Medical Immunology

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Lecture – 16 –

Ω Autoimmunity:

➢ **Natural Auto-Antibodies:**

- Autoimmunity is not very uncommon; because there are auto-antibodies in all of us (natural auto-antibodies).
- These natural antibodies are:
  1. Produced by the B1 (CD5) cells.
  2. IgM variety.
  3. Low affinity.
  4. Don't switch to other isotypes.
  5. no memory involved.
  6. You don't have to be exposed to the antigen or to be vaccinated to produce these antibodies; because these cells use our antigens as a model to produce these antibodies.

- Usually, there's no harm from these antibodies; because these antibodies are of low affinity and don't lead to pathologies.

- **Functions of the Natural Auto-Antibodies:**
  1. **First line of defense against bacteria and viruses:**
     They interact with the bacteria and viruses coming from outside to stop them temporarily until you produce an immune response and get rid of the pathogen.
  2. **Removal of debris from the body:**
     Broken down proteins in the body produce debris that combines with these antibodies and activates the complement to get rid of them.

     Ex: RBC's have CR1 (receptor for C3b) on their surface.
     So, any immune complex that has activated the complement and has C3b on its surface will attach to the RBC's that take these immune complexes to the spleen and hand them over the phagocytic cells present in the spleen.
     So, RBC's play a role in *clearance of immune complexes.*

  3. **Prevention of Autoimmune Diseases:**
     Suppose that you get a foreign antigen that comes into the body that's actually similar to some antigens in our body.
     So if this foreign antigen produces an immune response, it will produce antibodies that may cross-react with our own self antigens.
     So these auto-antibodies quickly interact with this antigen and blind it to prevent it from inducing an immune response and producing antibodies that may actually harm our body.

Note:
The immunoglobulins that cause pathologies and cause autoimmune diseases are usually of the IgG variety that have a high affinity.

Ω Etiology of Autoimmune Diseases:

- About 2-3% of any population have autoimmune diseases; so they're common.

- **Etiology of Autoimmune Diseases:**

1. Genetics:

- If you have a family member with an autoimmune disease, then other family members will be at a higher risk to develop an autoimmune disease.
- It doesn't have to be the same autoimmune disease; but it could be some other autoimmune disease.
- Also, certain HLA alleles might be associated with certain autoimmune diseases.
- *However, this genetic association is not 100% proved; because:*
  1. The concordance of the same autoimmune disease in identical twins is only 50%.
  2. The concordance of the same autoimmune disease in siblings with identical HLA haplotypes is less than 5%.

- A genetic element is also seen in the New Zealand black and white mice that are prone to develop a disease similar to systemic lupus erythematosus (SLE).

2. The Environment:

- The environment has something to do with autoimmune diseases; but it doesn't necessarily cause them, it might only make them better or worse.

A) Nutrition:
Example: In Rheumatoid Arthritis (RA), it's believed that eating lots of fish actually enhances the disease, while red meat exacerbates it.

B) UV Rays (Sun):
UV radiation from the sun can affect some autoimmune diseases.
Example:
People with Systemic Lupus Erythematosus (SLE) develop antibodies against DNA.
If people with SLE are exposed to the sun, the UV rays will break down DNA of the sun-exposed keratinocytes.
This broken down DNA combines with antibodies and produces an inflammation.
This is why women with SLE have a butterfly rash on their face that corresponds to the sun exposed skin.

However, this UV exposure doesn't necessarily cause this inflammation, it might only make it worse: the DNA will produce the antigens, you will produce more antibodies, more immune complexes will be formed, and the inflammation will manifest.

"SLE is adversely affected by UV radiation from the sun."

C) Paints:
Example:
Goodpasture's Disease.
Some people who work with paints can be exposed to solvents that can damage the basement membrane in the lungs and in the kidneys.
When you inhale these solvents, they will go through the basement membrane in the lungs, and once they come out, they will go to the kidneys and go through the basement membrane of the kidneys.
The injured basement membranes will expose new antigenic determinants that give rise to the production of antibodies against them.

D) Infection : if you have chronic infections by means of bacteria , virus there's abnormal expression of antigens on the cell ; so there're a lot of INF-gamma and the cell will use INF-gamma as second signal and we will have autoimmunity .

