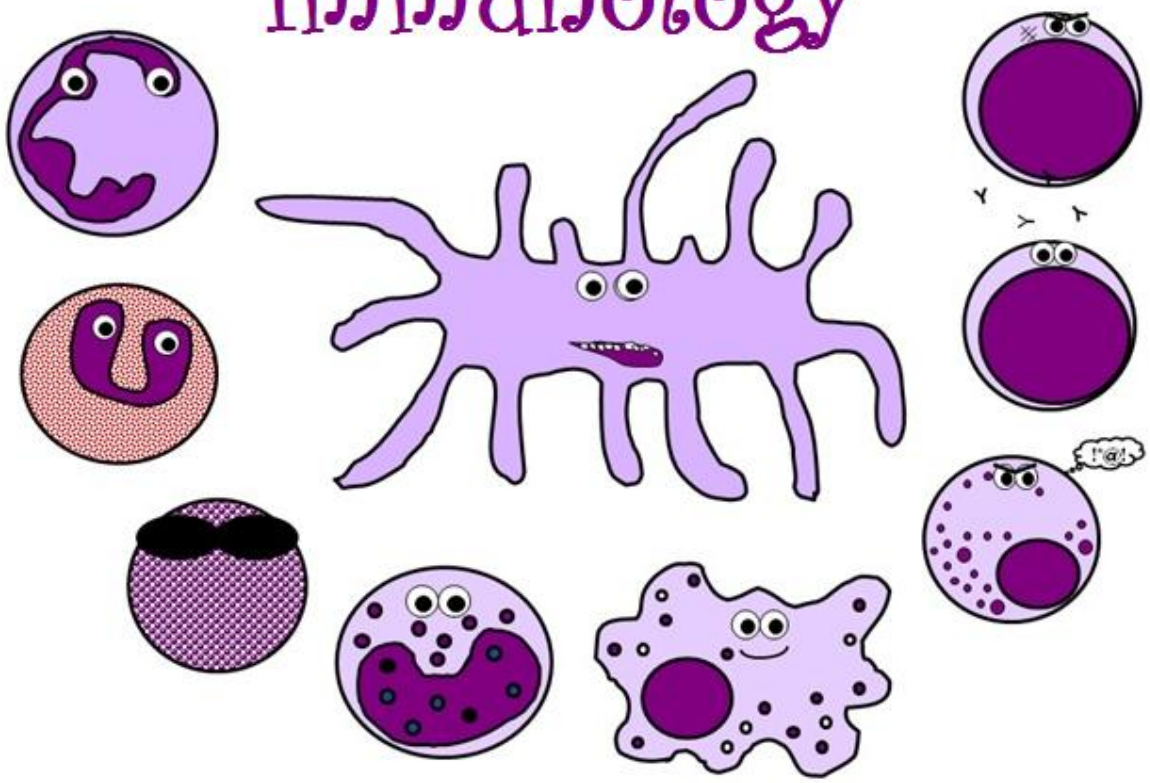
Immunology



◉Sheet ○Slides

Number: 15

Subject: Immunological Memory & Vaccines

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16/11/2016

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In this sheet we will discuss the Immunological memory and vaccines.

❖ Immunological Memory:

When we say immunological memory the first thing that comes to mind is the adaptive immune system memory, which is true, but also if we look at the innate immune system in a historical view, we will notice how it maintained its features across generations, like the TLRs. So we can view this as an Innate Memory. However, unlike the adaptive memory, innate memory is not updateable in our lifetime.

The Adaptive Memory is about B and T cells memories, and it is updatable, so every individual has different adaptive memory depending differences in exposure to pathogens.

