
WELCOME

Immunogenetics

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Diploma Microbiology 2020/2021

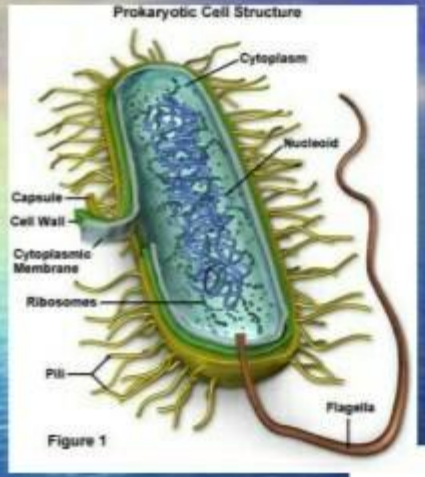
Immunogenetics

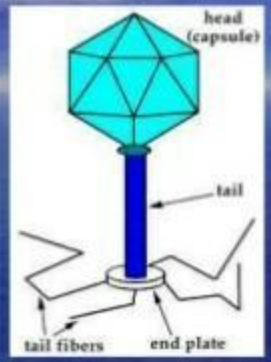
The term ‘immunogenetics ’refers to the scientific discipline that studies the molecular and genetic basis of the immune response. Genetic conditions that affect either the development or function of components of the immune system lead to an inability to control infectious pathogens or a susceptibility to autoimmunity or cancer. These primary immunodeficiency disorders have dramatically increased our understanding that certain components of the immune system are essential for controlling specific pathogens in humans. They have also informed our understanding of basic mechanisms involved in immune tolerance (autoimmunity) and immune surveillance (tumor immunity) under normal conditions.

Immunogenetics and Infectious Diseases

The human immune system is regulated by molecules coded by some genes, among which, are the genes of the human histocompatibility system, which code for human leukocyte antigens (HLA). These genes are located in the short arm of chromosome eerht otni dedivid era dna [1]6 classes, I, II & III.[2,3]

Antigens


Prokaryotic Cell Structure
Cytoplasm
Nucleoid
Capsule
Cell Wall
Cytoplasmic Membrane
Ribosomes
Pili
Flagella
Figure 1


head (capsule)
tail
tail fibers
end plate

Major Histocompatibility Complex (MHC)

- The MHC is a closely linked complex of genes that govern production of the major histocompatibility.
- In humans,MHC resides on the short arm of chromosome .6
- Three genes (HLA-A, HLA-B, HLA-C) code for class1 MHC proteins.
- Several HLA-D loci determine the class 11 MHC proteins i.e. DP, DQ , DR.
- HLA genes vary diverse (polymorphic) i.e. there are many alleles of the class 1 and 11 genes.

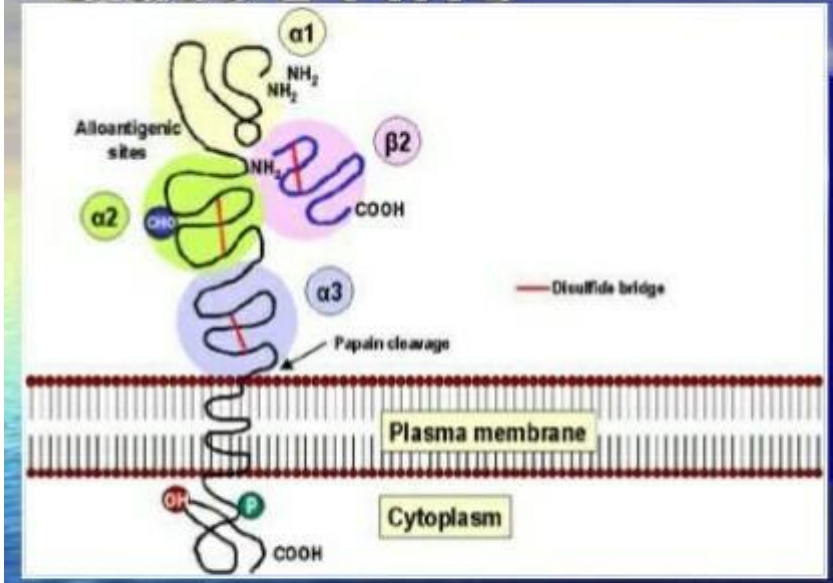
Major Histocompatibility Complex (MHC)

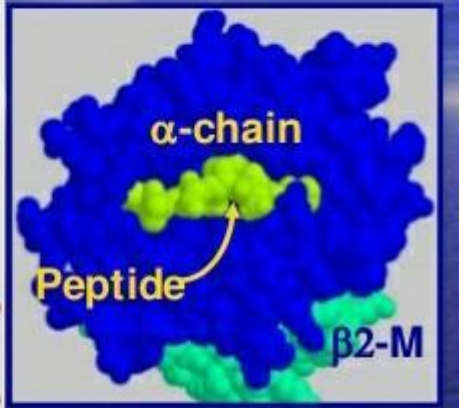
- Between the class1 and class11 gene loci, there is a third locus (class .(111
- This locus contains genes encoding tumor necrosis factor, lymphotoxin and two complement components (C2 and C.(4
- Class 111 antigens dont participate in MHC restriction or graft rejection.

MHC Class 1 Antigens

- Class 1 MHC antigens are: HLA-A, HLA-B, HLA-C.
- These antigens are glycoproteins found on surfaces of all necleotide human cells and on platelets.
- HLA-A contains 24 different antigenic specificities, HLA-B contains 52 and HLA-C contains .11
- Class 1 MHC antigens are involved MHC restriction of cell mediated cytotoxicity.

