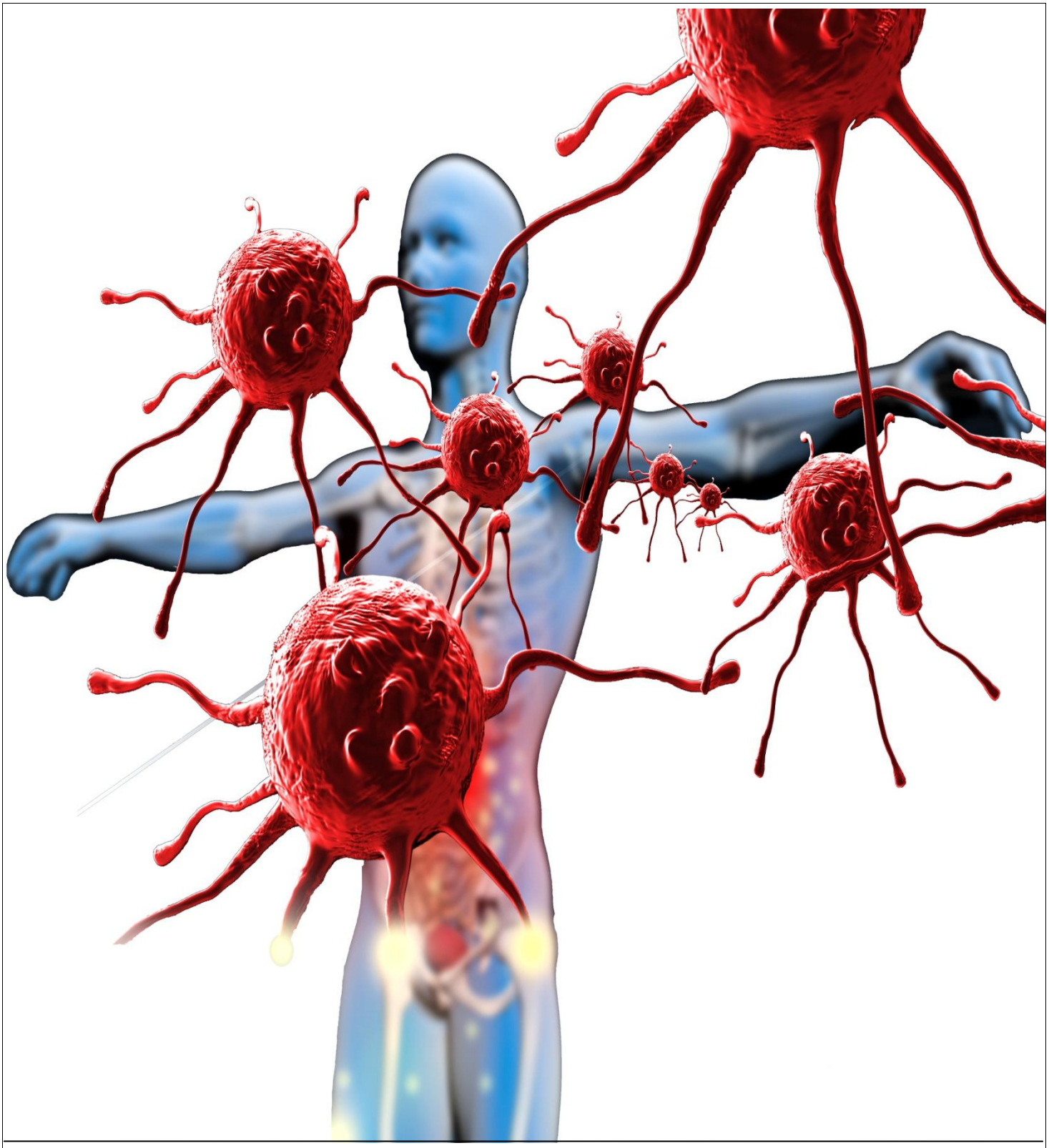


IMMUNOLOGY

Done By: Doa'a S. Dahboor

Dr. Hassan Abu Al-Ragheb

#14

By Mohammed Nawasreh

(وَأَنْ لَيْسَ لِلْإِنْسَانِ إِلَّا مَا سَعَى * وَأَنَّ سَعْيَهُ سَوْفَ يُرَى)

AUTOIMMUNITY

** Before we start ;

Correction :

The doctor corrected a piece of information mentioned in the last lecture : Mutations in some genes like AIRE and FOXP3 lead to lack of suppression of the immune response which results in autoimmune diseases . Mutation in AIRE gene results in APS (Autoimmune polyendocrinopathy Syndrome) and not IPEX as mentioned in the previous lecture . Indeed , IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked syndrome) is a result of mutation in FOXP3 i.e. an abnormality in regulatory T cells .

