recognizing diverse and unique microbial antigens

To Protect Ourselves From Essentially Every Possible Invader, We Must Generate Over 100 Million Different Antibodies---

Far More Than We Have Individual Genes For

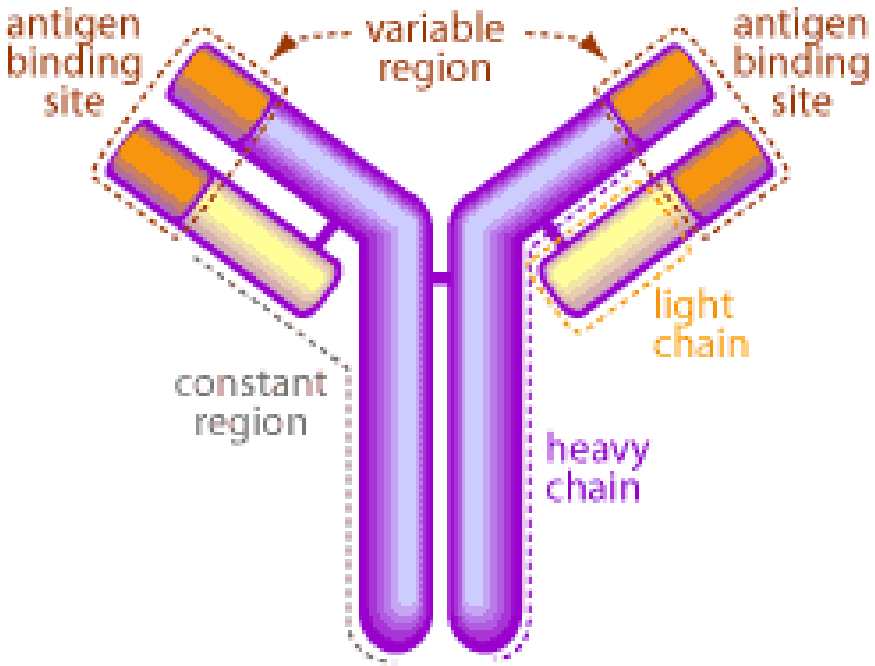
Susumu Tonegawa Determine How We Do It



Antibodies Are Composed of Two Identical Heavy Chains

And Two Identical Light Chains,

Each with Constant Regions and Variable Regions



To Generate The Needed Diversity, Each Variable Region Is Assembled From Families of Gene Segments Arranged In Clusters Along The Chromosome

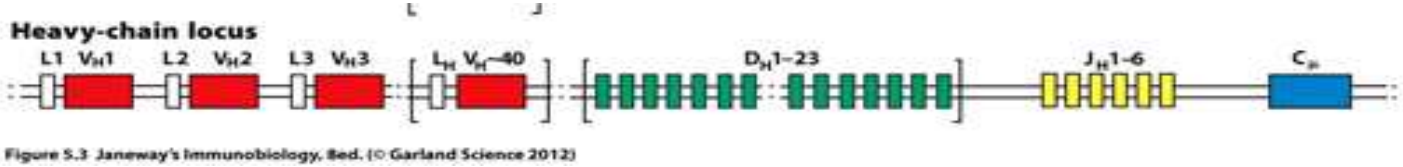
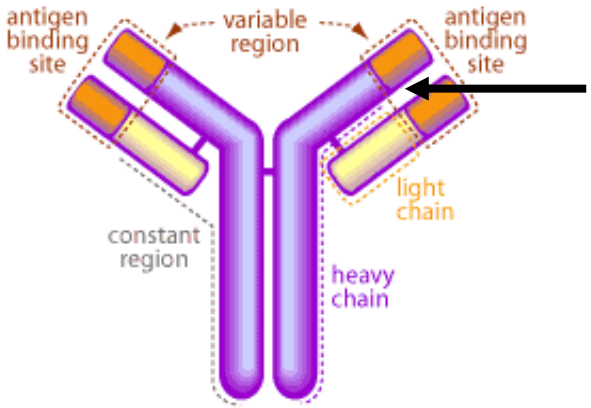
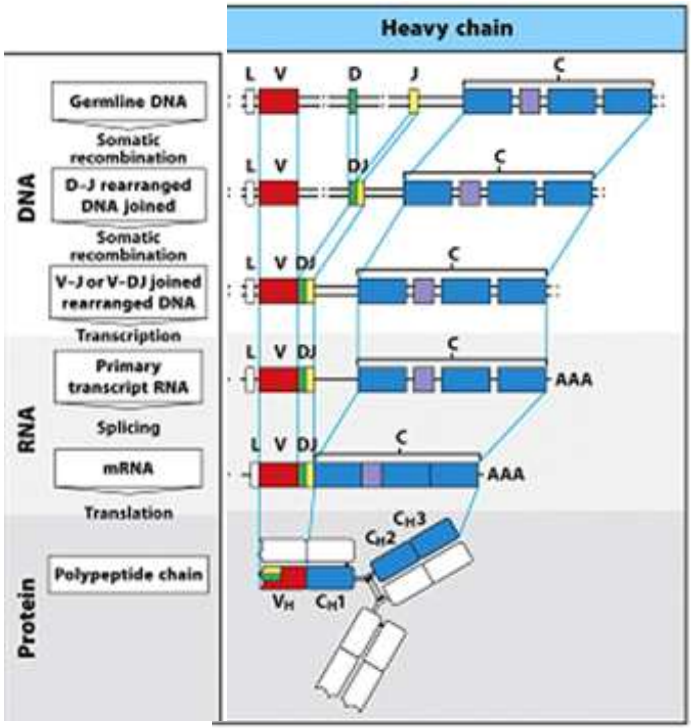


Figure 5.3 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

There are 40 V segments, 23 D segments and 6 J segments, and the variable region is a mix and match from these segments