Class I MHC



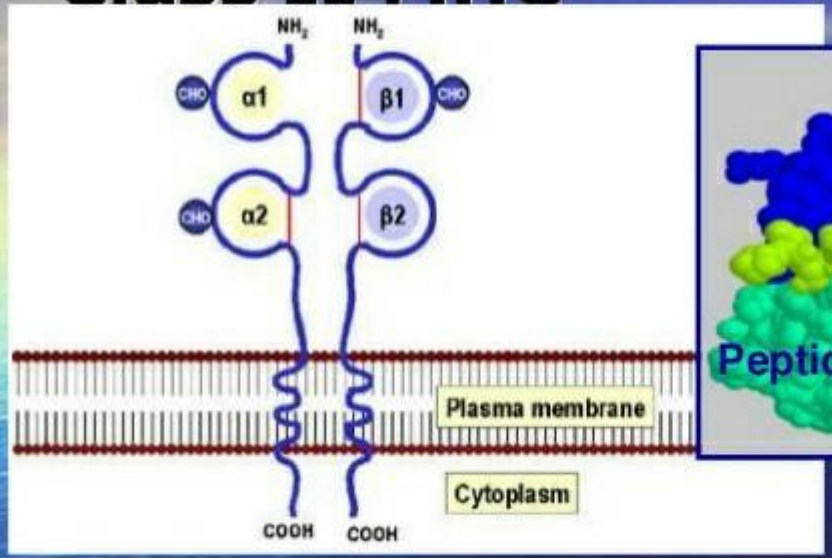


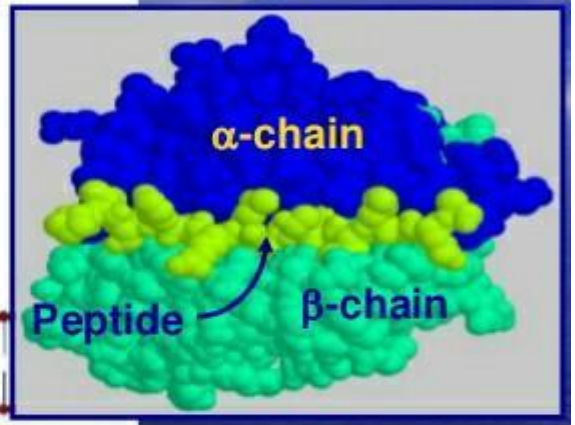
- α chain (43kDa), β2 microglobulin (12 kDa)
- β2-microglobulin – genes on chromosome 15
- Can accommodate 10 amino acids

MHC Class 11 Antigens

- Class 11 antigens are: HLA-DP, HLA-DQ, HLA-DR antigens.
- These antigens are glycoproteins found on the surface of macrophages, B-cells, Dendritic cells, langerhans cells of skin and activated T cells.
- HLA-DP contains 6 different antigenic specificities, HLA-DQ contains 9 and HLA-DR contains .20
- Helper T-cells recognize antigens on antigen-presenting cells only when the antigens are presented on the surface of cells on association with class 11 MHC.
- Class 11 antigens react with the CD4 molecule on the helper T-cells which secrete cytokines.

Class II MHC





- α chain (34kDa), β chain (29 kDa)
- Can accommodate ~15 amino acids

Class 1 MHC and Class 11 MHC

	MHC Class I	MHC Class II
Nomenclature	HLA-A, HLA-B, HLA-C	HLA-DP, HLA-DQ, HLA-DR
Found on	All nucleated somatic cells	Macrophages, B-cells, Dentritic cells, langerhans cells of skin and activated T cells
Recognized by	CD8 TC cells	CD4 TH cells
Functions	Presentation of Ag to TC cells leading to elimination of tumor or infected host cell	Presentation of Ag to TH cells which secrete cytokines

MHC features

- Linkage disequilibrium - the distribution of haplotypes is not random in a population.
- Diversity (polygenic/polymorhic) - many genes/alleles (>500 for HLA-B)->ability to respond to millions of antigens.
- Inheritance pattern - co-dominance.

MHC distribution

Tissue	MHC class I	MHC class II
Lymphoid tissues		
T cells	+++	+*
B cells	+++	+++
Macrophages	+++	++
Dendritic cells	+++	+++
Epithelial cells of the thymus	+	+++
Other nucleated cells		
Neutrophils	+++	–
Hepatocytes	+	–
Kidney	+	–
Brain	+	– †
Non-nucleated cells		
Red blood cells	–	–

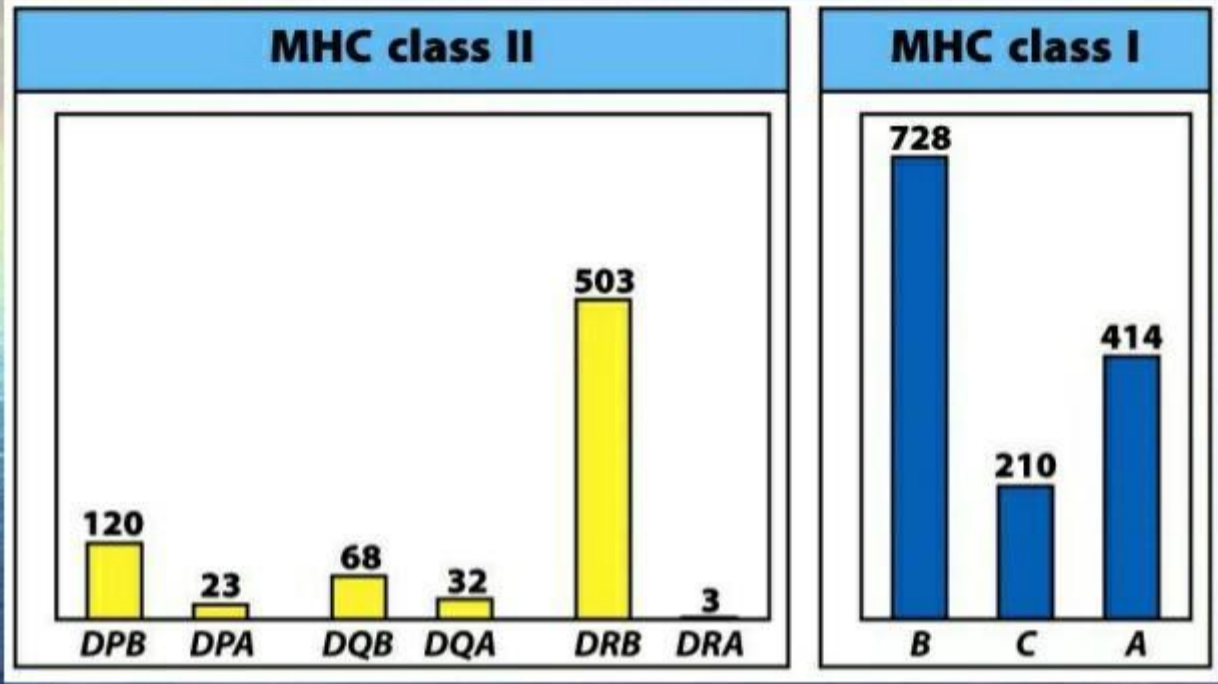
Gene polymorphism

Genetic polymorphism a yb dellortnoc tiart a fo ecnatirehni eht sa denifed si a sah elella nommoc tsael eht hcihw ni ,selella owt htiw sucol citeneg elgnis 1% tuoba fo ycneuqerfor greater. Genetic polymorphism is a difference in DNA sequence among individuals, groups, or populations.