One note about B cell regulation / tolerance :

A) Central tolerance : In bone marrow

At an early stage of B cell development (at the stage of immature B cell) , if the B cell encounters its respective antigen , one of the following will happen :

** The cell dies by apoptosis .

** Anergy .

** Receptor editing : Re-assembly of the BCR gene, this might give BCRs that are not self-reactive .

** Immunological ignorance of the antigen .

B) Peripheral tolerance : In peripheral tissues

For T-dependent antigens , tolerance is mainly due to lack of the help from T-helper cells . In this case , B cells cannot respond properly to the antigen since T cells are needed for that purpose .

For T-independent antigens , tolerance develops but the mechanism is not accurately known !

Now let's start discussing this lecture's topic : AUTOIMMUNITY ☺

Written by Doa'a S. Dahboor

** Natural autoantibodies :

All people do have autoantibodies in their bodies . So the phenomenon of having autoantibodies is actually a common feature that NORMALLY occurs . These natural autoantibodies are mainly of the **IgM variety** and they have **low affinity .** Because of these two features , natural autoantibodies don't give rise to pathologic conditions .

What's the significance (function) of these autoantibodies ?

Indeed , the exact function of these immunoglobulins is not well understood . One possible function of them is to get rid of your broken down antigens (e.g. debris from dead cells) . Natural autoantibodies clear these antigens from your circulation .

Another explanation of the presence of natural autoantibodies is to take part (give the head start) in innate (natural) immunity since they are NATURALLY present in our bodies. Natural autoantibodies may be useful against some pathogens like bacteria although they are originally made against our own antigens.

One suggested mechanism by which natural autoantibodies " fight " bacteria is blocking bacterial epitopes : Suppose that you have an autoantibody against X antigen which is naturally present in your body . If your body was invaded by a kind of bacteria that has X1 antigen on its surface which is very similar to your own X antigens , your (against X-autoantibodies) may block the bacterial X1 epitope due to its similarity to your own X antigen . Masking the bacterial epitope means that it's not visible anymore to your immune system components and thus no proper immune reaction occurs (i.e. your body will not produce antibodies against X1 since it's masked . This is protective for you because antibodies against X1 may attack your X antigen due to their similarity) . This mechanism can be considered a third explanation of the presence of natural autoantibodies .

The last explanation : As you know , auto-reactive B cells become apoptotic (die) or anergic . These apoptotic or anergic B cells release the receptors on their surfaces as they undergo apoptosis or anergy . These surface receptors are IgM antibodies and they are the normal autoantibodies we talked about . So the origin of normal autoantibodies is the cell surface receptors on auto-reactive B cells that have broken down due to apoptosis or anergy .

In a nutshell :

It's normal to have autoantibodies that possibly play a role in the immune response . These normal autoantibodies are of the IgM variety and have a low affinity thus they're not causative agents of autoimmune diseases .

Now let's discuss the autoantibodies that are involved in the pathogenesis of autoimmune diseases :

These PATHOLOGIC autoantibodies are of the **IgG variety** . They have **high affinity** and thus they are causative agents of autoimmune diseases that are really problematic ☹

Why do people get these pathologic autoantibodies ? The reason behind getting these autoantibodies is not fully understood . Nevertheless , autoimmune diseases are considered quite common , they are widespread in their spectrum .

** The doctor emphasizes that the immune response in autoimmune diseases is a typical immune response i.e. the way of initiation of the immune response in case of autoimmunity is the same as initiation of any immune response against any foreign antigen (e.g. bacteria). The only difference here is that the antigen is a self-antigen . Keep in mind that the normal IgM autoantibodies we talked about are made by CD5+ auto-reactive B cells .These IgM antibodies don't transform into IgG in normal conditions . They are not pathologic , they probably help our immune system do its job . Autoimmune reaction in autoimmune diseases is carried out by IgG molecules that are gotten from abnormal pathologic transformation of IgM antibodies .