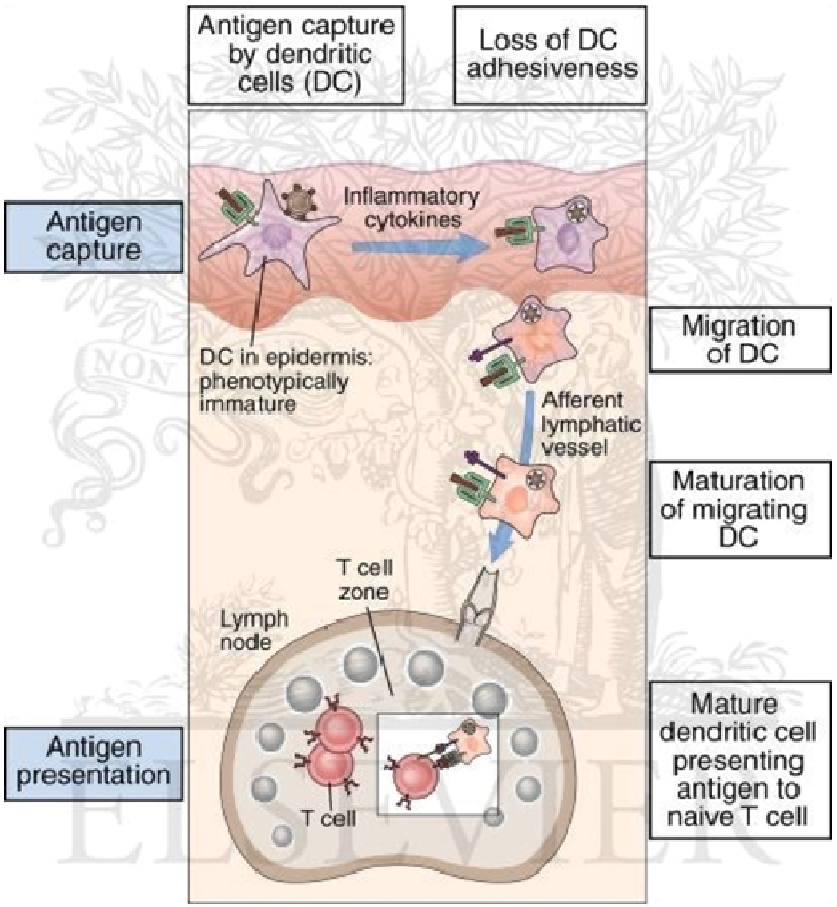


Antigen binding site composed of randomly combined V, D and J gene segments

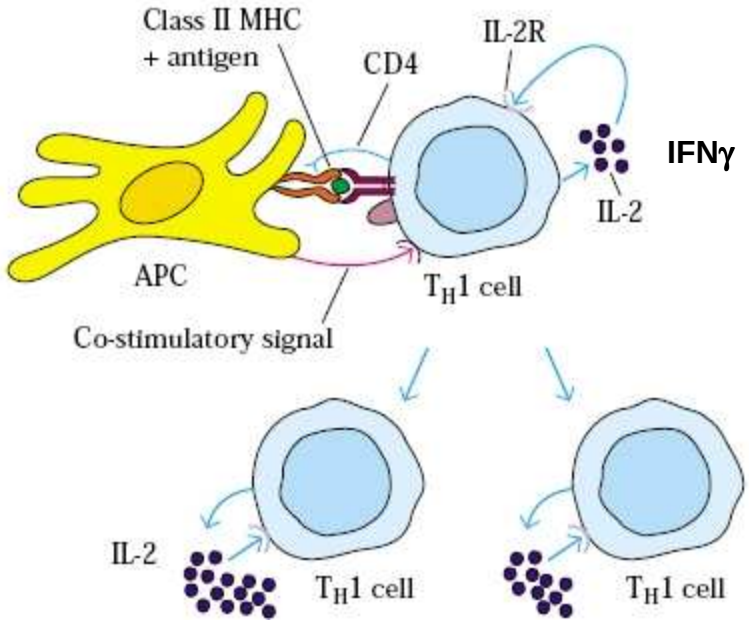


So how is the adaptive immune response initiated?

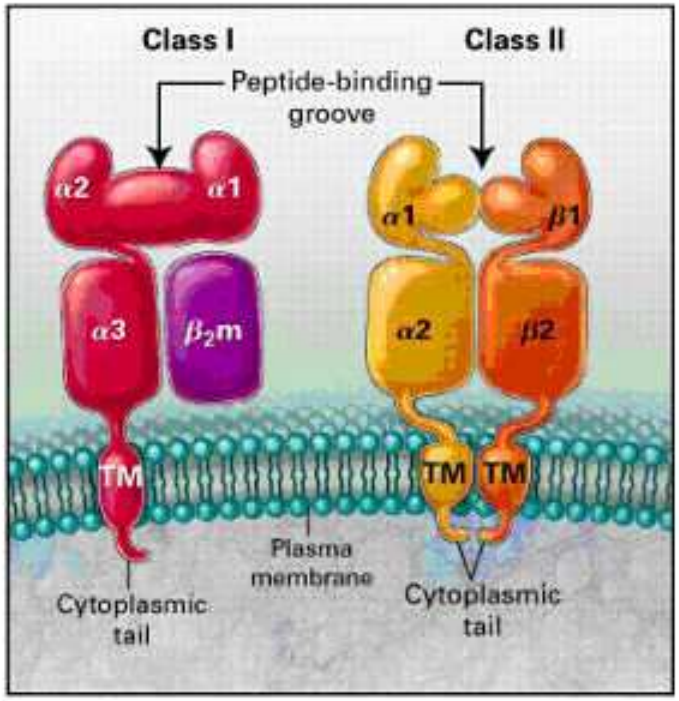
Dendritic Cells Internalize and Process Antigen, And Present It To Naïve T Cells in The Lymph Nodes



T cells That Recognize Antigenic Peptides Presented By Dendritic Cells Are Activated To Synthesize IL-2, Proliferate, And Secrete Proinflammatory Cytokines Such As IFN gamma



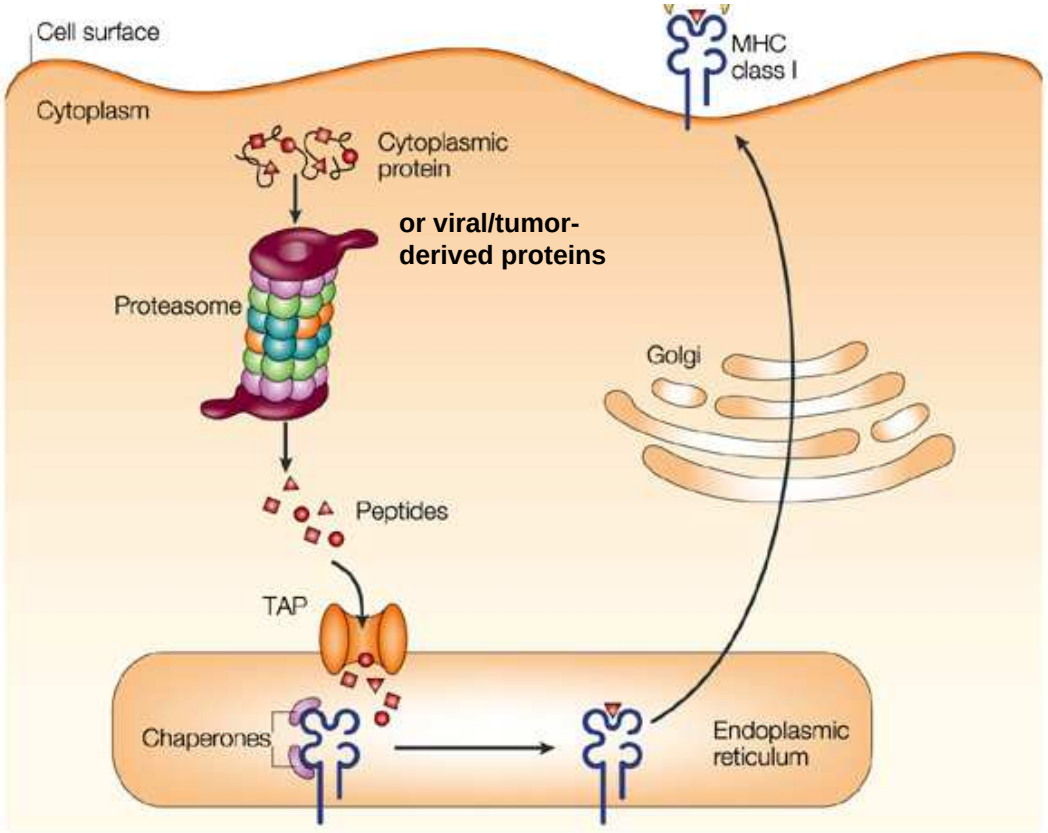
T cell Receptors Don't Bind Antigen Directly, But Rather Recognize Antigen in The Context Of MHC Class I and MHC Class II Molecules



