Genetics

Modified no.

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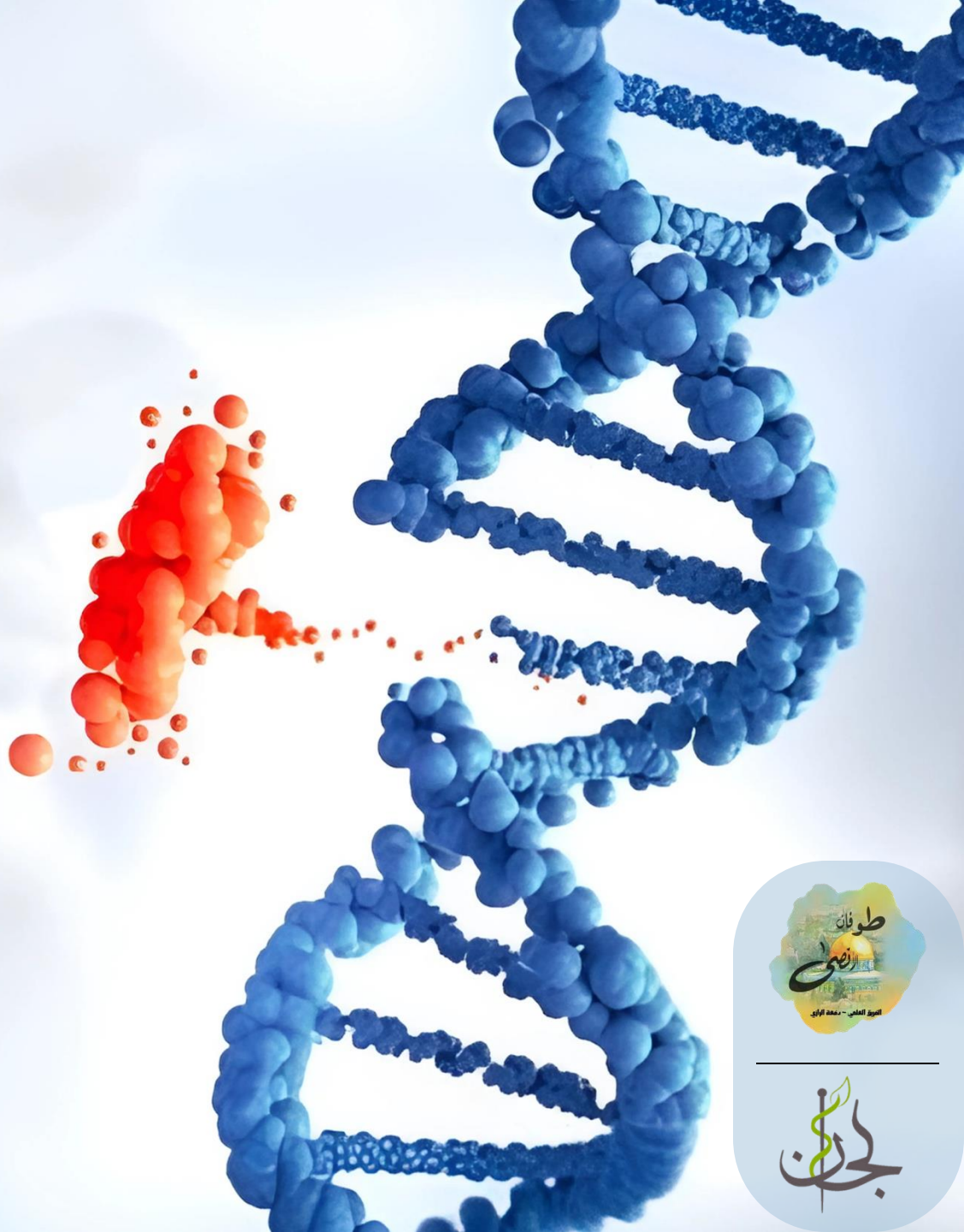

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In this lecture we're going to talk about the third class which has a major role in immunity, immune response and in compatibility which is "THE MAJOR HISTOCOMPATIBILITY COMPLEX (MHC)" which includes three major classes: Class I, II, and III

MHC is one of the most variable regions in the human genome, it compromises about 200 genes located on chromosome 6, spanning approximately 400 million bases that cover around 90 different genes that will express Class I, II, and III on the surface of the cells

THE MAJOR HISTOCOMPATIBILITY COMPLEX

Class I, II, and III Genes

- The MHC, which includes a series of more than 200 genes that lie in a 4- Mb region on the short arm of chromosome 6 (Fig. 9-8), is commonly classified into three groups: class I, class II, and class III.
- The class I MHC molecule forms a complex with foreign peptides that is recognized by receptors on the surfaces of cytotoxic T lymphocytes.
- Class I presentation is thus essential for the cytotoxic T-cell response. Some viruses evade cytotoxic T-cell detection by down-regulating the expression of MHC class I genes in the cells they infect. So, cytotoxic T cells cannot recognize or eliminate these viruses.

The short arm of chromosome 6 contains the MHC which is divided into three main regions:
Class I MHC: Includes HLA-A, HLA-B, and HLA-C.
Class II MHC: Includes HLA-DP, HLA-DQ, and HLA-DR.
Class III MHC: Includes genes encoding complement proteins.