** On one hand , an autoimmune disease may affect one organ only , i.e. the disease is SPECIFIC to that organ . Example : Pernicious anemia (Megaloblastic anemia) is a result of vitamin B12 deficiency . This deficiency is mainly due to decreased absorption of the vitamin . Absorption of vitamin B12 requires an intrinsic factor produced by the parietal cells of the stomach (The doctor said in the GIT but to be more precise and since we're talking about organ specificity it's in the stomach) . People with this disease develop autoantibodies against the intrinsic factor or against the gastric parietal cells that produce it .

** On the other hand . an autoimmune disease may involve a wide variety (wide spectrum) of autoantibodies that are directed against many antigens (e.g. anti-DNA , anti-platelets , ... , etc.) in many organs (e.g. skin , kidney , joints , blood , etc.). This is known as MULTI-ORGAN SYSTEMIC DISEASE . Example : SLE (Systemic Lupus Erythematosus) .

In between these two categories , there are some autoimmune diseases that affect 2 or 3 organs only (spectrum is limited to 2 or 3 organs unlike multi-organ systemic diseases that affect WIDER spectrum of organs by TOO MANY types of autoantibodies).

** Causes of autoimmunity :

1) Genetics : Remember when we talked about MHC molecules , we said that certain MHC alleles are associated with certain autoimmune diseases . Look at this table : (The doctor mentioned most of the (gene – allele) associations in the table , so I recommend memorizing them)

Disease	HLA allele	Relative risk*
Rheumatoid arthritis	DR4	4
Insulin-dependent diabetes mellitus	DR3 DR4 DR3/DR4 heterozygote	5 5–6 25
Multiple sclerosis	DR2	4
Systemic lupus erythematosus	DR2/DR3	5
Pemphigus vulgaris	DR4	14
Ankylosing spondylitis	B27	90–100

One possible - but not proved - explanation of this association is that these MHC alleles have something wrong that makes the MHC molecules present self-antigens in an abnormal way during the process of antigen presentation . The reason behind the doubt regarding this explanation is that it's true that high percentage of people who have the disease have the related HLA allele in their genome. On the other hand , not everybody with one of these alleles develops the corresponding disease . Example : High percentage of people with ankylosing spondylitis have B27 allele , but also you can find people with B27 allele who did not develop ankylosing spondylitis . So the relation is not fully understood and accordingly the mechanism by which this relation is caused is also not fully understood !

The problem could be caused by an abnormality in the MHC gene itself or in a related bad gene that lies near to MHC gene's locus and thus is inherited with it . This is known as linkage disequilibrium . So we can conclude that the association can be directly linked to the MHC molecule itself (the way it presents antigens by) or it could be linked to another nearby gene .

Wiki- :

Linkage disequilibrium is the non-random association of alleles at different loci i.e. the presence of statistical associations between alleles at different loci .

Before discussing genetic probabilities let's define the " concordance " :

Concordance : the probability that a pair of individuals will both have a certain characteristic, given that one of the pair has the characteristic. (wiki- definition)

✍ Monozygotic (identical) twins : If one of them has an autoimmune disease , the likelihood of the other one having the disease is 50% (concordance is 50% in this case , not 100% as expected according to pure genetics) .

✍ Dizygotic (non-identical) twins : If one of them has an autoimmune disease , the likelihood of the other one having the disease is 5% (concordance = 5%) .

✍ Siblings who have identical HLA haplotypes : If one of them has an autoimmune disease , the likelihood of the other one having the disease is less than 5% (concordance < 5%) .

So you can conclude that there's genetic predisposition for the autoimmune diseases but it is not the only factor . Other factors are involved such as deficiency of components of the complement system (ex. : C1 , C2 , C4 , ... etc.) . When these factors are deficient , there will not be efficient clearance of the immune complexes and that contributes in the pathogenesis of some autoimmune diseases (immune-complex diseases) .

One experiment that illustrates the issue of genetic predisposition for autoimmune diseases was done on a special strain of white and black New Zealand mice . This strain of mice showed higher susceptibility to develop some autoimmune diseases.