Differential presentation of peptides on Class I or Class II MHC molecules allows the immune system to determine whether it must respond to an intracellular or extracellular pathogen

Intracellular Proteins Are Presented to T cells on Class I Molecules

Ie, Viral Proteins and Tumor-Derived Proteins

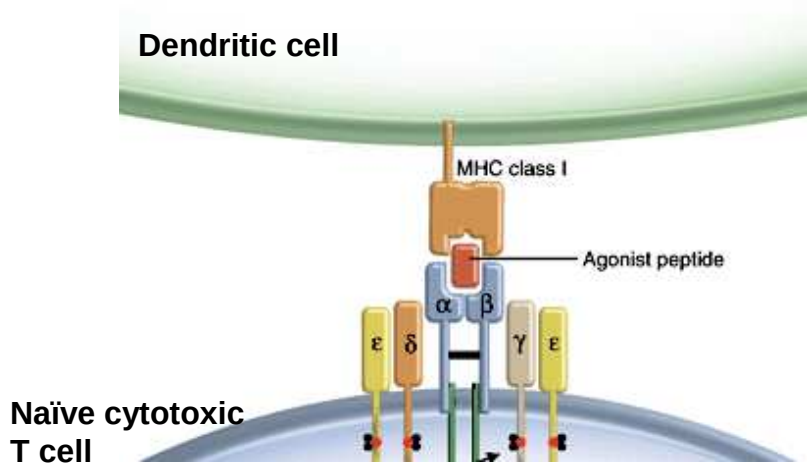


Nature Reviews | Immunology

The way our immune system kills tumor cells and virally infected cells is by generating cytolytic T cells that induce apoptosis of the targets

Since it's Cytolytic T cells That Can Kill Tumor Cells and Virally-Infected Cells,

It's Appropriate That These Are The T cells That Are Activated By Recognizing MHC Class I/Peptide Combinations



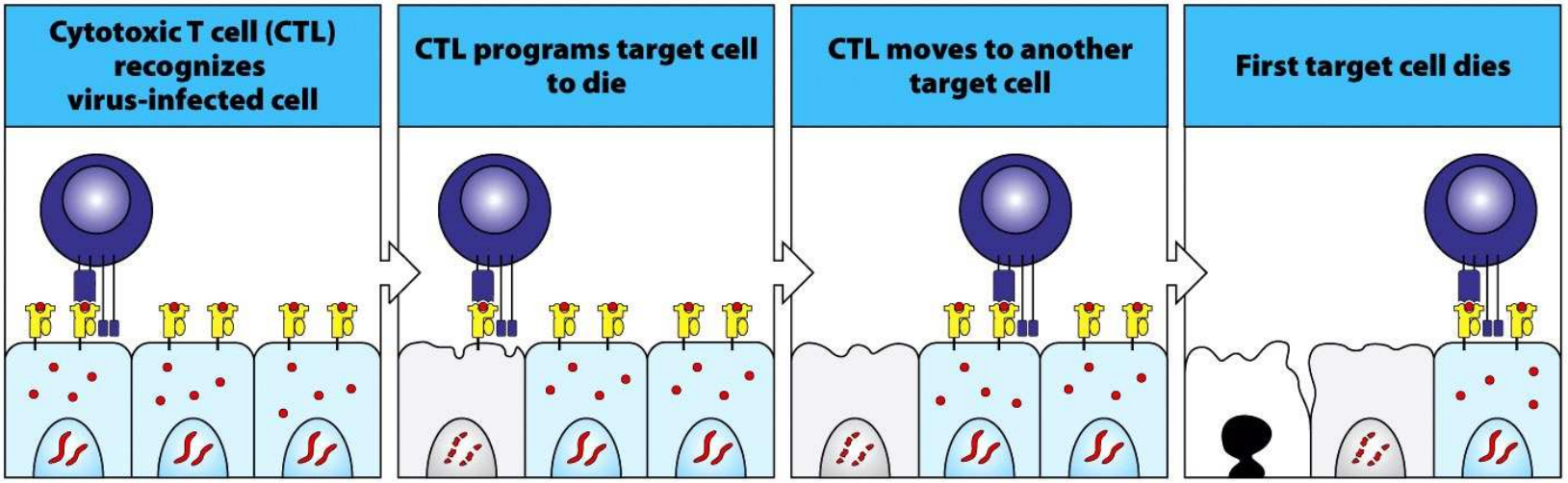
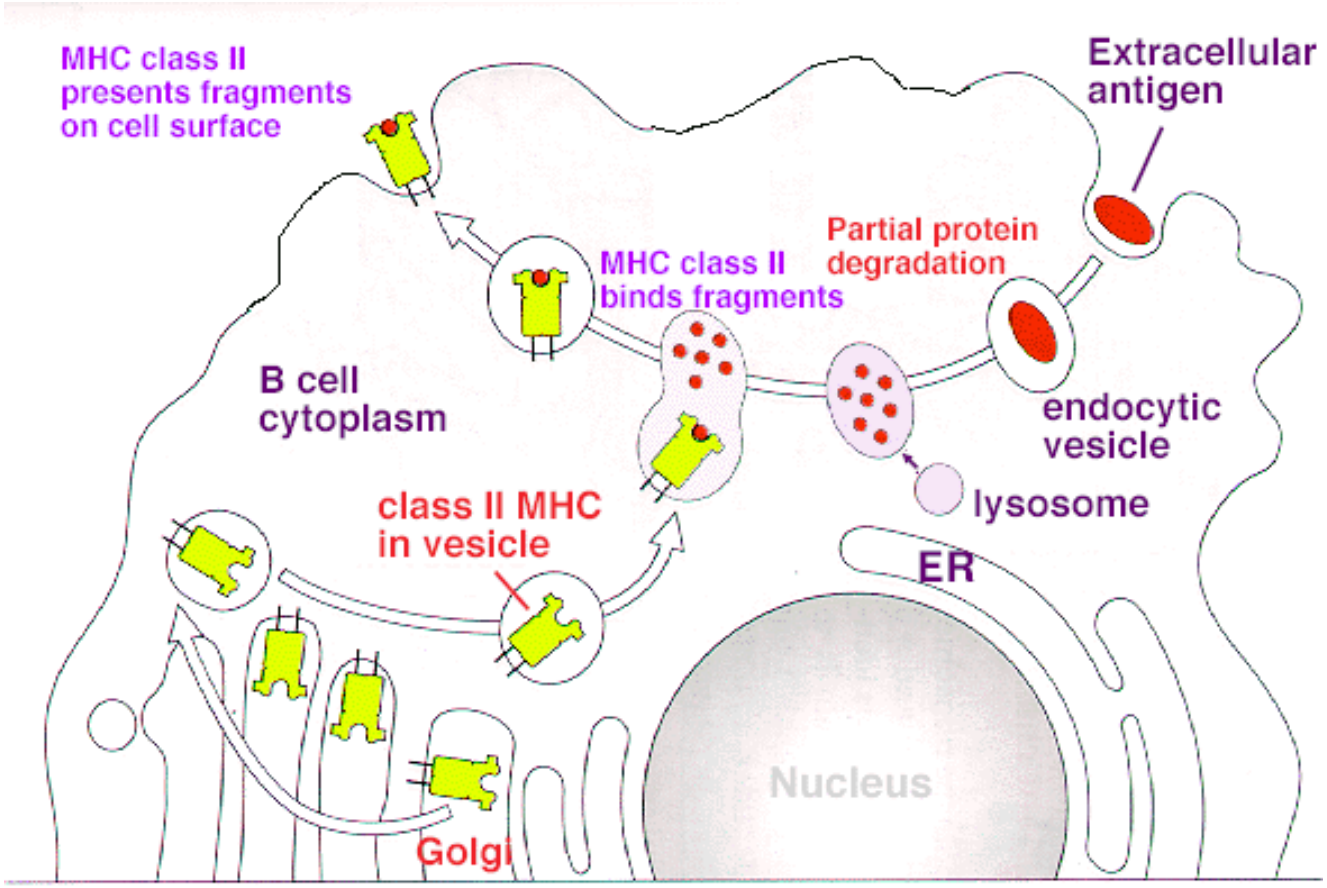