3. Sex Factors:

- Most autoimmune diseases affect women; this might be due to the fact that estrogen promotes the production of antibodies.
- **Examples (Women : Men):**
  SLE → 10 : 1.
  RA → 4 : 1.
  Grave's Disease → 8 : 1.
  Hashimoto's Thyroiditis → 10 : 1.
  Multiple Sclerosis → 3 : 1.

- However, there are some autoimmune diseases that are more prevalent in men, such as Ankylosing Spondylitis.
- Also, there are some autoimmune diseases that affect women and men equally, such as Diabetes Type I.

"So sex factors and sex hormones aren't 100% responsible for autoimmune diseases."

Ω Mechanisms of Autoimmune Diseases:

➢ Modification of the antigen:

- A substance that binds to the antigen and modifies it in such a way that it makes it immunogenic.
- Modifiers of the antigen:
  1. Mutations.
  2. Solvents.
  3. Drugs: it's very common.
     A) A drug might be given to the patient that combines with RBCs and gives rise to antibodies against RBCs causing (Drug Induced Hemolytic Anemia).
     B) A drug might be given to the patient that combines with platelets and gives rise to antibodies against platelets causing (Thrombocytopenic Purpura).
     C) Some drugs might cause drug-induced SLE.

- Once the modifiers of the antigens are removed; the patient's condition will improve, so he won't have the disease for the rest of his life.

➢ Polyclonal Activation:

- There are polyclonal activators of lymphocytes:
  1. LPS is a polyclonal activator of B-lymphocytes.
  2. Superantigens are polyclonal activators of helper T-lymphocytes.

- During a course of an infection, you will get non-specific polyclonal activation of these cells, so any cell can be activated, including the anergic cells. This polyclonal activation of B-cells and T-cells may give rise to antibodies directed against our self-antigens.

➢ Molecular Mimicry:

- An antigen that's similar to one of our self-antigens comes from outside and gives rise to an immune response, thus producing antibodies that cross-react with our own antigens thus causing an autoimmune disease.
- **Example:**
  Rheumatic Fever.
  You remember Streptococcus Group A (Streptococcus Pyogens) that have M-protein on their surface, and there are many serotypes of streptococcus pyogens depending on the M-protein (about 80 serotypes).
  If you get tonsillitis by certain serotypes (that have certain M proteins), you will develop antibodies that clear the infection, but the left over antibodies will cross-react with antigens in the endocardium causing endocarditis, and this inflammation will go on thus producing a fever.

Therefore, recurrent episodes of tonsillitis will exacerbate the rheumatic fever symptoms, and eventually the valves in the heart will be destroyed.
So the valves in the heart usually become stenosed and fibrosed, or rarely they become incompetent.
This fibrosis obstructs the blood flow, and causes heart failure.

Nowadays, rheumatic fever is very rare, because once people get tonsillitis, they will take antibiotics immediately, so they will clear the infection before the body gets a chance to produce antibodies against the M-protein.

- **Loss of Suppression:**

- How?
  1. Mutation in the AIRE gene in the medullary thymic epithelial cells will cause *autoimmune polyendocrinopathy.*
  2. With old age, the immune system will get tired, so the immune suppression will be lost, and the person will be at a higher risk to develop an autoimmune disease.
  3. If you don't have a thymus gland, or if your thymus is not functioning very well, you will be at a higher risk of developing an autoimmune disease.

*"Extra Info: for the **third point**, there's a genetic disorder called **DiGeorge's Syndrome (DGS)** that is associated with **thymic aplasia**. So, a person with DGS will be at an increased risk of developing autoimmune disorders, and this is probably what the doctor had in mind when he mentioned this point."*

- **Sequestration of Antigens:**

- Sequestration and hiding of self-antigens where they cannot be seen and reached by the immune system.
- However, if the barriers are disrupted, the antigens will be exposed, and the person will develop an autoimmune disease.

