Immunology 2017: Lecture 14 handout

Restraining the immune system & memory cells and vaccines

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This handout will cover three topics

1. Regulating the immune system

2. Memory cells

3. Vaccines

IMMUNE SYSTEM REGULATION

INTRODUCTION

The immune system can fight infections, once there is a pathogen the innate system attacks it and if there is a need for the adaptive system to interfere, it also will be activated.

لكن لا بد للحرب ان تضع اوزارها … so after the immune response succeeds in getting rid of the pathogen, the response must stop.

Downregulation (restraining) of the immune system happens via several mechanisms

1. *Inhibition of the immune response through certain mediators and receptors*.

2. *Death of immune cells, which normally have a short life span*

3. *Activation induced cell death:* for cells that don't normally have a short life span, but will die after activation

4. *Regulatory T cells that decrease the immune response*.

1. Inhibiting the immune response

Normally, as the immune system attacks a pathogen, there will be less and less available antigens to stimulate the immune system.. the enemies are dying and there isn't many left!

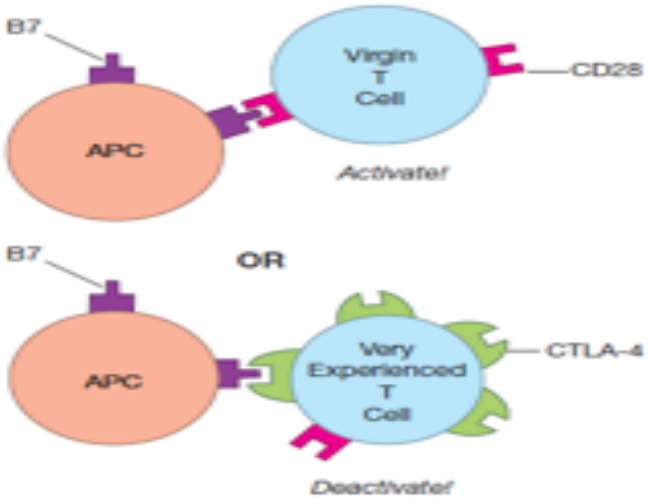
So as foreign antigen is eliminated, the level of activation of both the innate and the adaptive system decreases. This is the first step in turning off the immune system.

Moreover, B7 molecules which are important costimulatory signals when they bind CD28 receptor, can also bind to another receptor on activated T cells (CTLA 4). *This binding of B7 (on the dendritic cell) to CTLA 4 (on the activated T cell) will send an inhibitory signal and decrease the immune response*.

This inhibition occurs by two ways:

1. **The CTLA 4 antagonizes the CD28 signal within the T cell.**

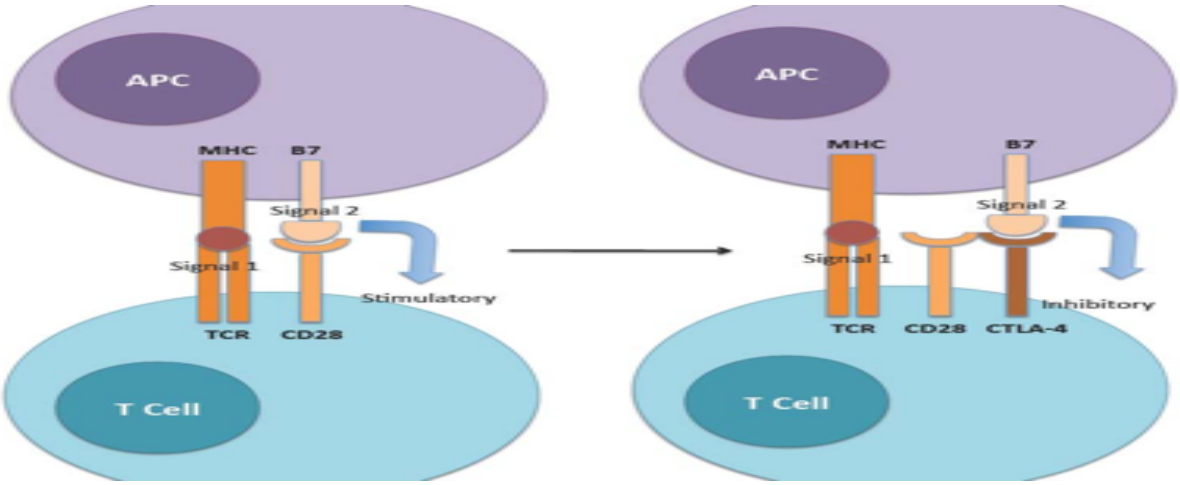
2. **CTLA-4 also suppresses activation by occupying B7 molecules because B7 binds to CTLA-4 with an affinity thousands of times higher than its affinity for CD28,**