Figure 8.30 The Immune System, 3ed. (© Garland Science 2009)

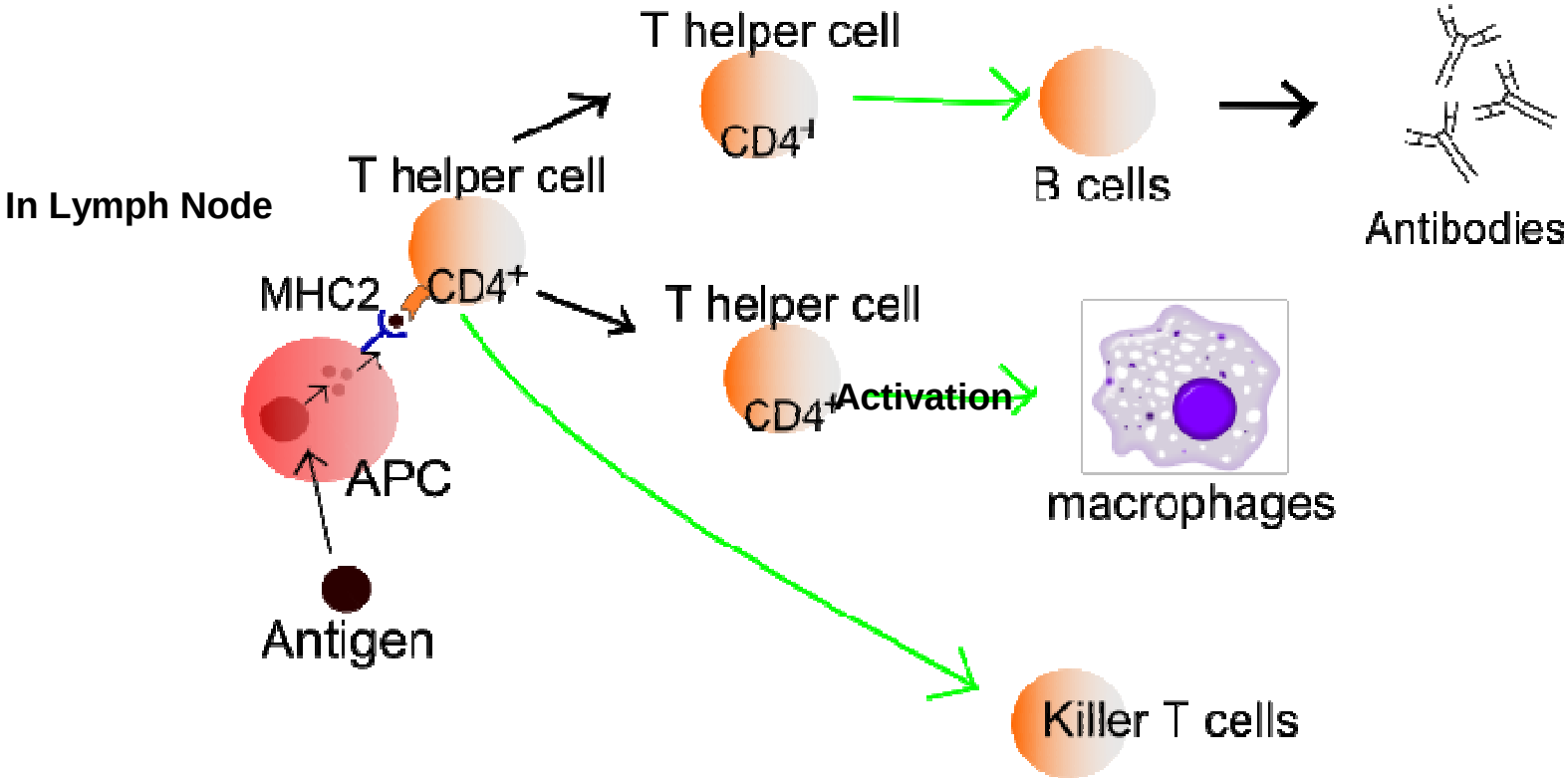
How Do MHC Class II Molecules Inform The Immune System of Extracellular Infections?

Phagocytes Are The Cells That Monitor The Extracellular Space for Pathogens, And These Are Also The Only (Mostly) Cells That Express MHC Class II Molecules