Sequestered Region	Intact Barrier	Disrupted Barrier
Brain	The blood brain barrier (BBB) prevents leukocytes from entering the brain. It's debatable whether this BBB actually exists anatomically or not. Maybe it's due to the lack of lymphatics in the brain, so it cannot harbor lymphocytes.	If the BBB is disrupted, you can get autoimmune diseases like Multiple Sclerosis (MS). **MS involves:** 1. **Antibodies** against the myelin sheath. 2. **T_{H17} cells** are the cells involved in the pathogenesis of MS.
Testis	The barrier is not really understood: 1. Maybe the barrier is due to the presence of sertoli cells. 2. The cells in the testis express Fas-L, so they kill T-cells that express Fas.	The barrier can be disrupted by a **Vasectomy:** if the vas deferens is ligated, then the sperms will accumulate, so they will disintegrate and release antigens, and you may produce antibodies against the sperms. This will lead to **sterility**, even if the vasectomy is reversed.
Eye	The lens, the cornea, etc.. They don't have a blood supply, so they are not exposed to the lymphocytes.	A penetrating injury to the eye disrupts the barrier in the eye, so the antigens of the lens will be released to the inside of the eye, and this will induce an immune response. The immune response is not only harmful to the eye that has been affected, but the eye becomes useless and has to be replaced with a glass eye. **Sympathetic Ophthalmia:** If the affected eye is not removed (the source of the antigen is kept) then the immune response will go on and on, and it will affect the other eye (it will go blind).

➢ **Idiotypic Network Theory:**

- This theory has been suggested but not proven.
- It suggests that: when you produce antibodies against a certain antigen, then these antibodies will be actually immunogenic, and you will produce anti-idiotypes that cause autoimmunity.
- The production of anti-antibodies doesn't stop one level; so you will produce antibodies against the anti-antibodies, and antibodies against the anti-anti-antibodies…. And so on.

- **Mechanism:**

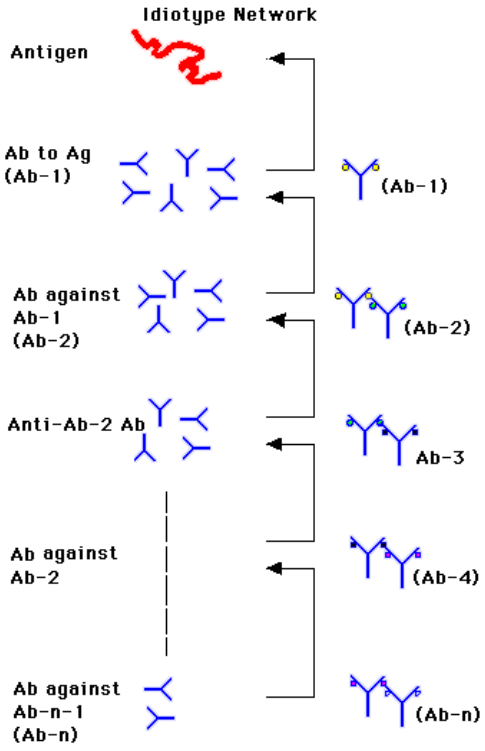
1. A virus has a certain receptor on its surface, and there are receptors on human cells (there's reciprocity or complementarity between them).

2. If a person gets infected by the virus, he will produce antibodies against the viral receptors, and these antibodies should be reciprocal (complementary) to the viral receptors.

3. The antibodies that are produced are actually similar to the receptors on the human cells.

4. The person will produce anti-antibodies (anti-idiotypes) against these antibodies, and since the antibody is similar to the receptor on the human's cells, then these anti-idiotypes will attach to the receptors on the human's cells and produce autoimmunity.

- This theory seems a little far-fetched and irrational; however there are viruses that cause autoimmune diseases (Mumps – Diabetes Type I), but this might be caused by the infection itself, not by the anti-idiotypes.



- **Aberrant Expression of MHC-II Molecules:**

- If you have a continuous infection or acute infection, you will produce lots of cytokines that may induce abnormal MHC-II molecules expression on Non-APCs (Endothelial cells and Epithelial cells), so these Non-APCs will express the antigen, and the secondary signal will be provided by something else to actually produce antibodies against your own antigens.
- This will lead to autoimmunity.

- **Left-Handed People:**

- Left-handed people are more likely to develop autoimmune diseases.
- The mechanism is not known; and this probably tells us that scientists aren't 100% about the mechanism of autoimmune diseases.

- The End -

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