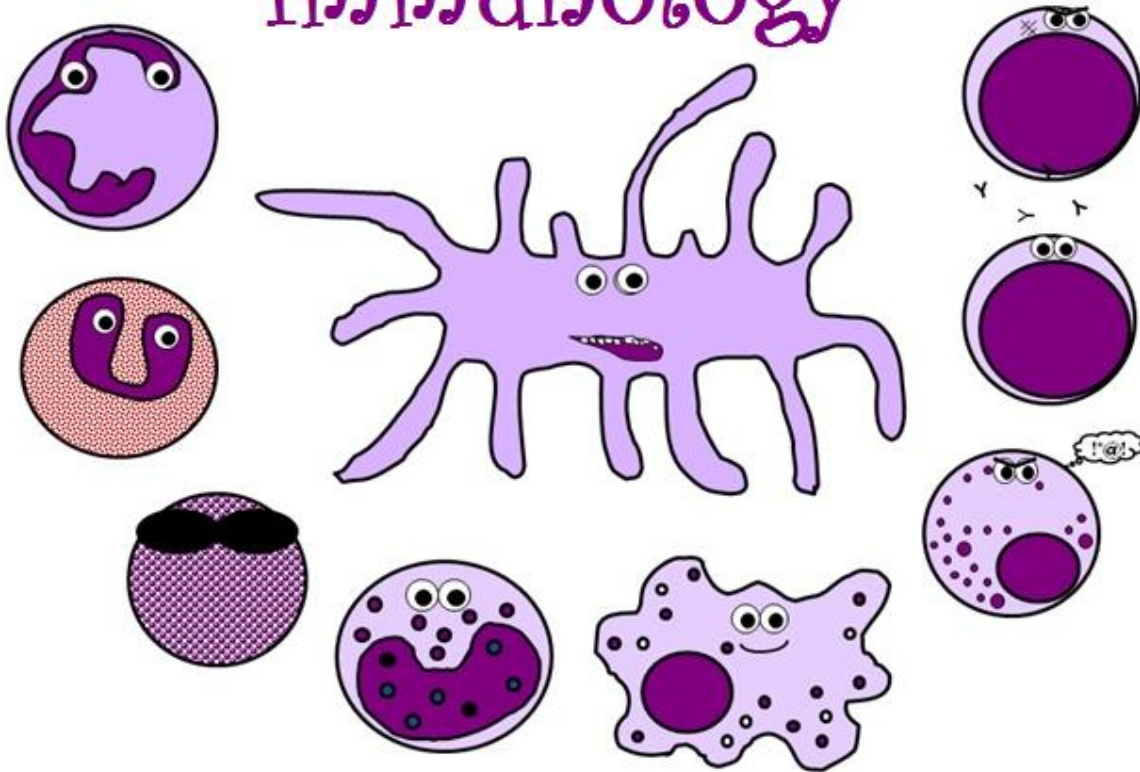




Immunology



● Sheet

○ Slides

Number: 25

Subject: A Critique of the immune system

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A Critique of the immune system

- This lecture will be about advantages and disadvantages of immune system.
 - Little revision, critical thinking & brain storming.
 - ~ Why the immune system is successful in fighting infections?
 - ~ And why there are *what we think* weaknesses in the immune system?!
-

❖ Evaluating the immune system:

- You've seen through the course that the immune system is potent and effective system, we reach 20-30 years and more without been infected to any major infection or disaster diseases .. So, as you can see the immune system is really doing a great job.!

Q: What makes the immune system an effective and potent system to fight the diseases? In other words what are the positives of our immune system?!

1) Wide perimeter coverage:

- What happens in our bodies between the immune system and the pathogens is more like a battle. So, the immune system should protect all borders, for that we have innate immune cells "especially macrophages" in almost all tissues in the body and entry, they are covering the whole perimeter to protect us from pathogens; pathogens that enters through skin, mucosal membrane (respiratory tract, GI tract, genital tract ..), and it did a very good job trying to protect the whole perimeter.

2) Quick response by the innate immune system (local response, multiple battles possible):

- **The importance of innate immune system** is its ability to respond very quickly to pathogens, this is very important, because if all immune cells in the body were responding like the adaptive immune system; the body would take weeks to start fighting the invasion... and nobody will survive!
- You have seen in many pathologies that affect the innate immune system, the problems were happening **very early on and very dangerous .. *the problems in the innate immune system are critical.***
- The fast response is very important, when pathogen enters through the skin barriers or the mucosal barriers, if they “the macrophages” couldn’t fight well with the help of other innate immune cells to buy time for the adaptive immune system to kick in, this will lead to big problem.