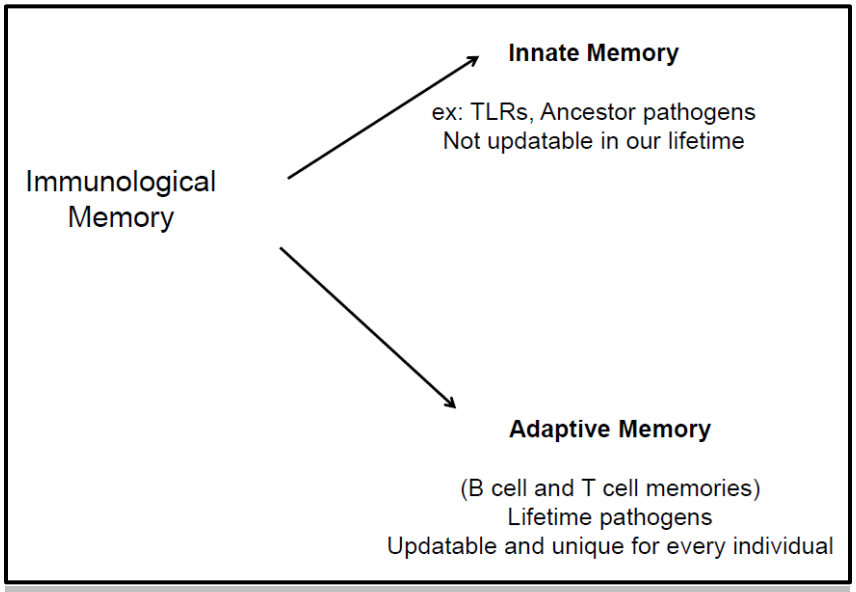

Figure 1: Immunological Memory.

- **B cell memory:**

A naïve B cell recognizes the cognate antigen, gets activated and it is in front of three fates:

a) Short-lived plasma cell: This cell will go to the bone marrow or the spleen and secrete huge amounts of antibodies to resolve the infection. As a result

of the high amount of antibody secreted this cell will get exhausted, therefore called short-lived, and this is beneficial in restraining the immune system.

b) Long-lived plasma cell: Mostly found in the bone marrow. This cell secrete much lower amounts of antibodies in comparison to short-lived plasma cell, but it lives for a longer duration and maintain the presence of a specific amount of antibodies in the long run. Despite that, this cell will get older and die.

c) **Central memory B cell:** Mostly found in secondary lymphoid organs. This cell will replenish the long-lived plasma cells, and also will maintain its own pool (so it is similar to stem cells in term of asymmetric division). In addition, if the body gets attacked again by the same pathogen, it will proliferate and form activated B cells that will give short-lived and long-lived plasma cells.

- **T cell memory:**

A naïve T cell (whether CD4+ or CD8+) recognizes the cognate antigen, gets activated and develops into:

a) Effector T cell: Which will fight the infection by producing cytokines (CD4+) or by killing the damaged cells (CD8+). With time, some of the effector cells will make **Memory effector T cells**. Comparing these cells to the long-lived plasma cells, these cells are **dormant** whereas long-*lived plasma cells are working at a low level. And being dormant is beneficial to the body because T cells are the main driver for a lot of immune functions, and prolong activation of them is dangerous. Memory effector T cells remain in the tissue and will get activated upon reinfection.

b) **Central memory T cell:** Just like the central memory B cell, it is similar to stem cells in term of asymmetric division. So it will maintain its own pool, and if reinfections occurs it will form activated T cells which will give us the effector T cells to fight the infection. Central Memory T cells remain in secondary lymphoid organs or in the bone marrow.

Comparing B and T cell memories

	B Memory	T Memory
Stem-cell-like cell memory	Yes	Yes
Somatic Hypermutation	Yes	No (don't produce antibodies)
Remain active after infection is done?	**Yes**, produce antibodies for life by long-lived plasma cells.	**No**, effector T cells go dormant

❖ Properties of Memory Cells:

1) As a result of clonal expansion of activated lymphocytes, Memory cells are **more numerous** in the circulation than naive ones (1000X more).

2) Memory B and T cells are **easier to activate** because they are less dependent on co-stimulation (less dependent on the two-key system). This may seem harmful because as we said the two-key system is protective. But remember that a memory cell is derived from a cell which passed the test and got into this two-key system and had the co-stimulation and we know that it's not autoreactive, so it's the cell that should proliferate and do the job.

3) Memory B cells are **already class-switched**. Which makes it much quicker and more effective.

4) Memory B cells produce antibodies that have **undergone somatic hypermutation**. So it has the best possible antibody to fight the infection.

❖ Maintenance memory cells:

As you know, lymphocytes need certain conditions to stay alive, like restimulation for example, so it was a confusing question to immunologist that how memory cells are maintained. It is not clearly understood but can be explained by:

- Remnants of the pathogen in secondary lymphoid tissue (Restimulation). This true in some diseases like cutaneous leishmaniasis as some parasites go dormant and controlled by the body.

- Cytokine and ligand-mediated slow proliferation of T and B memory cells without the presence of any pathogen remnant.

- Scientists also found that B memory cells through their B cell receptors or toll like receptors interact minimally with certain auto-antigens! It's minimal to the extent that it doesn't produce an immune response but still can give a survival signal to the cells.

❖ Vaccines:

- The concept of vaccines is not only about generating antibodies but also about generating memory helper T and B cells.

- Equally important, some vaccines are critical to produce memory killer T cells. This is important in intracellular pathogens (ex: Many viruses, Mycobacteria, Leishmania, Malaria…).
  It should be noted that these vaccines should be able to infect antigen presenting cells, so as the antigen presenting cell can present the intracellular antigens derived from the vaccine on MHC1.
  Another way to induce MHC1 presentation is cross-presentation. Sadly, immunologists have not been able to produce vaccines that utilizes cross-presentation to activate killer T cells yet.