This figure shows that B7 in the pic above stimulates T cell through binding to CD28, whereas in the pic below the activated T express more CTL 4 which binds to B7 and causes deactivation of the T cell.

Note that , most T cells display CD28 on their surface, so it is always available to assist with activation. In contrast, the bulk of a naive T cell's **CTLA-4 is stored inside the cell**. *However, beginning about two days after a virgin T cell is first activated, more and more CTLA-4 is moved from these intracellular reservoirs to the cell surface.*

SO: early in an infection, B7 binds to CD28 and acts as a co-stimulator. Then, after the battle has been raging for a while, B7 binds mainly to CTLA-4 to restrain the response.



Another molecule helps restraining the immune response was discovered, this is called programmed death 1 (PD-1). The ligand for PD-1 (PD-1L) appears on the surface of many different cell types in tissues which are under attack. And like CTLA-4, expression of PD-1 on the T cell surface increases after activation. The result is that the PD-1L protein on inflamed tissues binds to PD-1 on T cells that have been at work for a while, and stops them from proliferating.

SO: ***CTLA-4 functions to make reactivation of T cells less efficient, and PD-1 inhibits the proliferation of previously activated T cells***

2. The short half-lives of immune cells

Cells of the innate immune systems have short life span, days for neutrophils and a week for NK cells. This keeps immune response controlled

Also when NK die there isn't enough interferons produced to stimulate macrophages, so they go back to their resting stage.

Also cells of the adaptive immune system have short life span: DCs live only a week after migrating to lymph nodes, plasma cells live only 5 days.

The immunoglobulins also have short half-lives, the longest half-life is for IgG which is only three weeks.

3. Activation-induced cell death (AICD)

T cells usually live a long life, not like other cells of the immune system. This is because they need to keep circulating in lymphoid organs as we described in a previous lecture. **But once activated and finished their function, apoptosis will be stimulated via fas- fasL**

4. Regulatory T cells:

The previous three mechanisms we discussed explain how an immune response is decreased after it has been stimulated. But sometimes we need the immune response to be inhibited before it starts, to keep it to a minimum, and regulatory T cells are the ones responsible for this function.

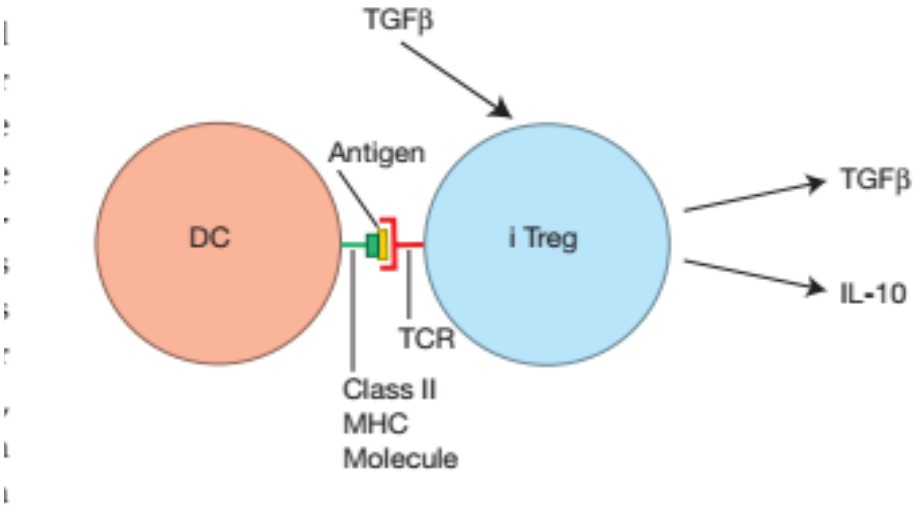
I hope you remember that we said in lecture 1 that there are three types of T cells**: T helper, T killer and T regulatory**. It's time now to talk about T regulatory cells which regulate; restrain, stop the immune response.