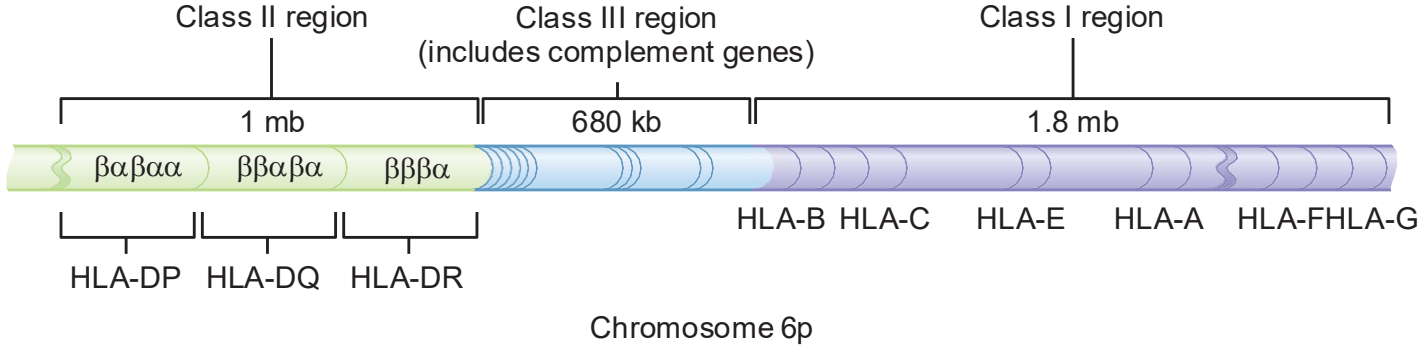


FIG 9-8 A map of the human major histocompatibility complex. The 4-Mb complex is divided into three regions: classes I, II, and III.

- Class I MHC molecules are composed of a single heavy glycoprotein chain with several domains: α1, α2, and α3. A single light chain called β2-microglobulin (Fig. 9-9A).

- The most important of the class I loci are labeled **human leukocyte antigens** A, B, and C **(HLA- A, -B,** and -**C),** these antigens are called HLA (Human Leukocyte Antigens) because they were first discovered on leukocytes and initially thought to be specific to them. However, it was later found that class I HLA antigens are present on all cells in the body. Each of these loci has dozens or hundreds of alleles, resulting in a high degree of class I MHC variability among individuals.

•The class I region spans 1.8 Mb and includes a number of additional genes and **pseudogenes.**

- **Pseudogenes: they are genes that have the same sequence of the coding genes but they don't undergo coding or transcription or translation because of some alterations.**