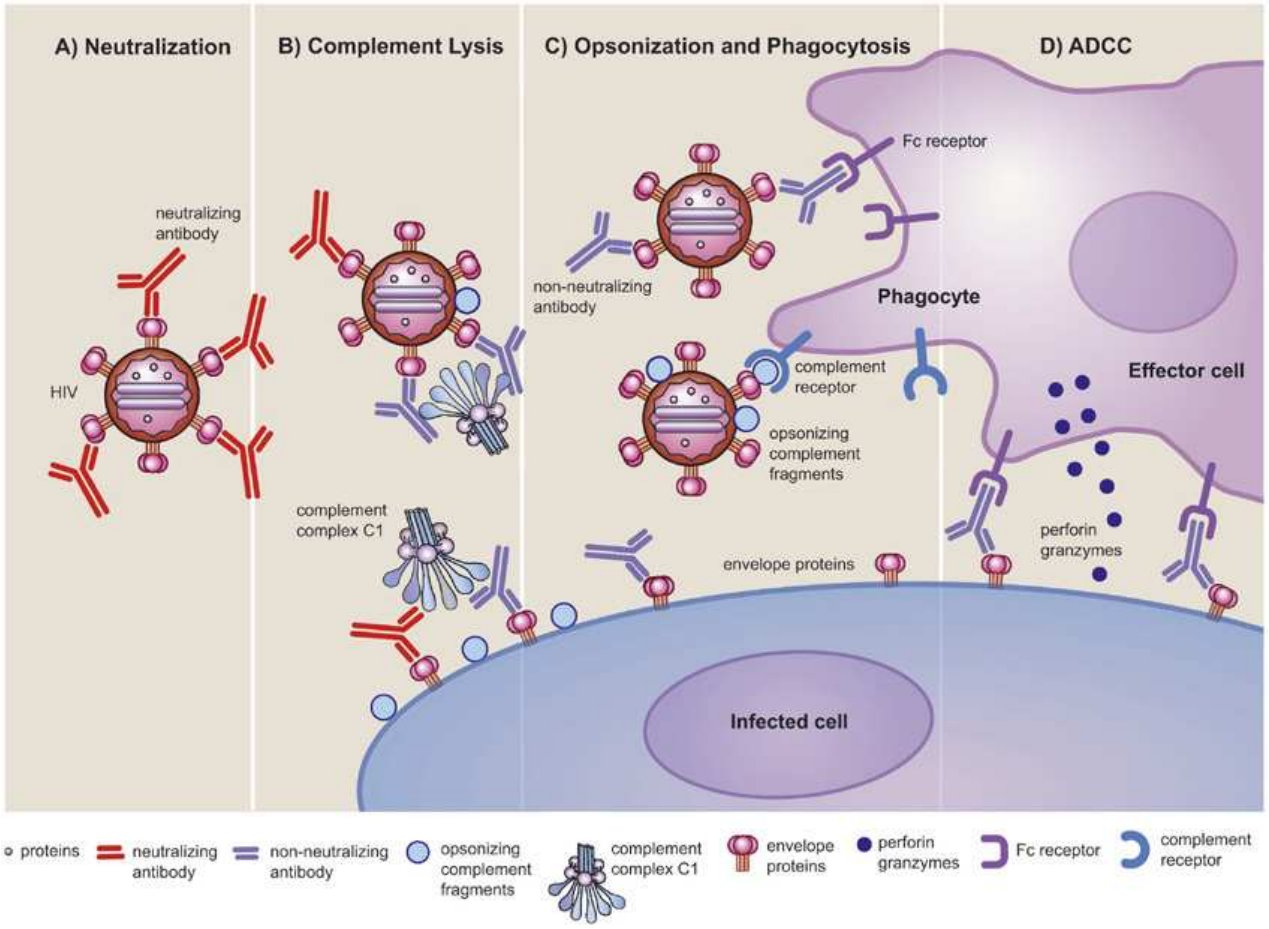


The Way The Adaptive Immune System Kills Extracellular Pathogens Is By Making Antibodies Against Them and By Further Activating Phagocytes

It's CD4 T Helper Cells That Recognize And Are Activated by MHC Class II Complexes, And Then Assist In These Two Activities



Antibodies Mediate A Number Of Different Functions

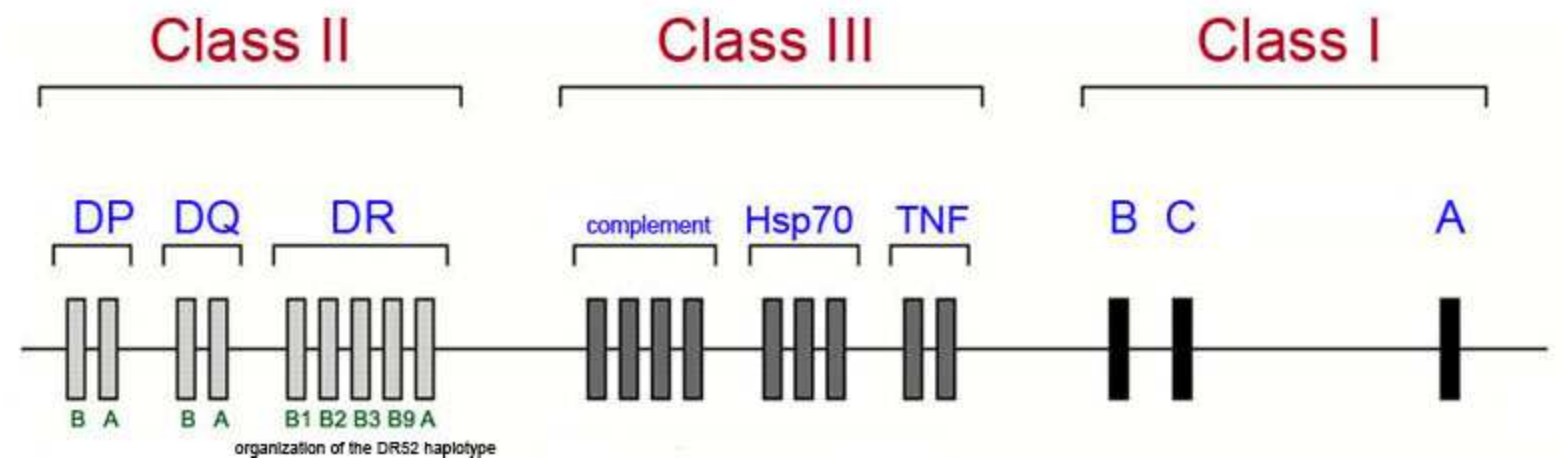


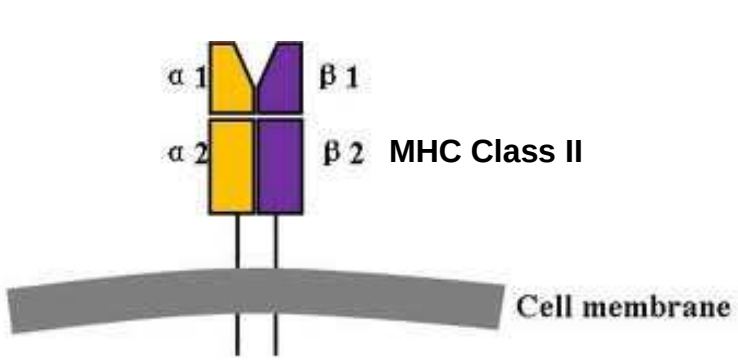
from M. Huber & A. Trkola (2007) Journal of Internal Medicine, 262(1)

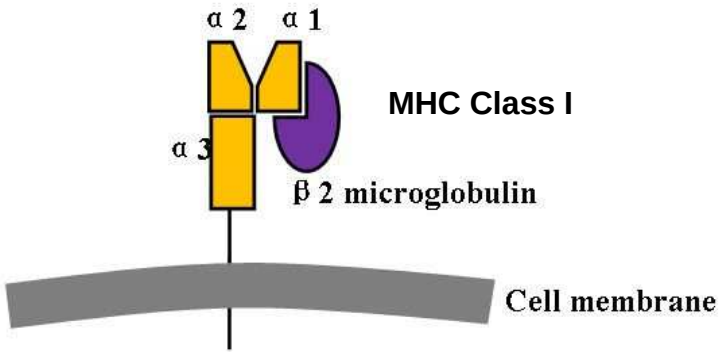
Each of Us Can Only Present Those Peptides To Naïve T cells That Fit Onto Our Own Class I and Class II MHC Molecules

We Each Have 6 Class I And 14 Class II MHC Molecules

Each Can Bind And Present Approximately 10,000 Different Peptides







In Spite of the Diversity of Our Own, Individual MHC Molecules, There is Always A Chance That Some Of Us Won't Be Able To Present *Any* Peptides From Some New, Virulent Pathogen, And Will Hence Succumb To The Infection