The surprise is: **these regulatory cells are actually T helper (CD4 +) cells that are induced to become regulatory; that's why we call them induced T regulatory cells (iTreg)!!**

You know that CD4+ cells can be induced to become Th1, Th2 or Th17 according to the cytokines secreted from the dendritic cells presenting antigens to them. In the same manner some *Th cells are induced to become iTreg if the main cytokine in the area is TGF beta. Once induced there iTreg start producing cytokines that decrease the immune response like TGF beta and IL10.*

IL10 blocks costimulatory signals of Th cells (B7) making it difficult for the DC to activate T cells

TGF beta: decreased proliferation of T cells and decreases ability of T killer cells to kill.



iTreg are important mainly in two situations:

A. They are impotent in **controlling intestinal immunity**, because we have many pathogns within the intestine, if response to these pathogens is not restrained we will have severe damage to the intestine

B. Prevent overreaction to environmental antigens so **decrease risk of allergic** reactions. They do so by inhibiting mast cell degranulation

Immunological memory

INTRODUCTION

Unlike the majority of medical students, the immune system has a strong memory! It can remember past invaders which helps in quicker protection against these invaders if they attack again.

B CELL memory!

When a naïve B cell is stimulated, three types of B cells are produced within the germinal centers of secondary lymphoid organs:

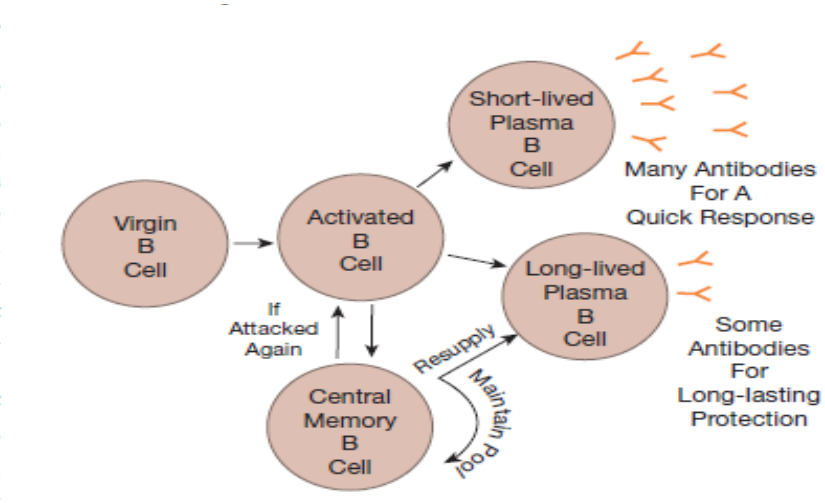
1. **Short lived plasma cells** that migrate to bone marrow or spleen and produce huge amounts of Ig to fight the infection

2. **Long lived plasma cells** which migrate to the bone marrow and produce moderate amounts of Ig . These are responsible for the life long immunity to previous invaders.

3. **Memory B cell**, also called **central memory B cell** which reside in secondary lymphoid organs. These do not produce antibodies. They function as memory "stem cells" which *slowly proliferate to maintain a pool of central memory B cells*, and to *replace long-lived plasma cells which have died*. In addition, if another attack occurs, central memory cells can *quickly produce more short-lived plasma B cells*

NOTE that both long lived plasma cell and memory B cells need T cell help to be produced. If B cells were activated by T cell independent activation then these two types of cells can not be produced.