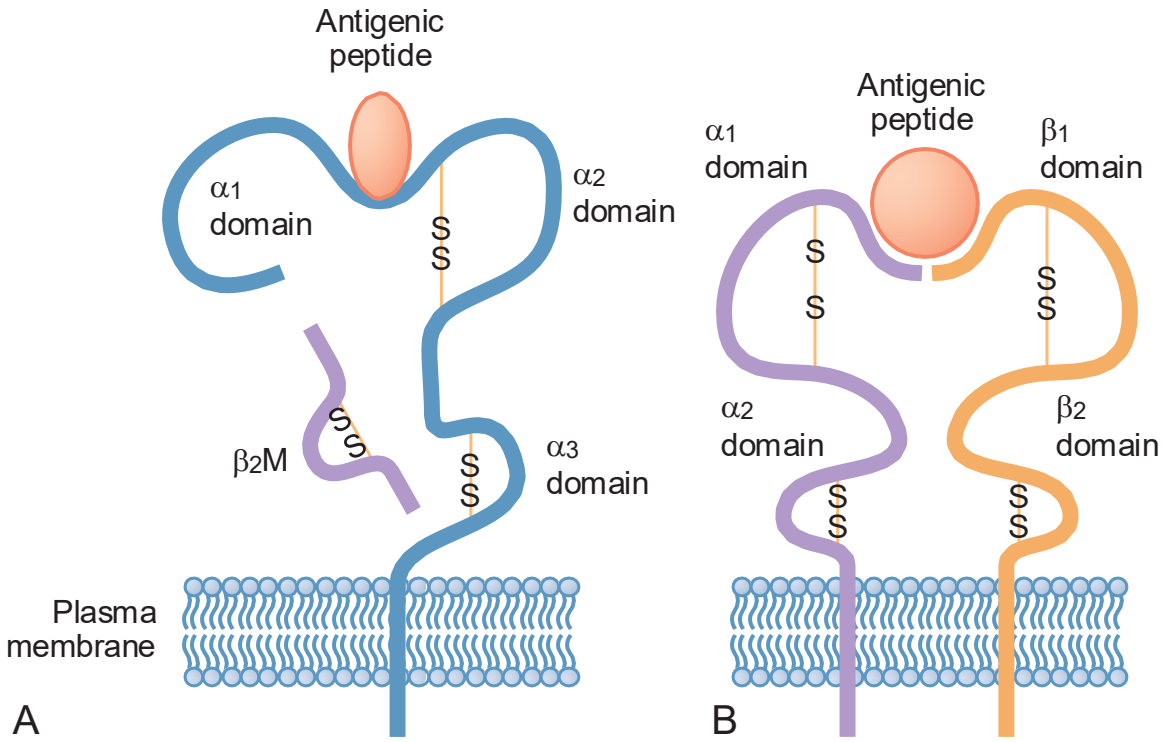


FIG 9-9 **A,** A class I major histocompatibility complex (MHC) molecule, showing the structure of the heavy chain, which consists of three extracellular domains (α_1, α_2, and α_3), a membrane- spanning domain, and a cytoplasmic domain. A groove formed by the α_1 and α_2 domains carries antigen peptide for presentation to T-cell receptors. The α_3 domain associates closely with the β_2- microglobulin (β_2M) chain. **B,** A class Ⅱ MHC molecule, showing the structure of the α and β chains. Each has two globular extracellular domains, a membrane-spanning domain, and a cyto- plasmic domain. The α_1 and β_1 domains form a groove into which peptide nestles for presentation to T-cell receptors. (Modified from McCance KL, Huether SE. *Pathophysiology: the Biologic Basis for Disease in Adults and Children*. 7th ed. St. Louis: Elsevier; 2014:234.)

- The class I molecules were first discovered in the 1940s by scientists who were experimenting with tissue grafts in mice.

- When the class I alleles in donor and recipient mice differed, the grafts were rejected. This is the historical basis for the term ***major histocompatibility complex, that determines whether to accept or reject the foreign tissues or cells.***

- In humans, matching of the donor's and recipient's class I alleles increases the probability of graft acceptance or transplant tolerance.

- Because grafts and transplants are a relatively new phenomenon in human history, the MHC obviously did not evolve to effect transplant rejection (compatibility testing). Instead, T cells, when confronted with foreign MHC molecules on donor cells, interpret these as foreign peptides and attack the cells.

- The major function of the MHC is to help the immune system distinguish self from non-self. This allows T cells to recognize and attack non-self (foreign) cells and ignore the body's own healthy cells.

- Whereas the class I MHC molecules are found on the surfaces of nearly all cells and can bind with cytotoxic T-cell receptors, the class II MHC molecules ordinarily are found only on the surfaces of the immune system's APCs (phagocytic cells: macrophages, dendritic cells and B lymphocytes).

- When associated with foreign peptides, they stimulate helper T cell activity after binding to the T cells' receptors, as described previously.

- The class II molecules are heterodimers consisting of an α and a β chain similar to each other, each of which is encoded by a different gene located on chromosome 6 (see Fig. 9-9B).

- In addition to the genes in the major class II groups *(HLA-DP, -DQ,* and *-DR),* this region includes genes that encode peptide transporter proteins *(TAP1* and *TAP2)* that help to transport peptides into the endoplasmic reticulum, where they initially form complexes with class I molecules before migrating to the cell surface.