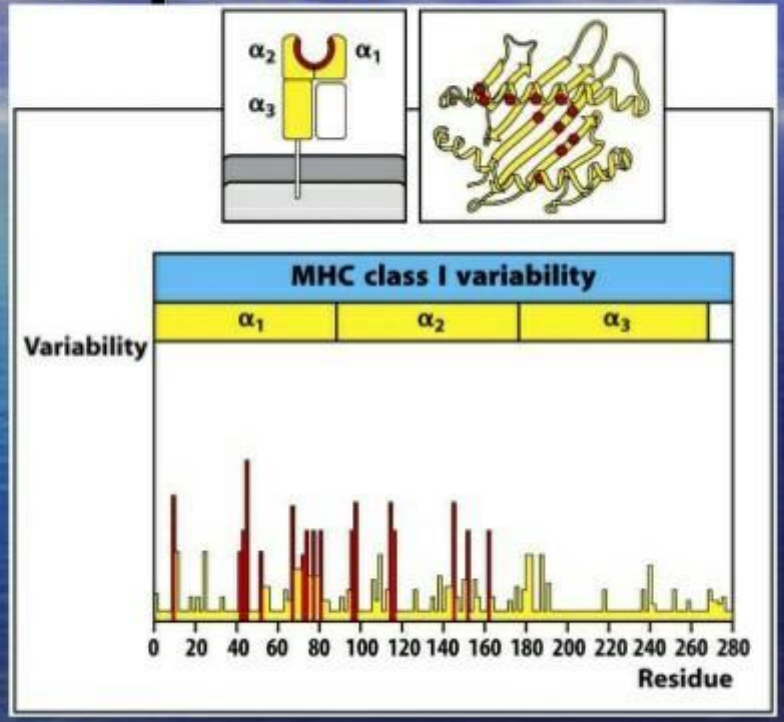
What is Genetic polymorphism?

(1) The existence together of many forms of DNA sequences at a locus within the population.
(2) A discontinuous genetic variation that results in different forms or types of individuals among the members of a single species.

Polymorphism



Polymorphism



Application of HLA in medicine

- Transplantation
- Forensic medicine
- Anthropological studies
- Regulating immune responses
- Disease association

Disease association

Examples of significant HLA and disease associations				
Disease	Associated Alleles	Frequency in		Relative Risk
		Patients	Control	
Ankylosing spondylitis	B27	90	9	87.4
Reiter's disease (syndrome)	B27	79	9	37.0
Acute anterior uveitis	B27	52	9	10.4
Psoriasis vulgaris	Cw6	87	33	13.3
Dermatitis herpetiformis	DR3	85	26	15.4
Celiac Disease	DR3	79	26	10.8
Insulin-dependent diabetes mellitus	DR3/4	91	57	7.9

Immunogenetics and genomics

Immunogenetic analysis of disease susceptibility has been encouraged by the identification of strong HLA associations
with several diseases of uncertain cause. Weaker HLA associations exist with a large number of infectious and non-
infectious diseases and the mechanisms of these effects are beginning to be uncovered. Extensive analyses of non-HLA
immunogenetic variants have also been undertaken and associations with a variety of genes identified .

Immunogenetics and genomics

Genetic linkage
analysis of multicase families has recently identified new major susceptibility loci for a few immunologically determined
common diseases. However, the greatest potential for the future lies in genome-wide searches for susceptibility genes
that individually might have quite modest effects but cumulatively have a large impact on individual risk. This new era of
immunogenomics promises to provide key insights into disease pathogenesis and identify multiple molecular targets.

Linkage disequilibrium

A1	B8
B8	DR3
A11	B5
A29	B12

Gene combinations occuring more frequently than expected by random combinations

Antigen Recognition

Antigens:

Processed, Unprocessed

Endogenous, Exogenous

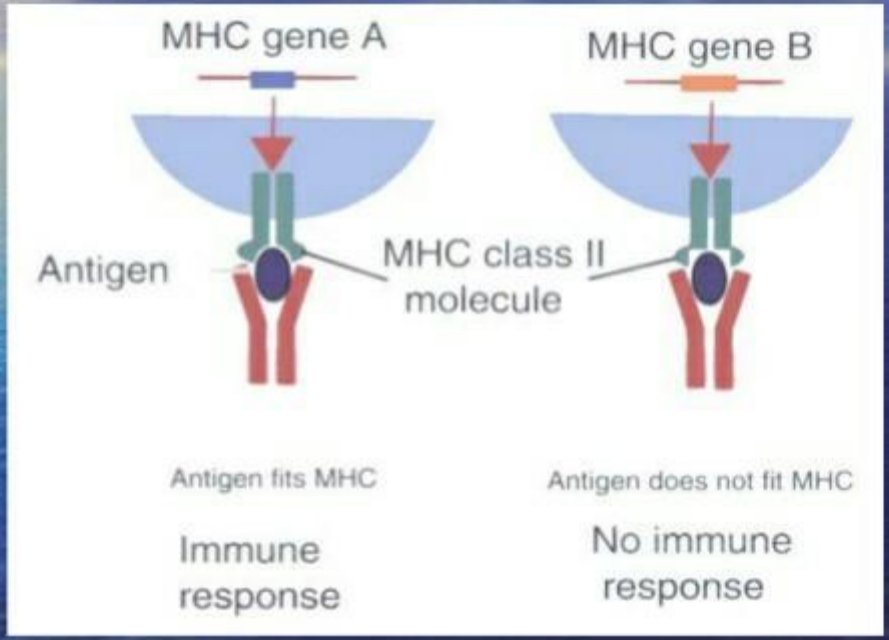
Self, Foreign

Receptors:

Ag-specific->adaptive

PRRs->innate

MHC restriction of immune response



Immune System

Immune System Functions

Scavenge dead, dying body cells
Destroy abnormal (cancerous)
Protect from pathogens & foreign molecules: parasites, bacteria, viruses
The Immune System has 3 Lines of Defense Against Foreign Pathogens:

.1Physical and Chemical Barriers (Innate Immunity)

.2Nonspecific Resistance (Innate Immunity)

.3Specific Resistance (Acquired Immunity)

Immune System

Physical and Chemical Barriers (Innate Immunity)

Physical and chemical barriers form the first line of defense when the body is invaded.