As A Species, We're Probably Protected

MHC Class I and Class II Molecules Are Also Highly Polymorphic

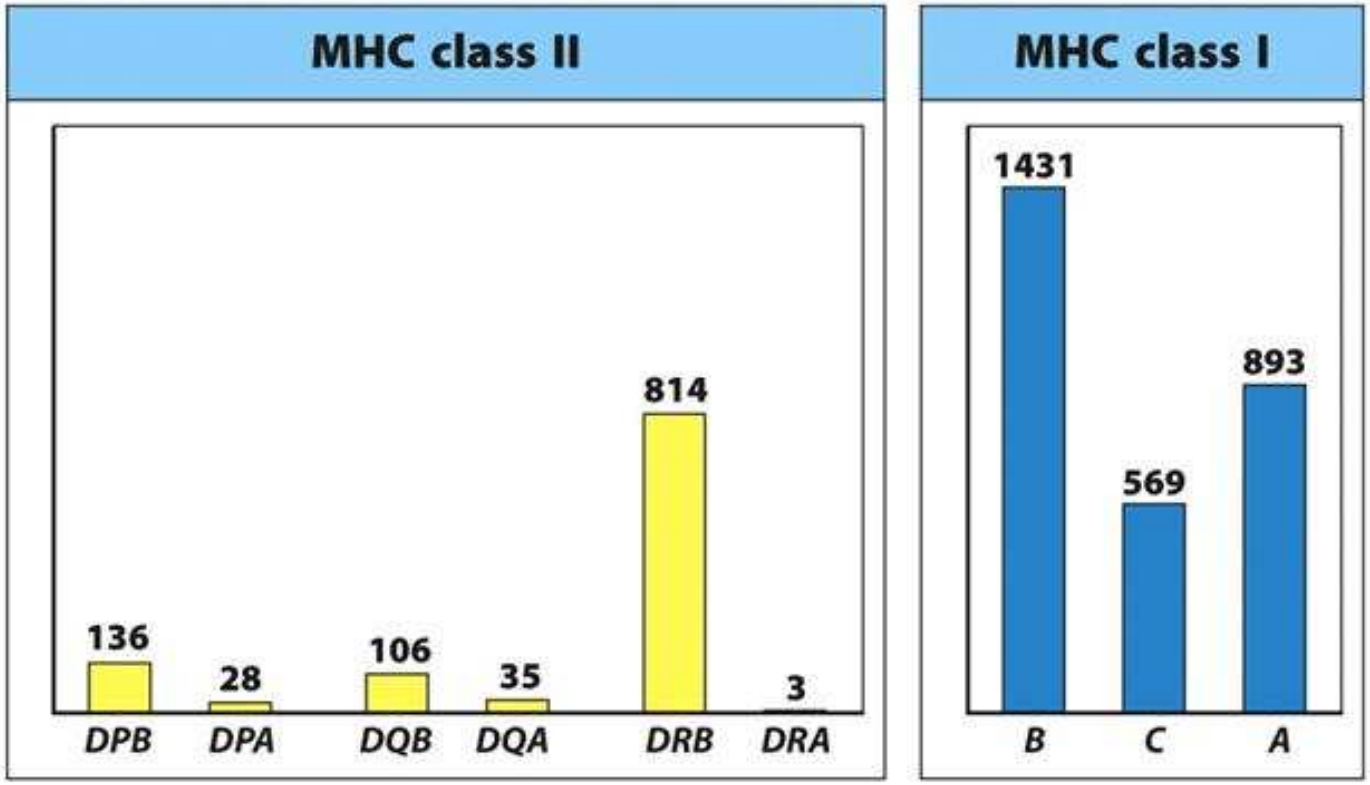


Figure 6.16 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

How is it that T cell Receptors even recognize MHC/peptide Complexes if they develop so randomly?

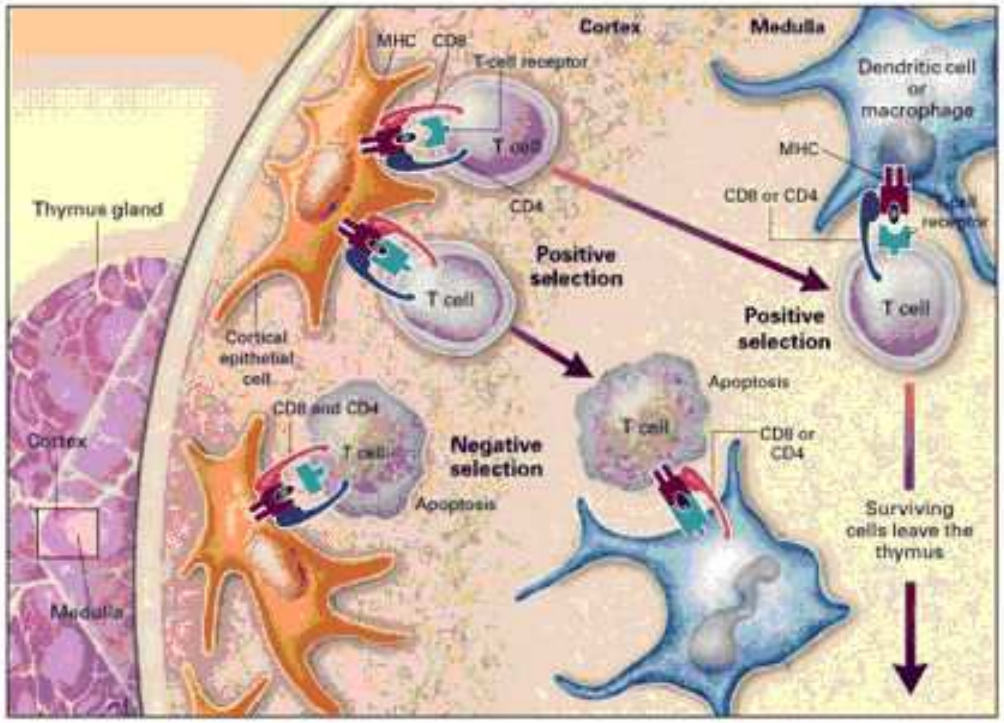
Since T Cell Receptors Are Generated Randomly,

T Cell Development Involves Selecting For Those

T Cells That Can Recognize Our Own MHC Molecules

…..And This Occurs In The Thymus

T cells Are First Selected In The Thymus For Their Ability To Recognize Self MHC/Peptide Complexes With Moderate to High Affinity