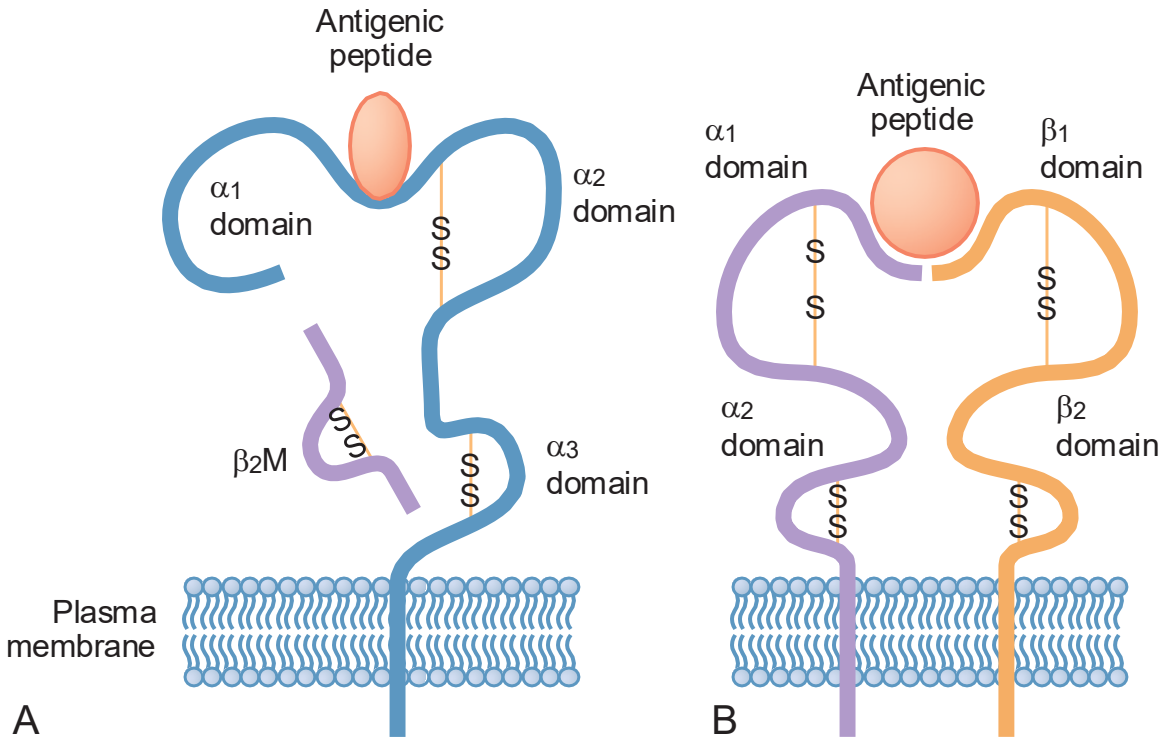


FIG 9-9 A, A class I major histocompatibility complex (MHC) molecule, showing the structure of the heavy chain, which consists of three extracellular domains (α_1, α_2, and α_3), a membrane- spanning domain, and a cytoplasmic domain. A groove formed by the α_1 and α_2 domains carries peptide for presentation to T-cell receptors. The α_3 domain associates closely with the β_2- microglobulin (β_2M) chain. **B,** A class II MHC molecule, showing the structure of the α and β chains. Each has two globular extracellular domains, a membrane-spanning domain, and a cyto- plasmic domain. The α_1 and β_1 domains form a groove into which peptide nestles for presentation to T-cell receptors. (Modified from McCance KL, Huether SE. *Pathophysiology: the Biologic Basis for Disease in Adults and Children*. 7th ed. St. Louis: Elsevier; 2014:234.)

- Like the major class I MHC loci, the major class II loci are highly polymorphic, expressing hundreds of different alleles. Indeed, the MHC loci are, as a class, the most polymorphic loci known in humans, It is rare for two individuals to have an identical MHC, except in the case of identical twins.

- Each MHC allele encodes a molecule with slightly different binding properties: some variants bind peptide from a given pathogen more effectively than others do. Consequently, a person who expresses a greater variety of MHC molecules has a better chance of dealing effectively with diverse infectious organisms.

- For example, someone who is homozygous for each of the major class I loci *(A, B,* and *C) (here we are referring to one molecule, because there are many of them)* expresses only three different class I MHC molecules in each cell, whereas someone who is heterozygous for each of these loci expresses six different class I MHC molecules in each cell (two chromosomes and each carries two different alleles) and can cope more successfully with pathogenic diversity (many thousands of MHC molecules are expressed on a typical cell's surface).
- More variability allows for better dealing with infectious pathogens.

- A higher degree of polymorphism in the general population increases the chance that any individual in the population is heterozygous.

- For example, HIV- infected persons who are heterozygous for the *HLA-A, HLA-B,* and/or *HLA-C* loci have longer survival times than those who are homozygous at these loci.

- In addition, greater MHC polymorphism in a population decreases the chance that an infectious pathogen can spread easily through the population. Thus, the high degree of polymorphism in MHC genes is thought to be the result of natural selection for allelic variation.

- In some cases, specific MHC alleles are known to produce proteins that are effective against specific pathogens. For example, the *HLA-B53* allele was shown to have a strong protective effect against severe malaria in the population of Gambia, and the *HLA-DRB1*13:02* allele protects against hepatitis B infection in the same population. These alleles produce MHC molecules that have higher-affinity binding of the infectious agents.

- Both class I and class II MHC molecules guide T-cell receptors (cytotoxic and helper, respectively) to specific cells.

- T-cell receptors recognize peptides only in combination with MHC molecules on cell surfaces, a phenomenon known as **MHC restriction.** Not all components of the immune system are MHC restricted.

- For foreign material to be recognized by a T cell, it must be presented on the cell surface bound to MHC molecules.

- Some virus-infected cells and tumor cells take advantage of MHC restriction: they suppress the expression of MHC molecules on their surfaces in an attempt to evade detection by T cells.
- Fortunately, natural killer cells (natural innate immunity) are activated by the absence, rather than the presence, of MHC molecules on cell surfaces and they are able to kill them. This activation is mediated by an important and diverse family of receptors found on the surfaces of natural killer cells, **killer cell immunoglobulin-like receptors (KIR).**

- These receptors inhibit natural killer cells when they bind to MHC class I molecules on the surfaces of normal cells but activate them when MHC class I molecules are absent.

- The class III MHC region spans 680 kb and contains at least 36 genes (less variable than others), only some of which are involved in the immune response. Among the most important of these are the genes encoding the complement proteins, which are part of the innate immune system. These proteins associate with infectious agents that attach to infected cells, allowing them to be recognized by phagocytic cells facilitating phagocytosis.

- The genes encoding the immunoglobulins, the T-cell receptors, KIR, and the class I and class II MHC proteins all share similar DNA sequences and structural features. Thus, they are members of a gene family, like the globin genes, the color vision genes, and the collagen genes.

- It is important to emphasize that the class I and class II MHC molecules differ greatly *among* individuals, but each cell within an individual has the same class I and class II molecules (this uniformity is necessary for recognition by T cells).
- In contrast, after VDJ recombination the T-cell receptors and immunoglobulins differ from cell to cell *within* individuals, allowing the body to respond to a large variety of different infectious agents.