Physical Barriers

- The skin has thick layer of dead cells in the epidermis which provides a physical barrier. Periodic shedding of the epidermis removes microbes.
- The mucous membranes produce mucus that trap microbes
- Hair within the nose filters air containing microbes, dust, pollutants
- Cilia lines the upper respiratory tract traps and propels inhaled debris to throat
- Urine flushes microbes out of the urethra
- Defecation and vomiting -expel microorganisms

Chemical Barriers

- Lysozyme, an enzyme produced in tears, perspiration, and saliva can break down cell walls and thus acts as an antibiotic (kills bacteria)
- Gastric juice in the stomach destroys bacteria and most toxins because the gastric juice is highly acidic) pH (3-2
- Saliva dilutes the number of microorganisms and washes the teeth and mouth
- Acidity on skin inhibit bacterial growth
- Sebum (unsaturated fatty acids) provides a protective film on the skin and inhibits growth
- Hyaluronic acid is a gelatinous substance that slows the spread of noxious agents

Nonspecific Resistance (Innate Immunity)

The second line of defense is nonspecific resistance that destroys invaders in a generalized way without targeting specific individuals:

***Phagocytic cells** .seussit ydob otni ssap taht seborcim lla yortsed dna tsegni etihw fo epyt a) setyconom morf devired sllec era segahporcam elpmaxe roF lortap ot seussit ydob retne dna maertsdoolb eht evael segahporcaM .(llec doolb tahw si siht ,eborcim a sretnuocne egahporcam eht nehW .snegohtap rof :sneppah

(1The microbe attaches to the phagocyte.

(2The phagocyte's plasma membrane extends and surrounds the microbe and takes the microbe into the cell in a vesicle.

Nonspecific Resistance (Innate Immunity)

(3The vesicle merges with a lysosome, which contains digestive enzymes.
(4The digestive enzymes begin to break down the microbe. The phagocyte uses any nutrients it can and leaves the rest as indigestible material and antigenic fragments within the vesicle.
(5The phagocyte makes protein markers, and they enter the vesicle.
(6The indigestible material is removed by exocytosis.
(7The antigenic fragments bind to the protein marker and are displayed on the plasma membrane surface. The macrophage then secretes interleukin-1 which activates the T cells to secrete interleukin cificeps rednu woleb debircsed sa ,2 . ecnatsiser

Nonspecific Resistance (Innate Immunity)

***Inflammation** era seussit ruoy nehw srucco taht esnopser eussit dezilacol a si doolb etihw erom sgnirb noitammalfnI .ilumits rehto ot esnopser ni dna degamad esnopser yrotammalfni ehT .dedavni evah seborcim eht erehw etis eht ot sllec niap ,taeh ,ssender ,gnillews secudorp

***Fever** na gnirud riaper eussit fo etar eht sesaercni dna htworg lairetcab stibihni .noitcefni

Specific Resistance (Acquired Immunity)

The third line of defense is **specific resistance** no seiler metsys sihT .**antigens** , .seborcim ngierof ni dnuof secnatsbus cificeps era hcihw

Most antigens are proteins that serve as the stimulus to produce an **immune response** morf semoc "negitna" mret ehT .**ANTI** ydob-**GEN**erating substances.

Here are the steps in an immune response:

Specific Resistance (Acquired Immunity)

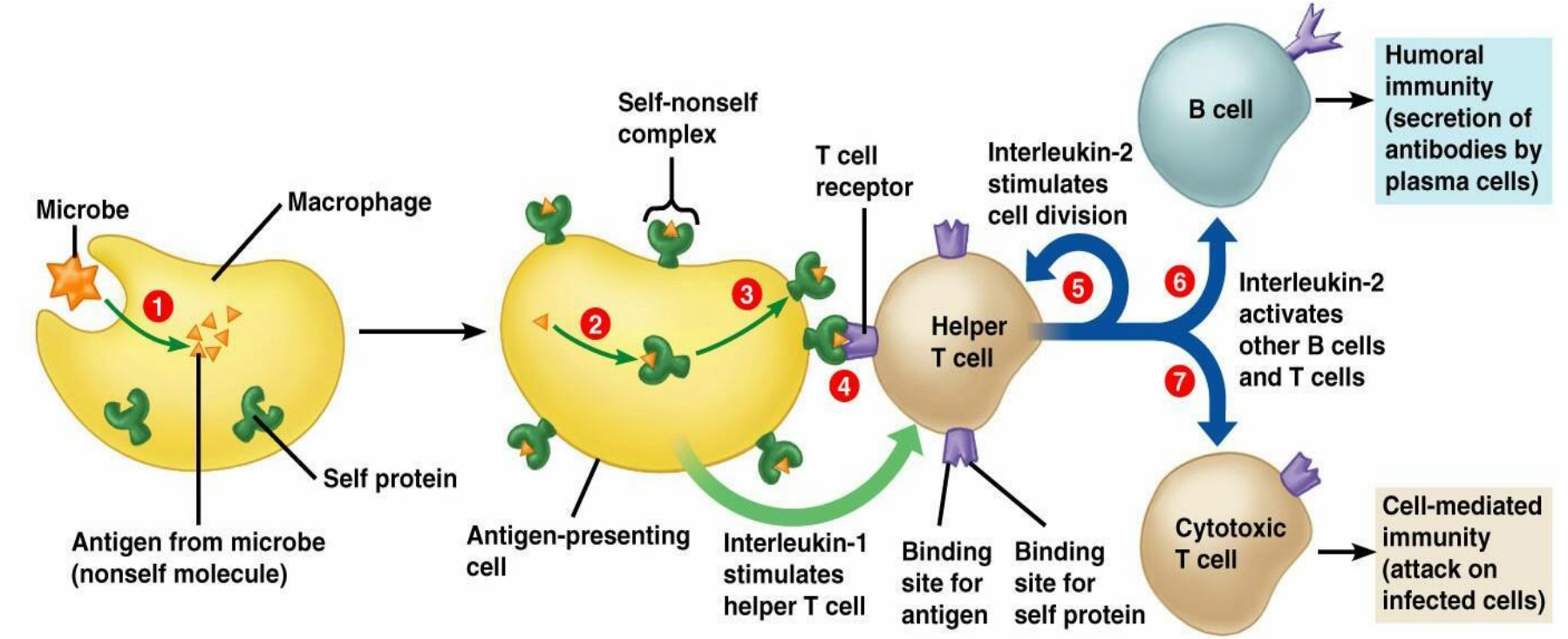
(1When an antigen is detected by a macrophage (as describe above under phagocytosis), this causes the T-cells to become activated.
The activation of T-cells by a specific antigen is called cell-mediated immunity.
The body contains millions of different T-cells, each able to respond to one specific antigen.