2) Sex : Many autoimmune diseases are associated with female gender .Examples :
SLE → Ratio of women to men is 10 : 1

RA (Rheumatoid arthritis) → Ratio of women to men is 3-4 : 1

Autoimmune diseases related to thyroid gland (thyrotoxicosis , graves' disease , ..,etc.) are also more common in women . Ratio of women to men is around 8 : 1

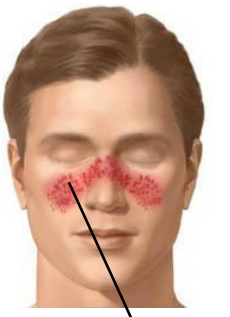
One possible explanation for this is that estrogen in females promotes synthesis of autoantibodies . Autoimmune diseases become worse in pregnancy so there must be a hormonal element that's related to the development of these autoimmune diseases .

The predominance of autoimmune diseases in women doesn't mean that men escape autoimmune diseases . Men can be affected by autoimmune diseases in general and in some diseases , they are affected more than women . Example :
Ankylosing spondylitis → Ratio of men to women is 10 : 1
Other autoimmune diseases affect males and females equally , ex : DM (diabetes).

3) Environment : Some environmental factors influence the development of autoimmune diseases . Example : In SLE , the most common manifestation is the appearance of (butterfly rash) on the face – See the picture . This manifestation is due to the breakdown of DNA in the areas exposed to sun (the face in our example) under the effect of UV light. This process is carried out by anti-DNA autoantibodies .

What's the problem with autoimmune diseases that makes them persistent ? Aren't they immune responses that should be terminated like any other immune response ?

Remember that a key factor for eliminating (turning off) immune reactions is the removal of the antigen ; once the antigen is removed , the immune response shuts down . In case of autoimmune diseases , the antigen can't be eliminated since it's SELF . It's present in the body all over the time . The patient is stuck with this self-antigen ☹ For example , in case of SLE , you can't get rid of the antigen which is your own DNA and thus the immune reaction persists.



Butterfly rash in SLE

** Goodpasture's disease : When antibodies against basement membrane's collagen of the kidney and pulmonary blood vessels are produced . This is common in people who work with solvents (certain chemicals) . It's suggested that when these solvents get into your body , they disrupt the collagen of the basement membrane , this exposes antigens that are not normally exposed to the immune system , the body reacts against these abnormally exposed antigens by producing antibodies against them .

** Rheumatoid Arthritis (RA) : The progression of this disease is affected by diet. Fish is beneficial for RA patients . By contrast , meat (if eaten in excess) worsens the condition . The mechanisms of these associations are not fully understood .

** Infections and microbes could be related to the progression of some autoimmune diseases . Example : Reactive arthritis is associated with chlamydia and salmonella infections . It's suggested that the infection caused by these pathogens promotes the presentation of self-antigens in an immunogenic form . This gives rise to certain immune diseases .

Again , it's suggested that the previously mentioned factors (including solvents , meat , ... , etc.) enhance the development of autoimmune diseases i.e. they're associated with autoimmune diseases by still unknown mechanisms . Keep in mind that the development of autoimmune diseases due to these factors' enhancement occurs only in a limited percentage of population who are exposed to them . Example : Not all people who work with solvents develop Goodpasture's disease , not every female develops SLE , not everyone who's exposed to UV light develops SLE (indeed DNA might be damaged / broken down by the sun after long exposure but the disease doesn't appear due to the absence of predisposition by other factors so the process is complicated and multi-factorial) ... , etc.

Notice that I used the word (enhance) and not (cause) since these factors are not direct causes of autoimmune diseases especially when other factors are involved . The only thing we are sure about is that they are RELATED to autoimmune diseases . These relations were proved statistically , however ; scientific evidence is still under research !

One more example that illustrates this : Based on statistical findings , left-handed people are more likely to develop autoimmune diseases . The reason behind that is not known !

**** Mechanisms by which autoimmunity is produced :**

1) Modification of auto-antigens : Some drugs may induce autoimmune hemolytic anemia or autoimmune thrombocytopenia . How does this occur ? The drug in this case works as a hapten , it attaches to RBCs' or platelets' surfaces . The combination of the drug and the cluster auto-antigen on the cell surface elicits an autoimmune response . The body starts producing autoantibodies against RBCs and platelets . When the patient stops taking the drug , it'll be cleared up from his body but nevertheless , it has contributed to an autoimmune phenomenon .