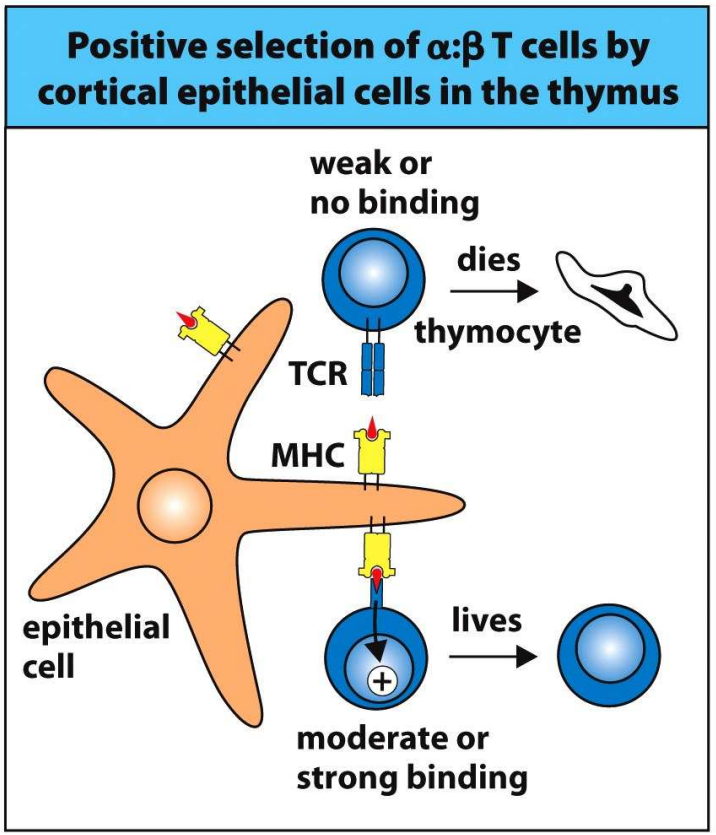
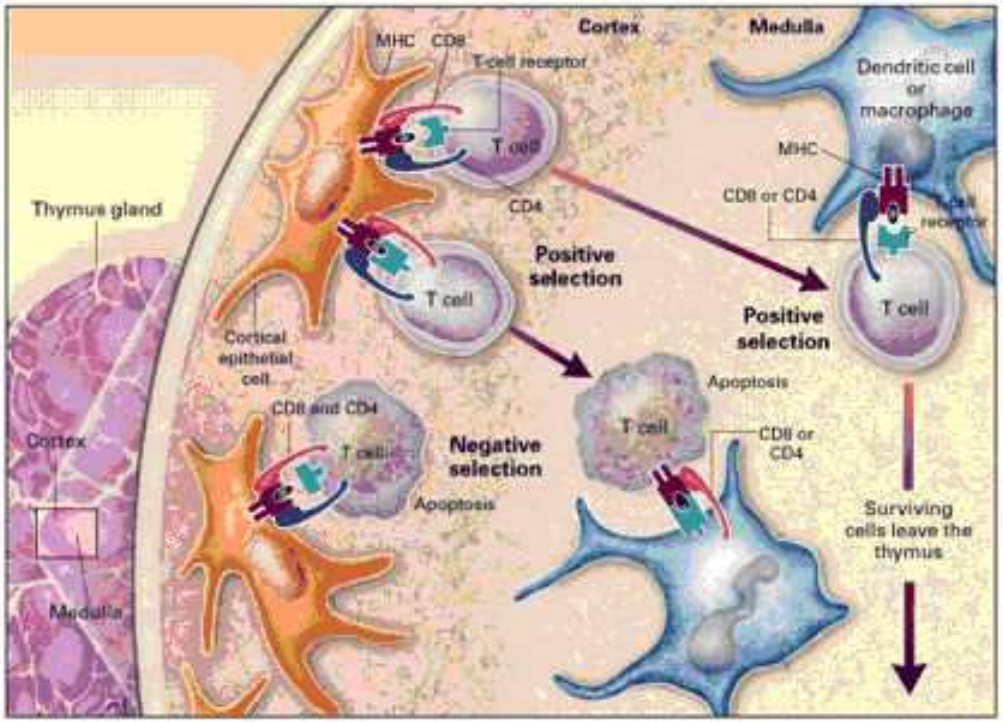
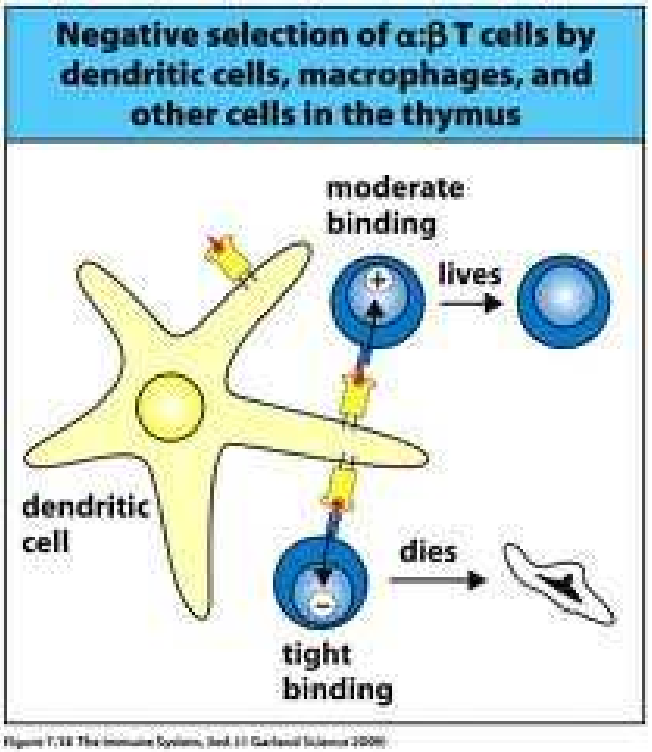


Figure 7.16 The Immune System, 3ed. (© Garland Science 2009)

In A Second Step, Those T cells That Recognize Self MHC/Peptide With Too-Great Affinity Are Deleted





Bottom line:

Good news: Surviving cells probably recognize MHC/foreign antigen with high affinity

Bad News: Surviving T cells may not have great affinity for the "self-like molecules" expressed by tumors

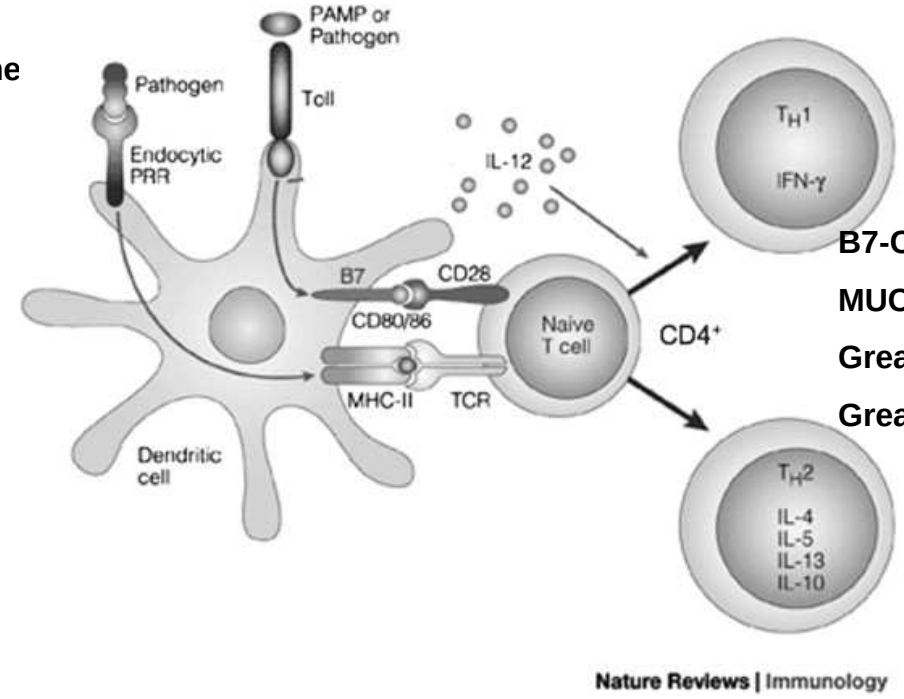
Autoimmunity Is Largely Controlled by Deleting T Cells That Recognize MHC/Self Peptides Too Well

BUT

A second mechanism of controlling autoimmunity is having dendritic cells help decide what is and isn't foreign.