(2The T-cells secrete interleukin 2 nikuelretnI .2causes the proliferation of certain cytotoxic T cells and B cells.
(3From here, the immune response follows 2 paths: one path uses cytotoxic T cells and the other uses B cells

Cytotoxic T Cell Pathway

- The cytotoxic T cells are capable of recognizing antigens on the surface of infected body cells.
- The cytotoxic T cells bind to the infected cells and secrete cytotoxins that induce apoptosis (cell suicide) in the infected cell and perforins that cause perforations in the infected cells.
- Both of these mechanisms destroys the pathogen in the infected body cell.

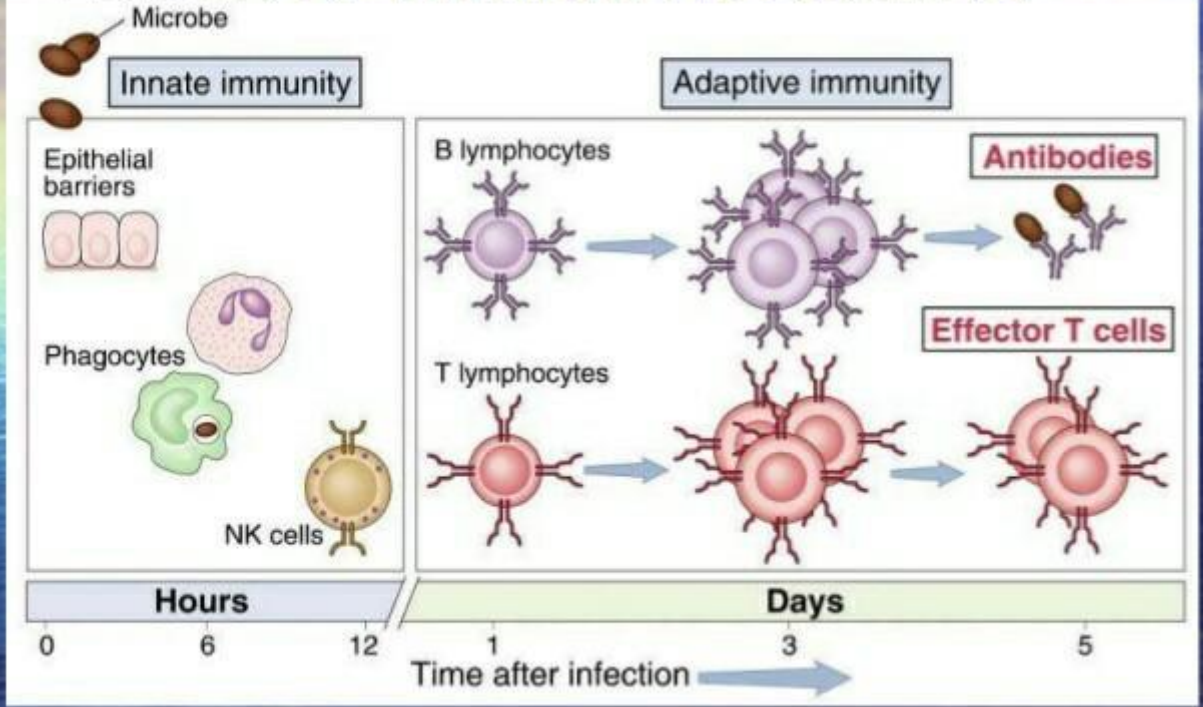
Activation of a helper T cell and its roles in immunity:

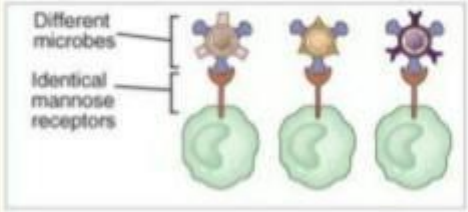
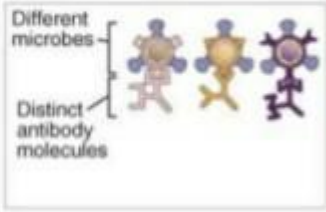
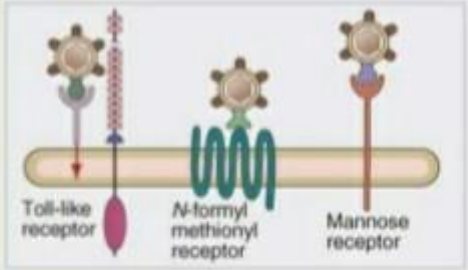
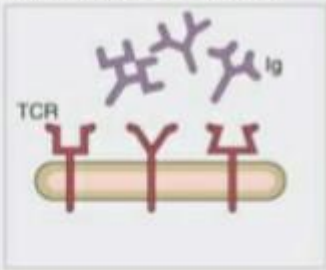


T Cell Pathway

*T-cells can either directly destroy the microbes or use chemical secretions to destroy them.
*At the same time, T cells stimulate B cells to divide, forming plasma cells that are able to produce antibodies and memory B cells.
*If the same antigen enters the body later, the memory B cells divide to make more plasma cells and memory cells that can protect against future attacks by the same antigen.
*When the T cells activate (stimulate) the B cells to divide into plasma cells, this is called antibody-mediated immunity.

Levels of immune response



	Innate immunity	Adaptive immunity
Specificity	For structures shared by classes of microbes ("molecular patterns") 	For structural detail of microbial molecules (antigens); may recognize nonmicrobial antigens 
Receptors	Encoded in germline; limited diversity 	Encoded by genes produced by somatic recombination of gene segments; greater diversity 
Distribution of receptors	Nonclonal: identical receptors on all cells of the same lineage	Clonal: clones of lymphocytes with distinct specificities express different receptors
Discrimination of self and nonself	Yes; host cells are not recognized or they may express molecules that prevent innate immune reactions	Yes; based on selection against self-reactive lymphocytes; may be imperfect (giving rise to autoimmunity)

Antibodies

Antibodies dellac osla) **immunoglobulins** taht snietorp depahs-Y era (s'gl ro gnikcatta ybereht ,snegitna cificeps ot dnib dna maerts doolb eht hguorht etalucric .seborcim

The antibodies are transported through the blood and the lymph to the pathogen invasion site.

The body contains millions of different B cells, each able to respond to one specific antigen.