2) Polyclonal activation : In the previous lectures , we discussed the issue of polyclonal activation which is non-specific activation . Polyclonal non-specific activation of B cells is induced by LPS (lipopolysaccharides) . Super-antigens can activate T helper cells non-specifically . When you have an infection , you probably get exposed to LPS and super-antigens that may activate some of the auto-reactive cells during the process of non-specific activation . This leads to production of autoantibodies and thus autoimmunity arises . Previously in this sheet we said that infections play a role in autoimmunity . Polyclonal activation is one mechanism by which they do so .

3) Molecular mimicry : (mimicry = مُحاكاة ، تقليد)

The best example is rheumatic fever : Infection by streptococcus pyogenes leads to production of antibodies against bacterial M antigens . These antibodies cross-react with cardiac antigens in some people (may be due to some kind of similarity between bacterial M antigen and these cardiac antigens), now we can call them autoantibodies . These autoantibodies attack the endocardium and more significantly the heart valves producing rheumatic fever . The heart is not the only affected organ , other organs like the joints and the skin may be affected . The disease becomes exacerbated after throat infections because in these infections more M protein is available in the body and thus there'll be more anti-M antibodies that attack the heart valves and damage them extensively . People with this disease must be given prophylactic penicillin until the age of twenty to prevent recurrence of streptococcus pyogenes attacks that worsen their condition .

4) Loss (breakdown)of sequestration : We discussed this in the previous lecture. There are places in the body that have immune privilege (ex. : lens , testes , brain , ... , etc.) . Injury to these areas with loss of the immune privilege (i.e. the barrier has been broken down and thus self-antigens are exposed) results in an autoimmune reaction .

For clarification : It was originally believed that antigens in immune-privileged sites are concealed from the immune system by physical barriers and therefore ignored .

5) Loss of suppression : Suppressor (regulatory) T cells are very important in the prevention of autoimmune diseases and excessive immune reactions toward foreign antigens . We mentioned 2 examples at the beginning of this sheet :
Example 1 : Mutation of FOXP3 (marker of regulatory T cells) →loss of regulatory T cells' function → autoimmunity (IPEX) .

Example 2 : Mutation of AIRE gene (autoimmune regulator) →autoimmunity (APS) .

** All people are prone to autoimmune diseases if their immune system gets "tired" to the extent it doesn't perform its function properly . This is more common in elderly people , as a result , most (but not all) autoimmune diseases are more common in old-aged / elderly people (ex. : RA , Hashimoto thyroiditis and thyrotoxicosis) . An example of an autoimmune disease that's commonly noticed in young population is SLE that tends to affect young women .

6) Aberrant expression of MHC molecules on non-APCs : Cytokines (especially interferon gamma) help APCs do their function by promoting expression of MHC class 2 molecules on APCs' surfaces . However , Excessive amounts of inflammatory cytokines (e.g. in case of chronic infection) lead to the expression

of MHC molecules on surfaces of aberrant cells i.e. non-APCs (e.g. epithelial cells) . The aberrant cells present self-antigens by MHC molecules on their surfaces . this results in an autoimmune reaction and an autoimmune disease may arise .

** Professor Hassan says that he's not gonna discuss all the autoimmune diseases and their pathogenesis . It's YOUR DUTY to look these diseases up and know the autoantibodies or the auto-reactive cells that are involved in each of them .

** Autoimmunity can be cell-mediated or humoral . So there are autoimmune diseases that are mediated by cells but these are difficult to be studied in labs since it's not easy to detect the auto-reactive cells . However , it's much easier to detect the autoantibodies that are involved in humoral autoimmune diseases thus these diseases are easier to be recognized , studied and dealt with , so we are more concerned with humoral autoimmune diseases in this context .