❖ **Local response:**

- It means that when we have reaction in a certain place, dendritic cells will recognize the antigen, internalise it, collect information on the type, size, and location of the attack and take it to the draining lymph node ..
- These responses are local: only those cells which are present in the neighborhood of the invasion will be affected, and only a limited number of secondary lymphoid organs (e.g., nearby lymph nodes) will be involved. (**Infection site & draining lymph node**).

Q: Why do we need the local reaction? What is the advantage?!

- This local reaction gives us the opportunity to fight more than one battle in different sites, the immune system should be able to recognize & fight pathogens in different sites in the body separately (for example: skin & GI tract).
- We don’t want a **systemic reaction**; because it can be aggressive reaction and cause a lot of inflammation & tissue damage.
- That’s why we talked about microenvironment and its importance, and cytokines in microenvironment in driving different responses. These cytokines and chemokines in order to act they have to be in a relatively high concentration in the microenvironment, this is achieved by the localizing.

3) Potent specific response by adaptive immune system (learns from experience):

- The adaptive immune system is the specific weapon to fight the pathogens. We need innate immune system to recognize any pathogen quickly and attack it “fast response”. However, we need specific weapons to fight the pathogens specifically.
- Adaptive immune system has a **memory**, makes it ready with high ability to fight infection.

~**Note:** Latest researches show that even innate immune system in a way or another has certain type of memory.

4) **Excellent communication between innate & adaptive systems:**

- The immune system with all its parts should communicate with each other to be more effective in fighting the pathogens like a one unit.
- The innate immune system recognizes the pathogen, and it will present the antigen to the adaptive immune system, it tells exactly what type of pathogen it is countering, the kind of peptide, the kind of MHC, the kind of cytokines it sustains, the kind of chemokines it's secreting .. all these give the clear message to the adaptive immune system, where it should go & what type of reaction should it do .. etc.!

~ **Note:** The innate immune system is the eyes that the adaptive immune system see through, and without it the adaptive immune system is blind.

5) **Chemokines & receptors managing an efficient trafficking system:**

- We talked about trafficking system “lymphocyte trafficking” {lecture 10} and how much it is important and complicated.
- The naïve cells should know how to move from secondary lymphoid organ to another and do screening.
- If those naïve cells went out to the tissues randomly; we have a huge possibility to have an autoimmune disease.
- We have a whole system of chemokines and receptors that dictate naïve cells where to go and dictate experience cells where they should go; therefore, they organize immune cells movement and their ability to recognize pathogens & fight infections.

6) Potent mechanisms to stop immune response when not needed{lecture 12}:

- Once the immune system is triggered, strong and dangerous weapons are being used, we have inflammation going on, we have necrosis and apoptosis, we are having a whole series of processes. So the body should recognize that the infection has ended and it should stop this immune reaction, and start over & give chance for new naïve B & T cells to circulate, new cells from innate immune system to take over .. start again from the beginning.
- We saw that we have many layers of tolerance and shutting down the immune response in order to stop the inflammation and prevent unnecessary damage.

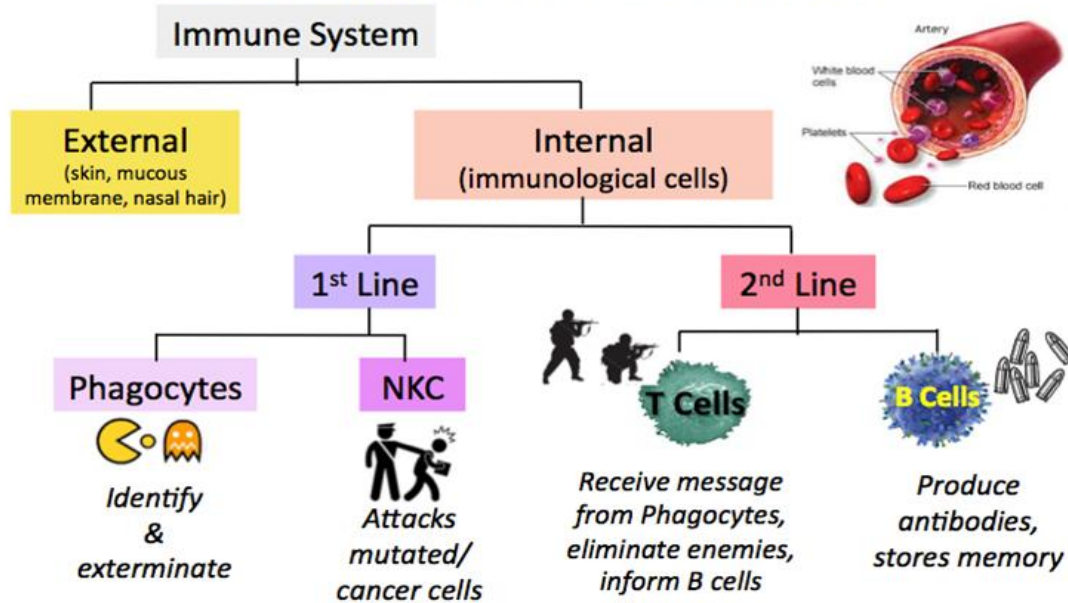
7) Strong ability to prevent auto-immune disease:

~ Tolerance mechanisms {lecture 14}:

- Central tolerance mechanism in the thymus (eliminate auto-reactive T-cells) and the bone marrow (eliminate auto-reactive B-cells), positive selection and negative selection for the T cells, this prevents us from auto-reactive lymphocytes.
- In reactive lymphocytes, even if they escape central tolerance and go to the peripheral organs and circulation, we have many mechanisms“peripheral tolerance” to protect us from autoimmunity, from this mechanisms it could be, our body ability to restrict trafficking pattern, T-regulatory cells that can suppress the immune response, lack of co-stimulation in tissues, increased expression of fas-fasL(*the doctor said and allergy here* □).. all play an important role in regulation of immune system.

~ **Immune system is quite very efficient& powerful system.!**

The Immune System Our Ultimate Line of Defence



~ The immune system is our ultimate line of defense “The figure”:

-We said that the immune system is divided to external & internal system.

- ✓ **External system** (skin, mucous membrane, nasal hair) they play a very important role in protecting us, they could be affected or breached.
- ✓ If they breached we have the **internal “immunological cells”** to fight the pathogens; the first & second line of defenses.
- ✓ First line is the innate immune system & the second line is the adaptive immune system.

- Macrophages are found in many areas, dendritic cells are found also in tissues.

Q: If they get overwhelmed, what comes to help from the circulation, from innate immune system?

- Neutrophils (very efficient in killing bacteria), natural killers “NK” (produce Interferon gamma “IFN γ ” which in turn activates further macrophages, kill virally infected & tumor cells ..).

- If the 1st line was not enough to overcome the infection and kill the pathogen .. then, the 2nd line of defense is activated!

- Activation of T&B-cells.

- T-cells: helper T-cells that produce cytokines drive an immune response, Cytotoxic T-cell help natural killer cells in killing virally infected cells & cancer

cells, T-regulatory cells that suppresses the immune response.

- B-cells: produce tons of antibodies to protect us (through neutralizing pathogens, opsonizing pathogens, complement pathways “classical”..) and at the same time can serve as antigen presenting cells to further activate the immune response, and they are antigen concentrators, also the memory cells to remember all this.

❖ Weaknesses of the immune system *Not real weaknesses*:

1) The adaptive immune system reacts relatively slowly to attacks.!

➔ Qs: When you get sick (e.g. cold), to have specific antibodies and specific T-cell responses it takes few weeks to have strong adaptive immune response “relatively long time” .. Why is that? Why isn’t the immune system developed in a way to react faster?! How to make it faster? And at what cost?

✓ Answers: We are talking about a few number of each antigen-specific lymphocytes in our body, remember {lecture 4} when we talked about RAG1 & RAG2 and VDJ recombination, we said at the end in our bodies there are lymphocytes that are specific (e.g. for Rabies we have certain B&T-cells that recognize antigens from the Rabies only).

* RAG1&RAG2 are enzymes that are responsible for the recombination processes, they bind to certain sequences called “RSS”

✓ **How many** of these we have in our body?

Few in number; around 20 cells for each specific antigen, these specific lymphocytes recognize their antigens in the lymph nodes “site of recognition”.

✓ So, initially the numbers of every specific lymphocytes are few, that’s why the adaptive immune system takes long time.

➔ **Why only 20 cell?** Why not more (e.g. 40-50) cells?

So instead of taking 5 days for the adaptive system to attack, why not one day or less? Why the immune system wasn't developed in this way?!

✓ **To give chance for the variety!**

#Remember we said that VDJ recombination can form lymphocyte that can recognize every single antigen on earth; this is proven and if not this means that we were dead; because of new strains and pathogens.

✓ SO, trying to make the adaptive immune system faster by increasing the number of specific types, will be on the expense of variety.

• Over the evolution of immune system we had possibilities;

1) Covering 100% of antigens with only 20 specific cells with innate immune system that help in binding time ..**OR,**

2) Covering 80% of antigens and adaptive immune system trigger in half-day "fast" ..

~ **Which one** has more survival advantage?!

- The **first one** with more variety for sure; if you have risk to leave 20% of antigens are not covered, you are giving a chance for a new pathogen to come and exterminate the whole mankind.

- So we **reached a balance** that our body can cover all the antigens by recombination mechanisms with sufficient amount of lymphocytes to trigger an immune response in a decent amount of time.

- Also, **if you increased the variety more** than this will be at the expense of the number of each antigen-specific lymphocyte; instead of having 20 cells, you will have only 5 for example.