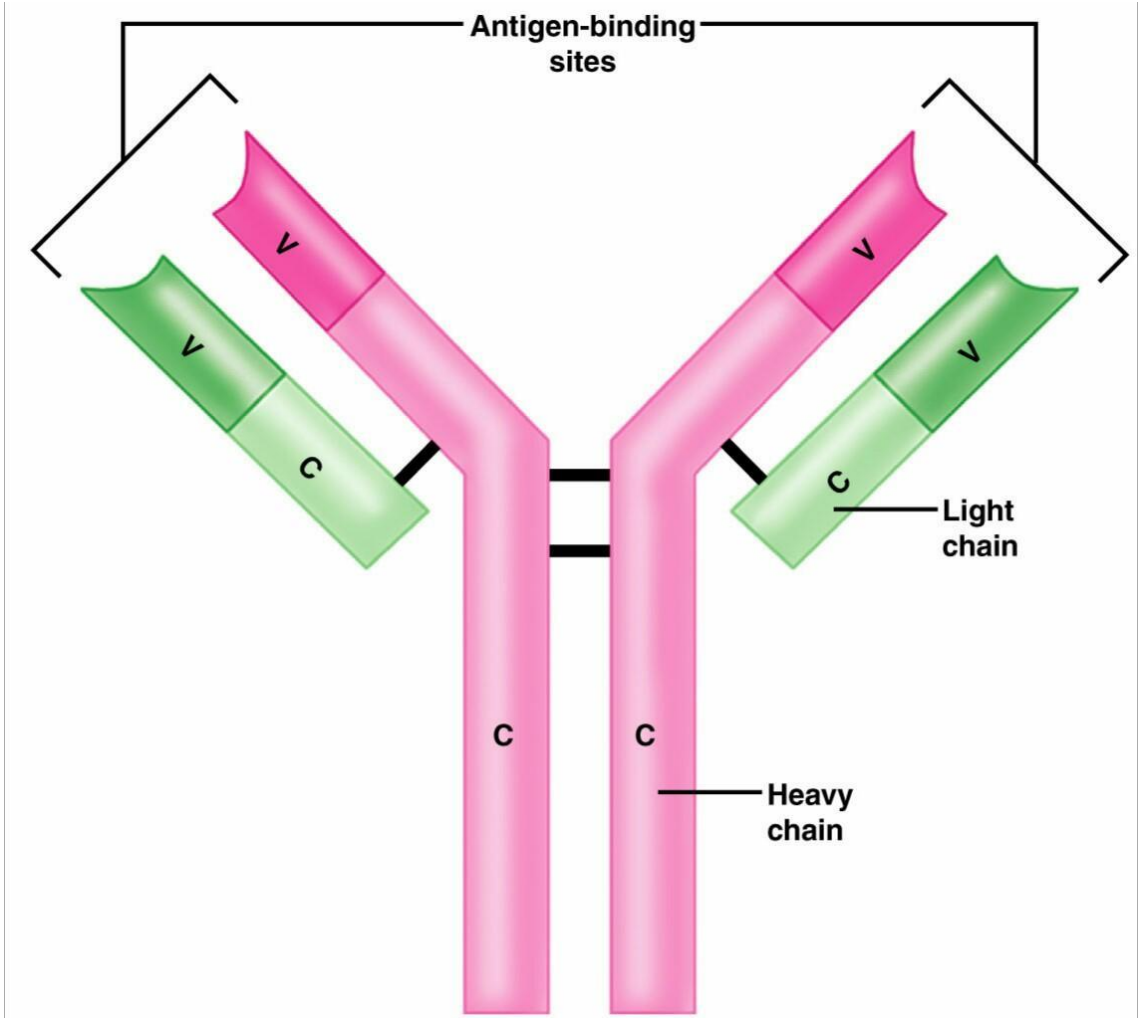
Antibodies

There are 4 classes of antibodies (listed from most common to least common):

IgG
IgM
IgA
IgE
IgD

Antibodies

Each antibody is made of four polypeptide (protein) chains: 2 **heavy chains** dna 2 **light chains** thgil htob dna rehto hcae ot lacitnedi era sniahc yvaeh htoB . a sniatnoc hcaE .rehto hcae ot lacitnedi era sniahc**constant region** a dna **variable region** elihw elucelom eht fo trap niam eht smrof noiger tnatsnoc ehT . 2 sah ydobitna hcaE.etis gnidnib-negitna eht smrof snoiger elbairav ehtantigen-binding sites.


Antigen-binding sites
V
V
V
V
C
C
C
C
Light chain
Heavy chain

Antibodies work in different ways:

.1Neutralizing an Antigen

The antibody can bind to an antigen, forming an antigen-antibody complex. This forms a shield around the antigen, preventing its normal function. This is how toxins from bacteria can be neutralized or how a cell can prevent a viral antigen from binding to a body cell thereby preventing infection.

Antibodies work in different ways:

.2Activating Complement:

Complement is a group of plasma proteins made by the liver that normally are inactive in the body. An antigen-antibody complex triggers a series of reactions that activates these proteins. Some of the activated proteins can cluster together to form a pore or channel that inserts into a microbe's plasma membrane.This lyses (ruptures) the cell. Other complement proteins can cause chemotaxis and inflammation, both of which increase the number of white blood cells at the site of invasion.

Antibodies work in different ways:

.3Precipitating Antigens

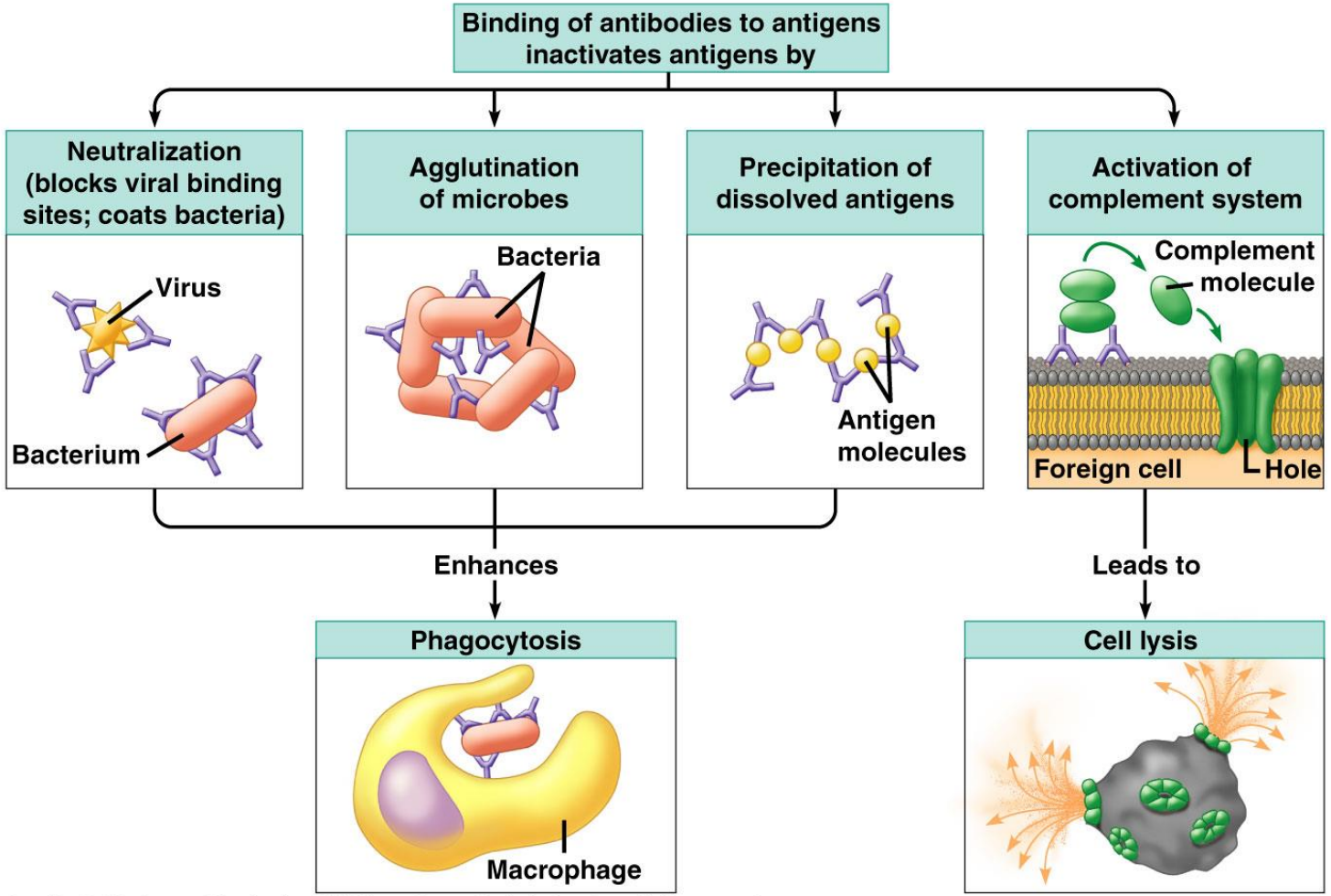
Sometimes the antibodies can bind to the same free antigen to cross-link them. This causes the antigen to precipitate out of solution, making it easier for phagocytic cells to ingest them by phagocytosis (as describe above).

Also, the antigens within the cells walls of the bacteria can cross-link, causes the bacteria to clump together in a process called agglutination, again making it easier for phagocytic cells to ingest them by phagocytosis.

Antibodies work in different ways:

.4Facilitating Phagocytosis

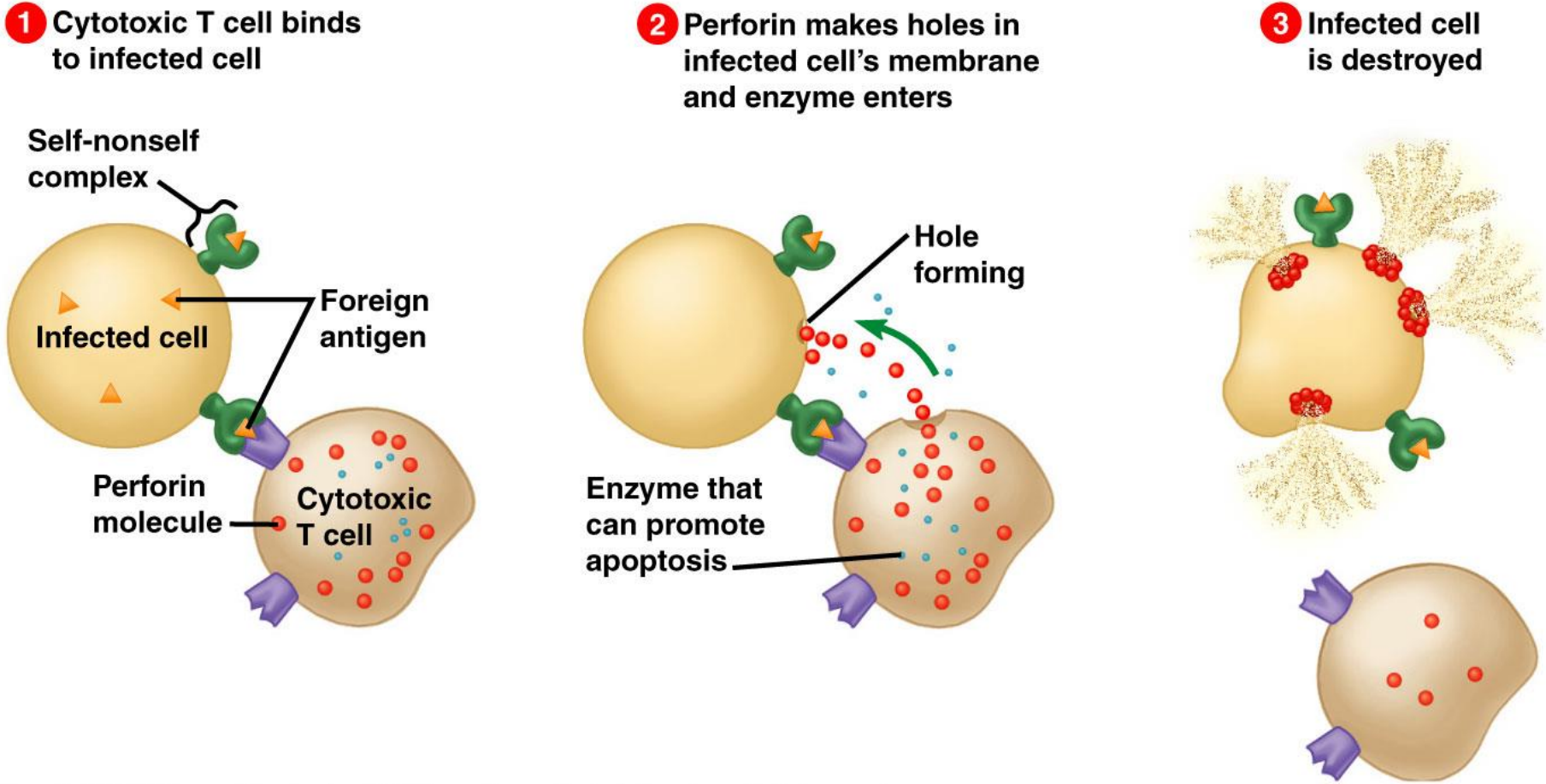
The antigen-antibody complex signals phagocytic cells to attack. The complex also binds to the surface of macrophages to further facilitate phagocytosis.