Please remember that we said in a previous lecture that B cell maturation needs T helper, this maturation includes: class switching, affinity maturation and differentiation (career choice)

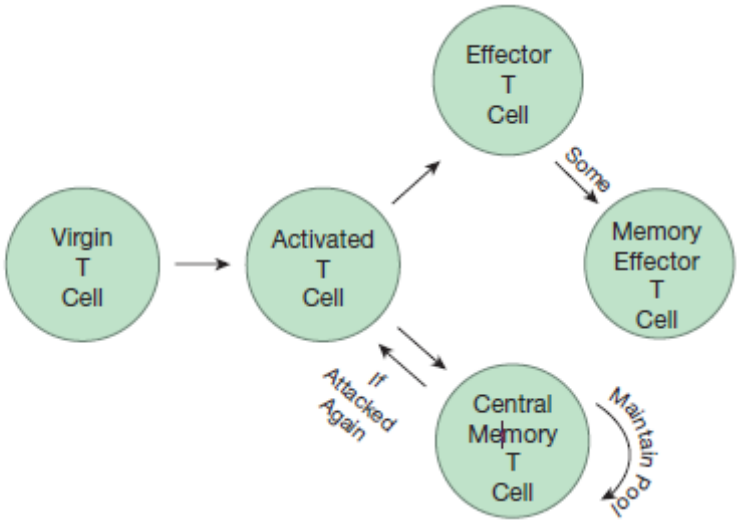


T CELL MEMORY!

There are two types of memory T cells

1. **Memory effector T cells**: after being activated T cells that react to the pathogens are called effector T cells. The majority (90%) of these die by apoptosis after the attack. The rest become memory effector cells that persist in tissues where the initial attack occurred, ready to proliferate and react if the same pathogen attacks.

2**. Central memory T cells**: these are activated T cells that didn't initially migrate to tissues; instead they remained in the secondary lymphoid organs. During a subsequent attack, central memory T cells are activated quickly and they proliferate. Most of them mature into effector cells, which join the memory effector T cells at the battle scene. The rest of the central memory T cells remain in the secondary lymphoid organs and wait for another attack by the same invader.



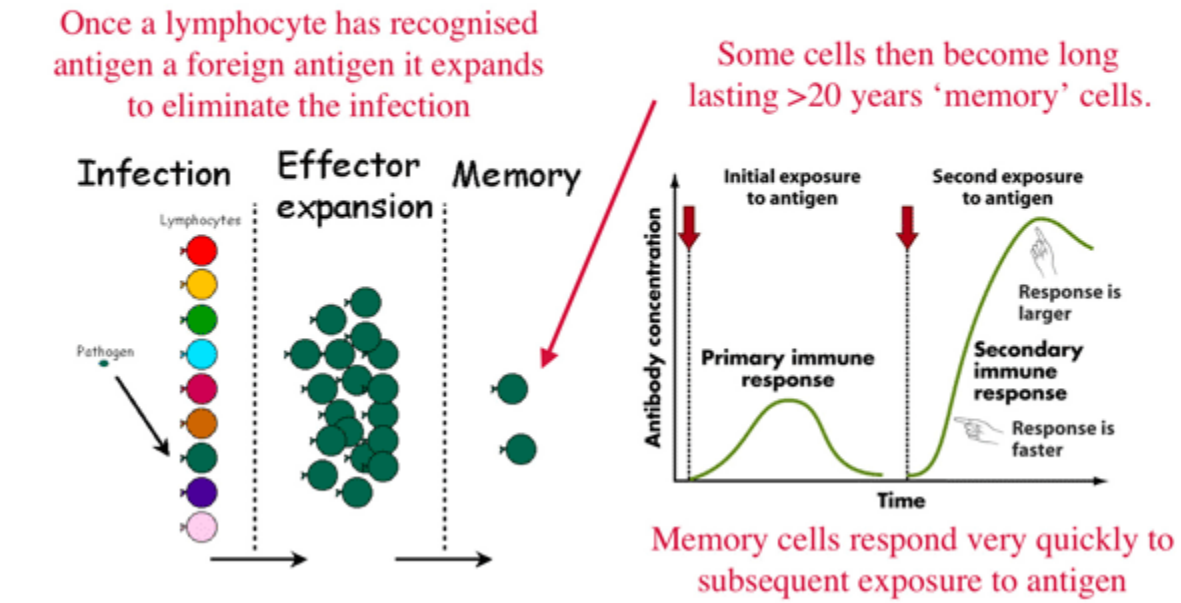
Why memory B and T react quicker than naïve cells ?