You need to know the function of these genes, the exact location isn't required

TABLE 9-1 Chromosome Location and Function of Major Immune Response Genes

GENE SYSTEM	CHROMOSOME LOCATION	GENE PRODUCT FUNCTION
Immunoglobulin heavy chain (*C*, *V*, *D*, and *J* genes)	14q32	Heavy chain, the first part of antibody molecule, which binds foreign antigens
Immunoglobulin κ light chain (*C*, *V*, and *J* genes)	2p13	Light chain, the second part of antibody molecule
Immunoglobulin λ light chain (*C*, *V*, and *J* genes)	22q11	Light chain, the second part of antibody molecule (either κ or λ may be used)
T-cell receptor α	14q11	One chain of the α-β T-cell receptor, which recognizes antigen with MHC molecule
T-cell receptor β	7q35	The second chain of the α-β T-cell receptor
T-cell receptor γ	7p15	One chain of the γ-δ T-cell receptor
T-cell receptor δ	14q11	The second chain of the γ-δ T-cell receptor
MHC (classes I, II, and III); includes *TAP1* and *TAP2*	6p21	Cell-surface molecules that present peptides to T-cell receptors. *TAP1* and *TAP2* are transporter molecules that process foreign peptides and carry them to the endoplasmic reticulum.
β_2-microglobulin	15q21-22	Forms second chain of the class I MHC molecule
RAG1, *RAG2*	11p13	Recombinases that participate in VDJ somatic recombination

- 90% of T cell receptors are heterodimers composed of alpha and beta chains. The remaining 10% consist of gamma and delta chains.
- All classes of MHC (1,2 and 3) are encoded by genes on chr 6.
- Beta2-microglobulin is associated with the heavy chain of MHC class I.

MHC and Disease Associations

- A number of diseases show significant associations with specific MHC alleles: persons who have the allele are much more likely to develop the disease than are those who lack it.

- Some examples, include the association of *HLA-B27* (i.e., allele 27 of the *HLA-B* locus) with ankylosing spondylitis and of *HLA-DQB1* with type 1 diabetes.

- An especially strong association is seen between several *HLA-DR* and *-DQ* alleles and narcolepsy, a disorder charac- terized by sudden and uncontrollable episodes of sleep.

- As Table 9-2 shows, most of the HLA–disease associations involve the class II MHC genes.
- MHC genes are associated with certain diseases.
- For example, the hemochromatosis locus has a strong association with the HLA-A3 allele, meaning that a person who carries this allele has a higher risk of developing hereditary hemochromatosis.
- Similarly, HLA-DQB1 and HLA-DQA1 alleles are associated with narcolepsy.
- These genetic associations are useful in population statistics to help predict an individual's risk of developing certain diseases.

The doctor read all the MHC associated loci

TABLE 9-2 Examples of Major Histocompatibility Complex and Disease Associations

DISEASE	MHC (HLA) ASSOCIATED LOCUS (LOCI)*	APPROXIMATE RELATIVE RISK†
Type 1 diabetes	DQB1, DQA1	10
Ankylosing spondylitis	B27	90
Narcolepsy	DR2 and DQA1, DQB1	>100
Celiac disease	DQA1, DQB1	10
Rheumatoid arthritis	DRB1, DQA1	5
Myasthenia gravis	C, DR3, DR7	2.5
Multiple sclerosis	DRB1	4
Systemic lupus erythematosus	DRB1	6
Hemochromatosis	A3	20
Malaria	B53	0.6059
Graves disease	DR3	5
Psoriasis	C	13
Abacavir (anti-HIV drug) hypersensitivity	B57	≈1000

*For simplicity, specific alleles are not shown here. For example, the *HLA-B57* allele associated with abacavir sensitivity is labeled *HLA-B*57:01*, and the allele associated with psoriasis is *HLA-C*06:02*.

†Relative risk can be interpreted loosely as the odds that a person who has a risk factor (in this case, an MHC antigen) will develop the disease, compared with a person who lacks the risk factor.

Thus, a relative risk of 4 for *DRB1* and multiple sclerosis means that persons with a specific *DRB1* allele are four times more likely to develop multiple sclerosis than are those without it. A relative risk <1 (as seen for malaria and *B53*) indicates that the factor is protective against the disease. These relative risks can vary among different human population groups.

- Some MHC–disease associations involve **autoimmunity,** in which the body's immune system attacks its own normal cells (as we have mentioned previously, during T cells maturation in the thymus, they will be trained not to attack the body's own cells, if this process failed, the T cell will attack the body cells).
- For example, type 1 diabetes is characterized by T-cell infiltration of the pancreas and subsequent T-cell destruction of the insulin-producing beta cells.

- In some cases, autoimmunity involves "molecular mimicry." Here, a peptide that stimulates an immune response is so similar to the body's own peptides that the immune system begins to attack the body's own cells. This phenomenon helps to explain the onset of ankylosing spondylitis, another autoimmune disease.

- Infections of *HLA-B27* –positive persons with specific microbes, such as *Klebsiella,* can lead to a **cross-reaction** in which the immune system mistakes peptides from some of the body's normal cells for microbial peptides.
- Another such example is given by rheumatic fever, in which a streptococcal infection initiates cross- reactivity between streptococcus and cardiac myosin.

- In each of these scenarios, the body already has a small population of self-reactive T cells, but they remain inactive and quite harmless until they are stimulated to proliferate by a foreign peptide that closely resembles a self peptide.

- Autoimmunity can also be caused by specific defects in the regulation of immune system components.

- For example, regulatory T cells help to prevent the formation of self-reactive immune cells and protect body cells from destruction and require a transcription factor, encoded by *FOXP3,* for their normal development.
- Mutations in *FOXP3* which encodes the proteins needed for T cells function result in a deficiency of regulatory T cells and an autoimmune disease called *IPEX* (*i*mmunodysregulation, *p*olyendocrinopathy, *e*nteropathy, *X* linked).