There are 3 major types of T cells:

.1Cytotoxic T cells

These cells secrete cytotoxin which triggers destruction of the pathogen's DNA or perforin which is a protein that creates holes in the pathogens plasma membrane. The holes cause the pathogen to lyse (rupture).



There are 3 major types of T cells:

.2Helper T cells

These cells secrete interleukin dna sllec T fo noisivid llec setalumits hcihw (2-l)2 eht thgif pleh ot sllec erom neve tiurcer sllec eseht ,sdrow rehto nI .sllec B .negohtap

.3Memory T cells

These cells remain dormant after the initial exposure to an antigen. If the same antigen presents itself again, even if it is years later, the memory cells are stimulated to convert themselves into cytotoxic T cells and help fight the pathogen.

Transplantation and Graft Rejection

Types of grafts

(1Autografts:

The transfer of an individual’s own tissues from place to place

e.g, Skin grafts (regularly accepted)

(2Isografts:

Transfer of tissues between genetically identical persons

e.g. Identical twins (accepted permanently)

Types of grafts

(3Allografts (homograft:(

-Transfer of a graft between genetically different members of same species

e.g. from one human to another

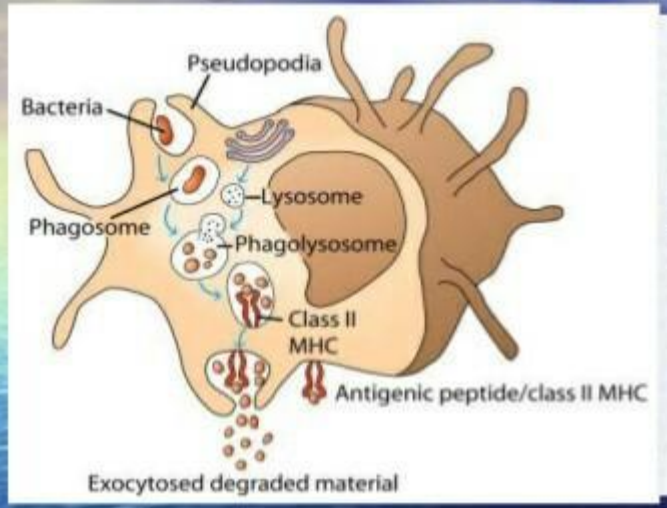
-Rejection occur if donor and recipient are not matched

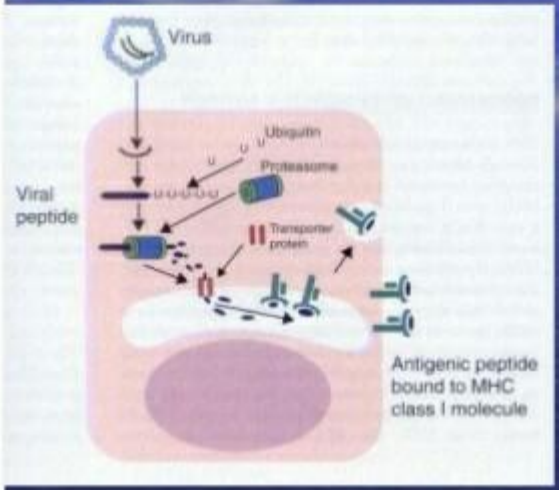
(4Xenograft (heterograft:(

-Transfer of tissues between different species

-Always rejected

Antigen Processing





exogenous

endogenous

Mechanism Of Graft Rejection

(1Both TH and TC are activated

-TC cells destroy graft cells by direct contact

TH cells secrete cytokines that attract and activate macrophages, NK cells and polymorphs leading to cellular infiltration and destruction of graft (Type IV)

-B cells recognize foreign antigens on the graft and produce antibodies which bind to graft cells and

*Activate complement causing cell lysis

*Enhance phagocytosis, i.e. opsonization (Type (11

*Lead to ADCC by macrophages, NK, PML

Mechanism Of Graft Rejection

-Immune complex deposition on the vessel walls induce platelets aggregation and microthrombi leading to ischemia and necrosis of graft (Type(11

Types Of Graft Rejection

(1Hyperacute rejection:

-It occurs hours after transplantation

-In individual with preformed antibodies either due to - blood groups incompatibility or previous sensitization by blood transfusion, previous transplantation

(2Acute Rejectio:

-It occurs 10 to 30 days after transplantation

-It is mainly T-cell mediated

Types Of Graft Rejection

(3Chronic or late rejection:

-It occurs over a period of months or years

-It may be cell mediated, antibody mediated or both

Graft Versus Host (GVH) Reaction

- An Immunologically competent graft is transplanted into an immunologically suppressed recipient (host)
- The grafted cells survive and react against the host cells i.e. instead of reaction of host against the graft, the reverse occurs
- GVH reaction is characterized by fever, pancytopenia, weight loss, rash, diarrhea, hepatosplenomegaly and death

Immunogenetics and Vaccination

Genetic diversity has underpinned the survival and expansion of human populations against a long history of varied microbial challenges, but may limit the universal immunogenicity of current vaccines against particular pathogens. Reduced or non-responsiveness is a barrier to total pathogen eradication for established vaccines, and remains the key impediment to licensure for a number of investigational vaccines. Genetic association studies have identified some determinants of vaccine immunogenicity, many of which act at single molecular interactions within complex pathways and networks. To date these immune modifying polymorphisms explain only a fraction of the known variation in vaccine responses and the most striking aspect of individualized immunity, immunodominance, remains a central issue in new vaccine design .

Immunogenetics and Vaccination

Vaccine personalization is likely to require not only a systems biology approach to understand broad vaccine response phenotypes, but also an understanding that the specificity of antigen recognition unique to every vaccinee and restricted by their human leukocyte antigen (HLA) genotype, determines the unique CD4 and CD8 T cell and natural killer (NK) cell repertoires available for vaccine induction. This chapter discusses the role of HLA and non-HLA loci, and pathogen-specific adaptations relevant to vaccines and explores ways these could be exploited in vaccine design and personalization.


Thank
You