** The doctor showed this table :

Table 18–4. Examples of T Cell–Mediated Immunologic Diseases

Disease	Specificity of pathogenic T cells	Human disease	Animal models
Insulin-dependent (type I) diabetes mellitus	Islet cell antigens (insulin, glutamic acid decarboxylase, others)	Yes; specificity of T cells not established	NOD mouse, BB rat, transgenic mouse models
Rheumatoid arthritis	Unknown antigen in joint synovium	Yes; specificity of T cells and role of antibody not established	Collagen-induced arthritis, others
Multiple sclerosis, experimental autoimmune encephalomyelitis (EAE)	Myelin basic protein, proteolipid protein	Yes; T cells recognize myelin antigens	EAE is induced by immunization with CNS myelin antigens; TCR transgenic models
Peripheral neuritis	P2 protein of peripheral nerve myelin	Guillain-Barré syndrome	Induced by immunization with peripheral nerve myelin antigens
Experimental autoimmune myocarditis	Myosin	?	Induced by immunization with myosin

Abbreviations: CNS, central nervous system; NOD nonobese diabetic; TCR, T cell receptor.

Doctor's comments about the previous table :

The table shows some autoimmune diseases with the autoantibodies involved in their pathogenesis :

✍ Type 1 DM : Antibodies against insulin receptors , antibodies against cells of islets of Langerhans and there may be auto-reactive cells against the pancreatic cells in these islets .

✍ RA : Antibodies against citrullinated proteins . Citrulline is an amino acid that's not normally present in human beings . Citrullinated proteins are proteins that contain citrulline in their amino acid sequence . Citrulline in these proteins is produced from enzymatically altered arginine .

The rheumatoid factor (RF) is also involved : Rheumatoid factor is an antibody of the IgM variety against the Fc portion of IgG antibodies (i.e. antibodies against antibodies) .

✍ MS (Multiple sclerosis) : Antibodies against basic protein in myelin sheath .

✍ Peripheral neuritis and experimental autoimmune myocarditis : These are examples of cell-mediated autoimmune diseases in which it's difficult to search for the auto-reactive cells in patient's body so we can say that routine examination for patients is not feasible in this case .

** The doctor showed another table and mentioned the diseases as well as the related antibodies , he said AGAIN that you should look for the autoimmune disease and the involved autoantibodies . The table is in the next page in order to make it clearer .

The doctor added that in Hashimoto thyroiditis there are antibodies against peroxidase and antibodies against thyroglobulin .

Also remember that various antigens are involved in SLE : anti-dsDNA antibodies, anti-RBCs , anti-WBCs , anti-platelets , ... , etc.

Table 18–2. Examples of Diseases Caused by Cell- or Tissue-Specific Antibodies

Disease	Target antigen	Mechanisms of disease	Clinicopathologic manifestations
Autoimmune hemolytic anemia	Erythrocyte membrane proteins (Rh blood group antigens, I antigen)	Opsonization and phagocytosis of erythrocytes	Hemolysis, anemia
Autoimmune thrombocytopenic purpura	Platelet membrane proteins (gpIIb:IIIa integrin)	Opsonization and phagocytosis of platelets	Bleeding
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (epidermal cadherin)	Antibody-mediated activation of proteases, disruption of intercellular adhesions	Skin vesicles (bullae)
Vasculitis caused by ANCA	Neutrophil granule proteins, presumably released from activated neutrophils	Neutrophil degranulation and inflammation	Vasculitis
Goodpasture's syndrome	Noncollagenous protein in basement membranes of kidney glomeruli and lung alveoli	Complement- and Fc receptor–mediated inflammation	Nephritis, lung hemorrhage
Acute rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis, arthritis
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetylcholine binding, down-modulates receptors	Muscle weakness, paralysis
Graves' disease (hyperthyroidism)	TSH receptor	Antibody-mediated stimulation of TSH receptors	Hyperthyroidism
Insulin-resistant diabetes	Insulin receptor	Antibody inhibits binding of insulin	Hyperglycemia, ketoacidosis
Pernicious anemia	Intrinsic factor of gastric parietal cells	Neutralization of intrinsic factor, decreased absorption of vitamin B_{12}	Abnormal erythropoiesis, anemia

Abbreviations: ANCA, antineutrophil cytoplasmic antibodies; TSH, thyroid-stimulating hormone.

End of the lecture , hope you enjoyed studying the sheet ☺

Good luck !

Dedicated to Dema Qawasmeh .

Written by : Doa'a S. Dahboor .