~ **So it is not a weakness. !!**

2) **Allergies!**

➔ **Qs:** Why we have this allergy and IgE responses?

Why the immune system failed to develop a better way to prevent the allergy?

Why we need IgE response, histamine secretion, cough, sneezing, anaphylactic shock, asthmas and other bad effects that accompanies the allergy? Why the immune system couldn't do better?!

✓ **Ans:** When we think of the immune system we have to think of the human nature where and when the immune system developed! It was developed

with the caveman & hunter gatherer life style not the modern man, so the development of the system tries to suits the time that it were developed in not in our life style nowadays.

- ✓ So, when we talk about the caveman, at that time there was high infection rate and high level of parasitic infection, and thus, IgE were critical for humans in that time, and the development of immune system to make an effective IgE system was critical in protecting them from parasitic infections, those people were exposed to a lot of infections.
 - By knowing that, what you think of the incidence of allergies in that time?
 - It was **extremely low**, so it was not an issue for the caveman. Allergy is a new issue; we are facing new problems because of modernization.
 - In terms of evolution it's a huge and very rapid of change, the development that happened in the last 150 years in our life style was way faster than any biological system to adjust.
 - Hundreds of thousands of years of pressure on a certain system are required to generate new variants and put pressure on them and select them in order to change the gene pool and have a deferent characteristics of a certain system.
 - Nowadays our chances are mostly with medical intervention.
- #Remember** what we said in the hygiene hypothesis {lecture 16}, being in an environment with high standards of hygiene and not exposed to pathogens and microorganisms, will increase the susceptibility to develop allergies and less protected against antigens.

3) Conflict between protecting us from autoimmunity and cancer? How come?

- ➔ **Qs:** We said that our body has the ability to protect us from autoimmune processes by making tolerance mechanisms, this tolerance mechanisms prevent autoimmune diseases to occur in our body (T-reg, anti-inflammatory cytokines .. etc.) However, this happen at the expense of developing cancer; our bodies become less able “from an immune prospective” to fight cancer .. Why is that?
- Why our immune system biased toward protecting us from autoimmunity at the expanse of cancer?

- ✓ **Ans:** This point and the next one are interconnected and to understand them let's answer the following question ..
- Was the caveman “at the time where immune system developed” live up to >50 years “to old age in general”?
 - **NO**, at that time the average age was very low, few people can live 30-35 years, aging wasn't a concern, most of them were dying because of pathogenic diseases (parasitic infections, bacterial & viral infections) .. cancer wasn't a concern; mostly **cancer is a disease of age**.
 - The main concern is the autoimmunity because it **occurs early on life**; so we should have strong mechanisms to protect us from autoimmune diseases, the human was not reaching the age that he will have the accumulation of mutations that are needed to develop a cancer. Therefore, the whole effort was toward restraining the immune system and preventing the autoimmunity.
- ~ Change of life style, medical abilities, equipment and knowledge, it increases the average of age .. and this lead us the next point “aging”.

4) Immune system goes weaker with age?

➔ **Qs:** Age extremities (very young& very old) have weak immune system “immune compromised”, Why shouldn't the immune system stay strong for a longer time?!

- ✓ **Ans:** As we said, this was not a concern in the time where the immune system developed; they are not aging enough to face this problem.
- Nowadays, we are aging enough to see them and we are living many years to accumulate enough mutations to develop a disease like cancer.

~ Those are not really weaknesses, if you take in consideration the time & environment where the immune system developed.

~ Despite the big changes that happened to our life style nowadays the immune system is still doing a great job! it still protecting us in a good way, only a few die of major infections and immune problems, we are living for a long time.

- Now we are having the cancer as the disease of the century.!

Q: If we found cure for major cancers in the next 5 years for example & the average of age became 120 years .. **Is it the end of the problem?!**

- **NO**, because with increasing in age this will give more chance to develop new mutations, and new diseases, we haven't reached this age to see these new diseases.

❖ **Conclusion:**

- The immune system is in a continues conflict with the pathogens & diseases, diseases will never end because they will keep improving genetically(at the protein level)and we are living actually longer and allowing things to change in our bodies; things nowadays we are not facing.
- The immune system is trying it best to fight back and to adjust, diseases and pathogens never give up, they keep changing, they keep trying to infect; because that's their survival mechanism, they fight for their lives.

~ You have to do researches and to think how to develop new strategies, new medications and therapies to fight back, the day you give up in .. the pathogens will not give up .. and this will be the end of humanity :(.

~ The sustainable of mankind is in your hands and your ability to fight and fight and fight, NEVER EVER GIVE UP ♥ .. !

End of text.

End of course.

~ So sorry for being late :((

~ &Sorry for any mistake.

~ Good luck in your finals :) ..