- Other common diseases that involve autoimmunity include rheumatoid arthritis, systemic lupus erythematosus, psoriasis, and multiple sclerosis.
- It is estimated that approximately 5% of the population suffers from some type of autoimmune disease.

The next topics are very easy, we will talk about ABO blood groups, RH system and the incompatibility between the different blood groups, meaning that if someone receives an inappropriate blood type for his blood group, what would be the immune response of his body to it?

The ABO and Rh Blood Groups

The ABO System

- There are four major ABO blood types: A, B, AB, and O.(which depends on the existence of the antigens A,B, both or none on the surface of the RBCs)

- The first three groups respectively represent persons who carry the A, B, or A and B antigens on their erythrocyte surfaces.
- Those with type O have neither the A nor the B antigen.

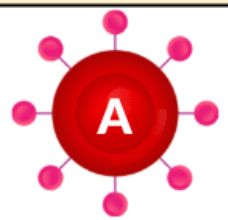
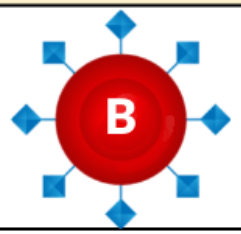
- Persons who have one of these antigens on their erythrocyte surfaces possess antibodies against all other ABO antigens in their blood stream.
- These antibodies are formed early in life as a result of exposure to antigens that are identical to the A and B antigens but are present in various microorganisms(so for example, the human who has A antigens on his RBCs will form antiB antibodies that are expressed by the microorganisms in his body).

- If a type B person received type A or AB blood, his or her anti-A antibodies would produce a severe and possibly fatal reaction.

- Type O persons, who have neither the A nor the B antigen and thus both anti-A and anti-B antibodies, would react strongly to blood of the other three types (A, B, and AB).
- It was once thought that type O persons, because they lack both types of antigens, could be "universal donors" (anyone could accept their blood).

- Similarly, type AB persons were termed "universal recipients" because they lacked both anti-A and anti-B antibodies.
- However, when patients are given transfusions of whole blood containing large volumes of serum, the donor's antibodies can react against the recipient's erythrocyte antigens. Hence, complete ABO matching is nearly always done for blood transfusions.(usually we give only RBC transfusions without the plasma, but if we need to give whole blood (RBCs and plasma) we should be careful that the donor doesn't have antibodies in his plasma against the recipient RBCs)

Extra picture

ABO BLOOD GROUPS	Blood Group A	Blood Group B	Blood Group AB	Blood Group O
RBC Type				
Anitbodies in plasma	 Anti-B	 Anti-A	NONE	 Anti-B Anti-A
Anitgens in RBCs	 Antigen A	 Antigen B	 Antigen A Antigen B	NONE

The Rh System

- The Rh blood group is encoded by two tightly linked loci, one of which is labeled *D.* The other locus produces Rh antigens labeled *C (C, c)* and *E(E,e)* through alternative splicing of the messenger RNA.

- The *D* locus is of primary interest because it is responsible for Rh maternal–fetal incompatibility and the resulting disease, hemolytic disease of the newborn (HDN).
- Persons with the *DD* or *Dd* genotype have the Rh antigen on their erythrocytes and are Rh-positive. The recessive homozygotes, with genotype *dd,* are Rh-negative and do not have the Rh antigen. About 85% of persons of European ancestry are Rh-positive and about 15% are Rh-negative.

- Unlike the ABO system, in which antibodies normally are formed in response to antigens presented by other organisms, anti-Rh antibody production requires a stimulus by the human Rh antigen itself.
- An Rh-negative person does not begin to produce anti-Rh antibodies unless he or she is exposed to the Rh antigen, usually through a blood transfusion or during pregnancy.

- There are usually no difficulties with the first Rh-incompatible child, because very few of the fetus's red blood cells cross the placental barrier during gestation. When the placenta detaches at birth, a large number of fetal red blood cells typically enter the mother's blood stream. These cells, carrying the Rh antigens, stimulate production of anti-Rh antibodies by the mother.

- These antibodies persist in the blood stream for a long time, and if the next offspring is again Rh-positive, the mother's anti-Rh antibodies enter the fetus's bloodstream and destroy its red blood cells. As this destruction proceeds, the fetus becomes anemic and begins to release many erythroblasts (immature nucleated red cells) into its blood stream. This phenomenon is responsible for the descriptive term *erythroblastosis fetalis*. The anemia can lead to a spontaneous abortion or stillbirth.

- Because the maternal antibodies remain in the newborn's circulatory system, destruction of red cells can continue in the neonate. This causes a buildup of bilirubin and a jaundiced appearance shortly after birth. Without replacement transfusions, in which the child receives Rh-negative red cells, the bilirubin is deposited in the brain, producing cerebral damage and usually death. Infants who do not die can develop intellectual disability, cerebral palsy, and/or high-frequency deafness.

- Among persons of European descent, approximately 13% of all matings are Rh-incompatible (it is very important to be considered).