Dendritic cells can only effectively present antigen when they express B7.

B7 is only induced when the phagocyte encounters a Pathogen/PAMP.



B7-CD28 interaction leads to:

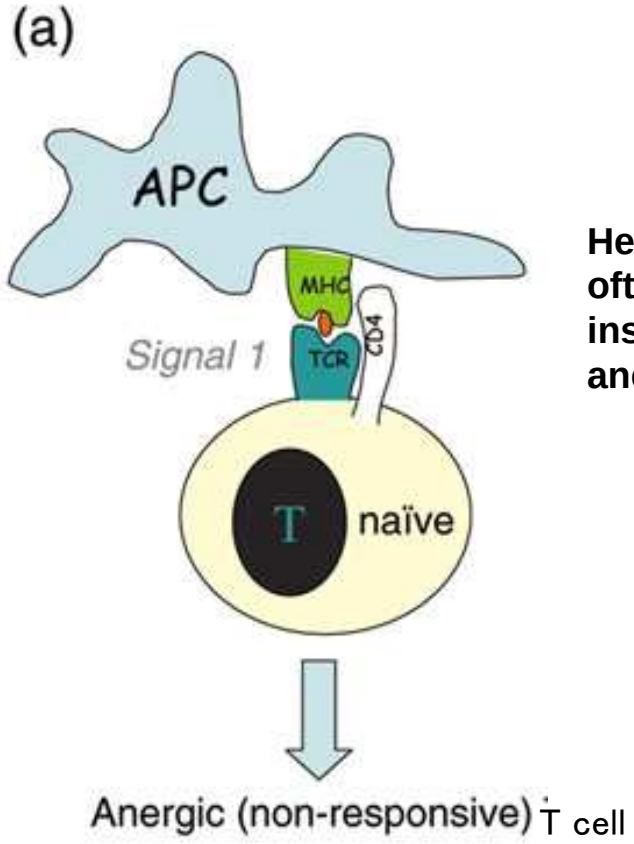
MUCH LONGER LASTING ACTIVATION

Greater IL-2 Transcription

Greater IL-2 mRNA stability

T Cells Stimulated In The Absence Of Co-Stimulation Become Anergic or Unresponsive

Making them difficult to stimulate later even under more favorable circumstances



Tumor Antigens Are Not PAMPS

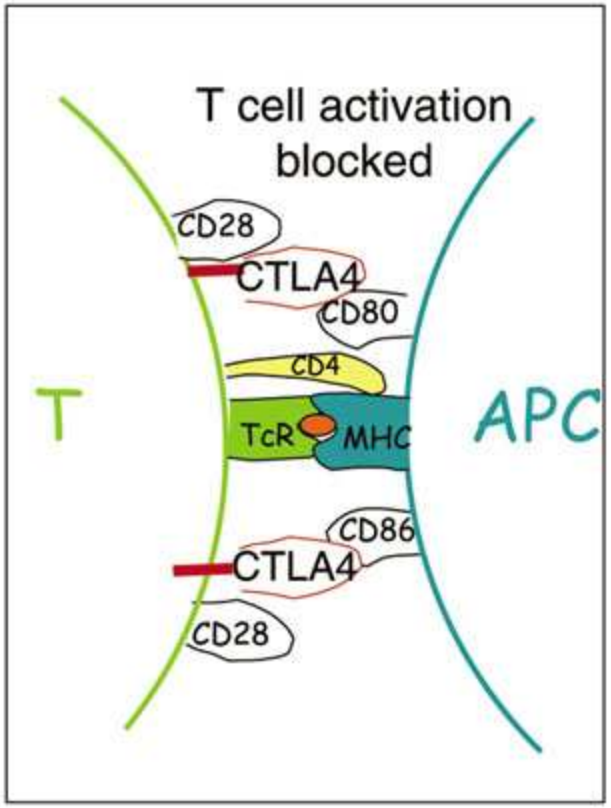
Hence often tumor antigens are often not effectively presented, so instead of anti-tumor responses, anergy results.

Once T cells Are Activated, CTLA4 Is Expressed, Which Competes With CD28 For B7 Binding

As a Mechanism For Dampening The Immune Response

Current Anti-Tumor Therapies Take Advantage of This Phenomenon

By Blocking CTLA-4 With Antibodies



CTLA4Ig

Arthritis Research & Therapy

What Are Potential Limitations To A Successful, Natural Anti-Tumor Immune Response?

1) Tumors largely express self antigens;

T cells with high affinity to self antigens are deleted during development.

2) Effective antigen presentation by APCs requires the B7 co-stimulatory molecule to be expressed along with MHC/foreign peptide

Without PAMPS, the self molecules of tumors may not be stimulating the B7 costimulatory molecule needed to activate T cells.

Pattern Recognition Receptors are able to identify structures that are typically associated with:

A) Macrophages

B) Red Blood Cells

C) Platelets

D) Microbes

Binding of microbial molecules by toll-like receptors on a phagocytic cell should lead to:

- Activation of the phagocyte
- Death of the phagocyte by apoptosis
- Production of IL-2 and IL-2 receptors
- Induction of T cell receptors on the phagocyte cell membrane.

Chemokines are:

A) Only associated with the innate response

B) Chemoattractant molecules

C) Adhesion molecules

D) Cytotoxic molecules that are in the granules of phagocytes

Negative selection of T cells occurs in the:

a) Lymph node
b) Spleen
c) Thymus
d) Bone marrow

On activation, T cells express IL-2 receptors. What is the source of IL-2?

A) Antigen presenting cells

B) NK cells

C) B cells

D) T cells

MHC Class I molecules present peptides derived from:

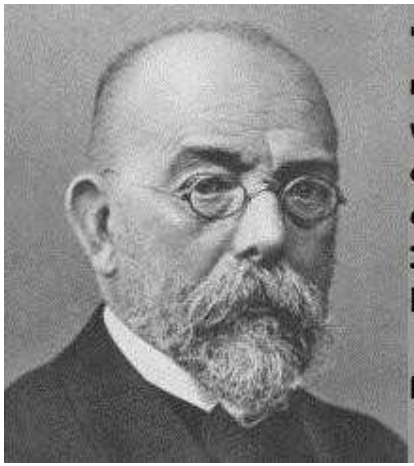
A) Ingested antigens

B) Degraded intracellular proteins

C) Opsonized microbes

D) Extracellular pathogens

The Germ Theory of Disease Wasn't Established Until The Mid to Late 1860s



"However, on many occasions, I examined normal blood and normal tissues and there was no possibility of overlooking bacteria or confusing them with granular masses of equal size. I never found organisms. Thus, I conclude that bacteria do not occur in healthy human or animal tissues."

Robert Koch