> Cross-presentation is the ability of certain antigen-presenting cells to take up, process and present extracellular antigens with MHC class I molecules to CD8 T cells (cytotoxic T cells).
>
> *Wikipedia*

- **Strategies for Vaccine Development:**

1) Indeed, vaccine **should not affect health** or lifestyle of patient.

2) Another challenge in Vaccine development is to **find out which memory cell is required for protection**.
   For example, antibodies produce by the body against HIV are not sufficient for protection. So to develop a vaccine for it, this vaccine should not generate memory B cells, we must choose the proper type of cells to be produced by the vaccine.

3) Usually Memory Killer T cells are required. And as mentioned before, this requires APCs to be infected by the virus and this is too risky. As a result, immunologist weren't able to produce many vaccines that require memory killer cells generation.

- **Types of vaccines:**

1) Non-infectious Vaccines 2) Attenuated Vaccines 3) Carrier Vaccines

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1) Non-infectious Vaccines:

Examples: Flu vaccine, Typhoid and Pertussis vaccines, and the most popular one, which is Salk vaccine for Polio.

Mechanisms:

- Whole organism inactivated by a chemical (ex. Salk vaccine): Salk is the name of the scientist who developed this vaccine. He brought the Poliovirus and treated it with a cross-linking agent (like Formaldehyde), this will maintain the structure of the virus but prevent its functions. This was a big breakthrough, as there was 350,000 Polio cases per year in the late 80s. Today, it is less than 60 cases per year in the whole world.

- Toxoids made of toxins (ex. Diphtheria, Tetanus): A toxoid is a toxin converted to a non-toxic form while maintaining its antigenicity, so it can activate the immune system.

- Certain parts of pathogens (ex. Acellular pertussis vaccine): This reduces the risk of reversion of the antigen to virulence, which is an issue in attenuated vaccines. In these vaccines we just keep certain immunogenic components that are able to do the job.

- Genetically engineered viral proteins (ex. Hep B and HPV vaccines): Here, we know the DNA sequence that produce the antigens of the organism, we use genetic engineering to produce the desired DNA sequences and put them in a viral vector to produce the corresponding antigens, and then inject the antigens to the patient (Also, we can inject the viral vector, and it will produce the antigens in the patient).

Drawbacks: Will not generate memory Killer T cells.

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2) Attenuated Vaccines:

Examples: Vaccine for Measles, Mumps, and Rubella (MMR), and Sabin Poliovirus vaccine.

Mechanisms: There are many mechanisms to make these vaccines. One example is growing the pathogen in a host cells that differ from those that the pathogen usually infects. This will make the pathogen to accumulate mutations that will attenuate this pathogen (Obviously, it must stay antigenic).

And this is the mechanism that the scientist Sabin used in developing a poliovirus vaccine. He grew the virus in monkey kidney cells instead of human nerve cells.

Advantages: Produce memory Killer T cells.

Drawbacks:

- The vaccine can infect people with a weak immune system,

- The vaccine can mutate back to wildtype in rare cases (reversion). This happens because the virus find its real host cells which may help it to mutate back to the wild type (1 per 3 million people vaccinated by Sabin vaccine gets sick).

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3) Carrier Vaccines:

Mechanism: Introducing a single (or few) genes of the pathogen into a virus that doesn't cause disease. So we use the virus vector as a Trojan horse.

Advantages: - Can induce memory killer T cells.

- Safe.

This method was tried in Thailand with an HIV vaccine; modest results.

❖ Will there be an AIDS vaccine?

We must put these points into consideration:

- An effective HIV vaccine must generate memory Killer T cells:
    - Non-infectious approach: Won't work because no memory killer T cells will be produced.
    - Attenuated approach: Could generate memory Killer T cells, but it is too risky due to virus high mutation rate.
    - Carrier Vaccine: Could generate memory killer T cells, but so far modest results

- Even if memory killer T cells were produced, it will not be effective against mutated viruses! And this is a big challenge because HIV has high rate of mutation. This is why it's said that HIV is always one step ahead the immune system; the immune system recognizes the HIV strain, produces antibodies and killer T cells, the HIV produces a new strain, the immune system recognizes the new strain, HIV produces a different one…

- Work is being done on discovering broadly neutralizing HIV antibodies. By finding a conserved antigen in the HIV which won't be mutated.

It must be acknowledged that HIV is not the only obstacle: Malaria, Leishmania, tuberculosis, HSV (no vaccines!).