- A simple therapy now exists to avoid Rh sensitization of the mother. During and after pregnancy, an Rh-negative mother is given injections of Rh immune globulin, which consists of anti-Rh antibodies. These antibodies destroy the fetal erythrocytes in the mother's blood stream before they stimulate production of maternal anti-Rh antibodies.

- Because the injected antibodies do not remain in the mother's blood stream for long, they do not affect subsequent offspring. To avoid sensitization, these injections must be administered with each pregnancy (every time the mother gets pregnant, we should give her an injection again).
- The Rh-negative mother must also be careful not to receive a transfusion containing Rh-positive blood, because this would also stimulate production of anti-Rh antibodies.

- A rarer form of maternal–fetal incompatibility can result when a mother with type O blood carries a fetus with type A or B blood. (When a small amount of anti-A or anti-B are of the IgG class, as IgG has the ability to cross the placenta and reach the fetus blood causing a mild destruction)

- The hemolytic disease produced by this combination is usually so mild that it does not require treatment.

- Interestingly, if the mother is also Rh-negative and the child is Rh-positive, the ABO incompatibility *protects* against the more severe Rh incompatibility.
- This is because any fetal red blood cells entering the mother's circulatory system are quickly destroyed by her anti-A or anti-B antibodies before she can form anti-Rh antibodies.

IMMUNODEFICIENCY DISEASES

- **Immunodeficiency disease** results when one or more components of the immune system (e.g., T cells, B cells, MHC, complement proteins) are missing or fail to function normally (that means the body has congenital loss of the genes which produce one type or more of these cells or one of their components).

- **Primary immunodeficiency diseases** are caused by abnormalities in cells of the immune system and are usually produced by genetic alterations. To date, more than 100 different primary immunodeficiency syndromes have been described, and it is estimated that these diseases affect at least 1 in 10,000 persons.

- **Secondary immunodeficiency** occurs when components of the immune system are altered or destroyed by other factors, such as radiation, infection, or drugs.
- For example, the human immunodeficiency virus (HIV), which causes acquired immunodeficiency syndrome (AIDS), attacks macrophages and helper T lymphocytes, central components of the immune system. The result is increased susceptibility to a multitude of opportunistic infections.

- B-cell immunodeficiency diseases render the patient especially susceptible to recurrent bacterial infections, such as *Streptococcus pneumoniae.*

- An important example of a B-cell immunodeficiency is X-linked agammaglobulinemia (XLA). Patients with this disorder, the overwhelming majority of whom are male, lack B cells completely and have no IgA, IgE, IgM, or IgD in their serum.

- Because IgG crosses the placenta during pregnancy, infants with XLA have some degree of humoral immunity for the first several months of life. However, the IgG supply is soon depleted, and the infants develop recurrent bacterial infections. They are treated with large amounts of γ-globulin.
- XLA is caused by mutations in a gene *(BTK)*(Bruton's tyrosine kinase) that encodes a B-cell tyrosine kinase necessary for normal B-cell maturation(so this mutation will affect B cells maturation).

- Mutations in the genes that encode the immunoglobulin heavy and light chains can cause a form of autosomal recessive B-cell immunodeficiency.

- T-cell immunodeficiency diseases directly affect T cells, but they also affect the humoral immune response, because B-cell proliferation largely depends on helper T cells. Thus, in the most severe T-cell defects, affected patients develop severe combined immune deficiency (SCID). Without bone marrow transplants, these patients usually die within the first several years of life.(because B cells function rely on T helper cells, loss of T helper cells will affect B cells)

- About half of SCID cases are caused by X-linked recessive mutations in a gene that encodes the γ chain found in six different cytokine receptors (those of interleukins 2, 4, 7, 9, 15, and 21). Lacking these receptors, T cells and natural killer cells cannot receive the signals they need for normal maturation.
- These receptors all interact with an intracellular signaling molecule called Jak3(which is a kinase enzyme). Persons who lack Jak3 as a result of autosomal recessive mutations in the *JAK3* gene experience a form of SCID that is very similar to the X-linked form.
- Mutations that lead to the absence of these cytokines receptors or mutations that lead to the absence of Jak3 singling molecule —> SCID

- About 15% of SCID cases are caused by adenosine deaminase (ADA) deficiency, an autosomal recessive disorder of purine metabolism that results in a buildup of metabolites that are toxic to B and T cells. This type of SCID, as well as the X-linked form, can be treated by bone marrow transplantation, and some cases are being treated successfully with gene therapy.

- SCID can also arise from mutations in *RAG1* or *RAG2*, two of the genes involved in VDJ recombination and the proper formation of T-cell and B-cell receptors. These mutations produce a combined B-cell and T-cell immunodeficiency, although normal natural killer cells are produced.

- Several immune system defects result in lymphocytes that lack MHC molecules on their surfaces. These are collectively termed *bare lymphocyte syndrome* (lymphocytes without MHC), one form of which is caused by mutations in the *TAP2* gene.
- *TAP2* encodes a protein that helps to transport peptides to the endoplasmic reticulum, where they are bound by class I MHC molecules. A defect in the TAP2 protein destabilizes the class I MHC molecules so that they are not expressed on the cell surface.