1. There is a large number of memory cells that recognize the specific antigen compared to the number of similar cells during the first invasion

2. Memory cells are easier to be activated, we need less co stimulatory signals for these cells. A possible explanation for this accelerated differentiation is that the gene loci for cytokines and other effector molecules are fixed in an accessible chromatin state in memory cells, in part because of changes in methylation and acetylation of histones (epigenetic changes)

3. Regarding B cells, the memory B has undergone class switching and affinity maturation so it is equipped with the right weapons for the pathogens and can react better than inexperienced B cells.

IMMUNE MEMORY



NOTE

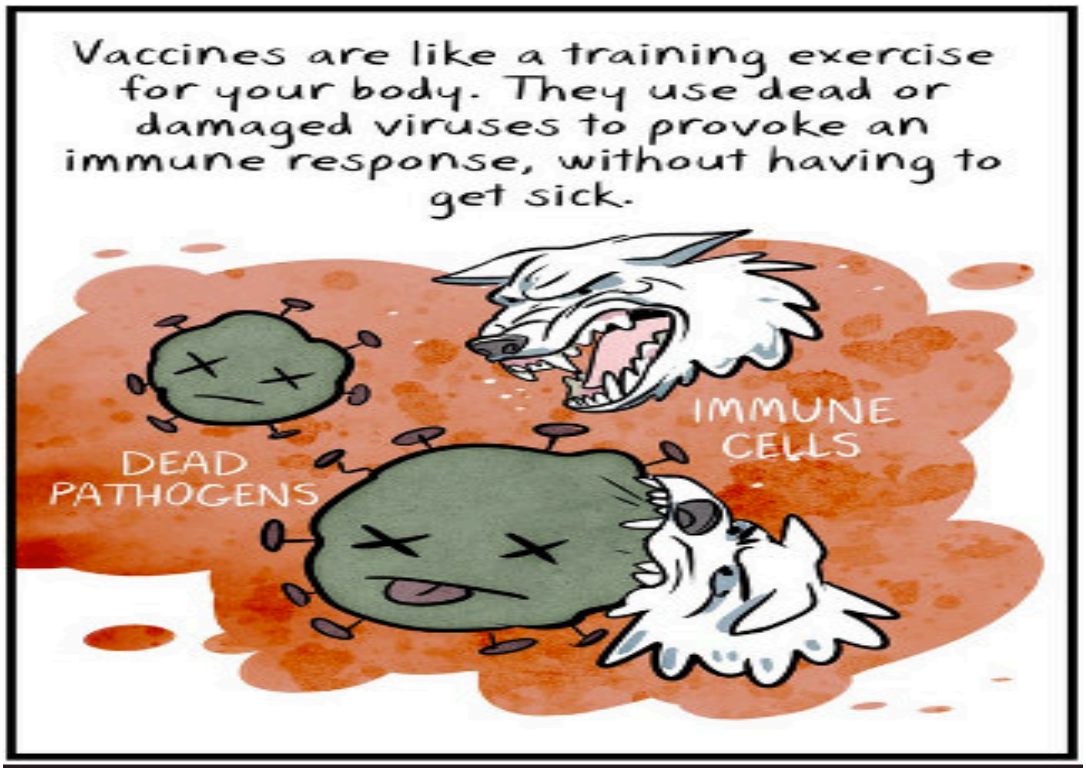
Memory cells express increased levels of antiapoptotic proteins (BCL 2 and BCL-xl) , which may be responsible for their prolonged survival.

T KILLR MEMORY:

Memory killer T cells also can be produced during a microbial attack, but for this to happen, the microbe must infect an antigen presenting cell.

VACCINES

Our immune system is able to produce memory cells that can give life long immunity. We can medically induce the production of these memory cells which will help in providing immunity to the host without suffering the initial attack. This happens via vaccines which mimic a pathogen's attack but do not cause harm to the host.