- Because exposure to MHC molecules is necessary for normal T-cell development in the thymus, bare lymphocyte syndrome results in a severe reduction in the number of functional T and B cells. Bare lymphocyte syndrome can also be caused by defects in several different transcription factors that bind to promoters in the class II MHC region. The result is a lack of class II MHC molecules on APCs, a deficiency of helper T cells, and a consequent lack of antibody production. (So at the end, any loss of an immune system element would cause several immune problems)

- Chronic granulomatous disease (CGD) is a primary immunodeficiency disorder in which phagocytes can ingest bacteria and fungi but are then unable to kill them.
- This brings about a persistent cellular immune response to the ingested microbes, resulting in the formation of the granulomas (nodular inflammatory lesions containing macrophages) for which the disease is named. These patients develop pneumonia, lymph node infections, and abscesses in the skin, liver, and other sites.

- The most common cause of CGD is an X-linked mutation, but there are also at least three autosomal recessive genes that can cause CGD. The gene that causes X-linked CGD encodes a subunit of cytochrome b, a protein that the phagocyte requires for a burst of microbe-killing oxygen metabolism.

- Multiple defects in the various proteins that make up the complement system have been identified. Most of these are inherited as autosomal recessive disorders, and most result in increased susceptibility to bacterial infections.

- Finally, a number of syndromes include immunodeficiency as one of their features.

- One example is the DiGeorge sequence (caused by deletion of the long arm of chr 22) , in which a lack of thymic development leads to T-cell deficiency.

- Wiskott-Aldrich syndrome is an X-linked recessive disorder that involves deficiencies of platelets and progressive T-cell dysfunction. It is caused by loss-of-function mutations in a gene *(WAS)* whose protein product is expressed in hematopoietic cells, where it relays signals from the cell surface to the cytoskeleton. Wiskott-Aldrich syndrome, like SCID, has been successfully treated with gene therapy.

- Immunodeficiency is also seen in several syndromes that involve DNA instability (e.g., ataxia telangiectasia, Bloom syndrome, Fanconi anemia).

This table is for revision, you are required to know the ones that were mentioned in the lecture only

TABLE 9-3 Examples of Primary Immunodeficiency Diseases

CONDITION	MODE OF INHERITANCE	BRIEF DESCRIPTION
X-linked agammaglobulinemia	XR	Absence of B cells leads to recurrent bacterial infections
SCID (γ chain cytokine receptor defect or ADA deficiency)	XR, AR	T-cell deficiency leading also to impairment of humoral immune response; fatal unless treated by bone marrow transplantation or gene therapy
SCID due to Jak3 deficiency	AR	Protein kinase deficiency leading to T-cell deficiency, NK cell deficiency, and impaired humoral immune response.
SCID (also Omenn syndrome) due to *RAG1* or *RAG2* deficiency	AR	Lack of recombinase activity impairs VDJ recombination, which leads to B-cell and T-cell deficiency
SCID due to interleukin-7 α chain deficiency	AR	T-cell deficiency leading to impaired B-cell response
Zap70 kinase deficiency	AR	Lack of cytotoxic T cells; defective helper T cells; impaired antibody response
Purine nucleoside phosphorylase deficiency	AR	Purine metabolism disorder leading to T-cell deficiency
Bare lymphocyte syndrome (BLS)	AR	Deficient MHC class I expression (*TAP2* mutation) leads to T-cell and B-cell deficiency in type 1 BLS; mutations in transcription factors for MHC class II genes lead to a relative lack of helper T cells in type 2 BLS
Complement system defects	Mostly AR	Increased susceptibility to bacterial and other infections
DiGeorge anomaly	AD, sporadic	Congenital malformations include abnormal facial features, congenital heart disease, and thymus abnormality leading to T-cell deficiency
Ataxia telangiectasia	AR	DNA repair defect characterized by unsteady gait (ataxia), telangiectasia (dilated capillaries), and thymus abnormality producing T-cell deficiency
Wiskott-Aldrich syndrome	XR	Abnormal, small platelets, eczema, and abnormal T cells causing susceptibility to opportunistic infections
Chediak-Higashi syndrome	AR	Partial albinism, defective lysosomal assembly, giant cytoplasmic granules, abnormal natural killer cells, and neutrophils leading to recurrent bacterial infections
Leukocyte adhesion deficiency	AR	Mutations in integrin receptor genes produce phagocytes that cannot recognize and ingest microorganisms, which results in severe bacterial infections
Chronic granulomatous disease	XR, AR	Phagocytes ingest microbes but cannot kill them; leads to formation of granulomas and recurrent infections
Hyper IgE syndrome	AD, AR	Recurrent staphylococcal infections, markedly elevated serum IgE levels, progressively coarse facial features
IRAK-4 deficiency		Toll-like receptor defect caused by deficiency of interleukin-1 receptor associated kinase-4 (IRAK-4), resulting in extracellular bacterial (especially *Streptococcus pneumoniae*) infections.

AD, Autosomal dominant; *AR*, autosomal recessive; *SCID*, severe combined immune deficiency; *XR*, X-linked recessive.

وصلت لهون؟ انت يا مبدع أنهيت في قريب الأسبوع:
- 37 محاضرة UGS
- 12 محاضرة ريسيرتش
- 6 محاضرات جينتكس
هاانت🔥🔥، بس ردّد معي:
اللهم إنّي أسألك علمًا نافعًا.. ورزقًا طيبًا.. وعملًا متقبلًا..

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!