There are several types of vaccines

1. Non- infectious vaccines
2. Attenuated vaccines
3. Carrier vaccines

1. NON INFECTIOUS VACCINES

In this type of vaccination we use a **killed** pathogen or part of a pathogen, which are **not infectious**, to cause immunity. There are several types of non-infectious vaccines:

1. **Killed viruses** that cannot infect cells but will contain antigens that can activate B or T cells

Example: Polio vaccine is killed by formaldehyde which denatures its proteins

Common flu vaccine also is a killed viral vaccine

2. **Killed bacteria**: Typhoid and pertussis vaccines are killed bacterial vaccines

3. **Attenuated bacterial toxins (toxoids**). These are treated with aluminum salts to weaken them.

Example: diphtheria and tetanus vaccines

: Also pertussis acellular vaccine

4. **Viral proteins produced by genetic engineering: like vaccines to:** HBV (hepatitis B virus) , HPV (human papilloma virus)

Note that non-infectious vaccines generate memory helper T cells and B cells but not memory killer T cells (because antigen presenting cells will not be infected : the virus is dead and unable to infect any cell and as we said for memory CD 8 T cells to be produced the virus must infect an Ag presenting cell. Because in this situation T helpers are needed and T dependent activation is essential for memory cels to develop).

2. ATTENUATED VACCINES

Another strategy for producing a vaccine is to use a weakened or "attenuated" form of the microbe. Virologists noticed that when a virus is grown in the laboratory in a cell type which is not its normal host, the virus sometimes accumulates mutations that weaken it. The polio vaccine, for example, was made by growing poliovirus, which normally reproduces in human nerve cells, in monkey kidney cells. This strategy resulted in polioviruses which were still infectious, but which were so weak they could not cause the disease in healthy individuals.

The vaccines for measles, rubella, and mumps, are attenuated viral vaccines.

An attenuated vaccine is tested on animals to get a general idea of whether the attenuation procedure has worked. However, to be sure the weakened microbe can stimulate the production of memory cells, without causing disease, it must be tested on human volunteers.

One important feature of attenuated virus vaccines is that they can produce memory killer T cells. This is because the attenuated virus can **infect antigen presenting cells** and stimulate the production of CTLs before the immune system has had a chance to destroy the weakened invaders.

However, because an attenuated vaccine contains a microbe that is infectious, there are safety issues. When a person has recently been vaccinated with an attenuated virus vaccine, he may produce enough virus to **infect some of the people with whom he comes in contact**. This **can be an advantage if those people are healthy, because it spreads the immunity around, producing what is called *herd immunity*.**

However, for the immunosuppressed, this type of vaccination can have serious infections.

A second potential safety issue with an attenuated virus vaccine is that the virus **may mutate**, and these mutations may restore the strength of the virus. Although this is **not a very likely scenario, some healthy people who received the polio vaccine have contracted polio because the weakened virus mutated and regained its ability to cause disease.**

3. CARRIER VACCINES

A relatively new strategy for vaccine preparation uses genetic engineering to introduce a single gene from a pathogenic microbe into a virus that doesn't cause disease.

This engineered virus can then be employed to carry the gene of the pathogenic microbe into human cells. The idea is that if the carrier infects the vaccine recipient's antigen presenting cells, these cells will produce the pathogenic microbe's protein as well as the carrier's own proteins. As a result, inoculation with a carrier vaccine should generate memory killer T cells that can protect against a future attack by the real pathogen. Importantly, there is no chance that this vaccine will cause the disease it is designed to protect against – because only one or a few of the pathogen's many genes is "carried" by the vaccine.

VACCINE ADJUVANTS

In order for a vaccine to mimic the invasion of a pathogenic microbe, the immune system must view the vaccine as both **foreign and dangerous**. This is not a problem for a vaccine which uses attenuated virus – because a weakened virus naturally provides both signals. However, for vaccines composed of only one or a few microbial proteins, providing the requisite danger signal can be a serious problem. Indeed, if a foreign protein is injected into a human, the immune system generally just ignores it because it poses no danger.

Because of this requirement for a danger signal, it is common practice to combine vaccines with an adjuvant (derived from a Latin word meaning "help"). Most of the vaccinations you have received probably contained aluminum hydroxide or "alum," which functions, at least in part, by providing that important danger signal.