بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

Immunology 2017 , Handout 15

Self tolerance and MHC restriction

Dr Heyam Awad

INTRODUCTION

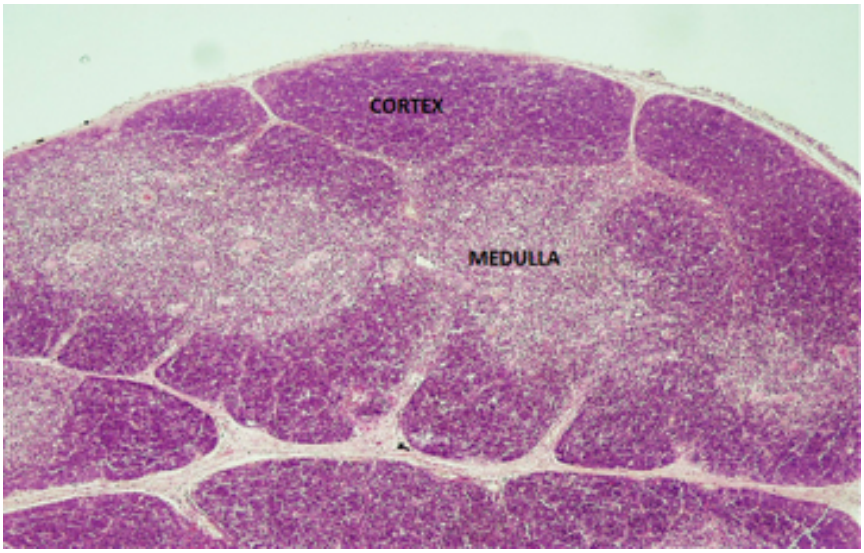
Till now we discussed immunologic reactions including innate and specific immunity, immunological memory and regulation of the immune system.

In this lecture we will talk about self-tolerance : how our immune cells are trained not to attack self-antigens.

T CELL TOLERANCE

T cells mature in the thymus where the self reactive T cells are eliminated.

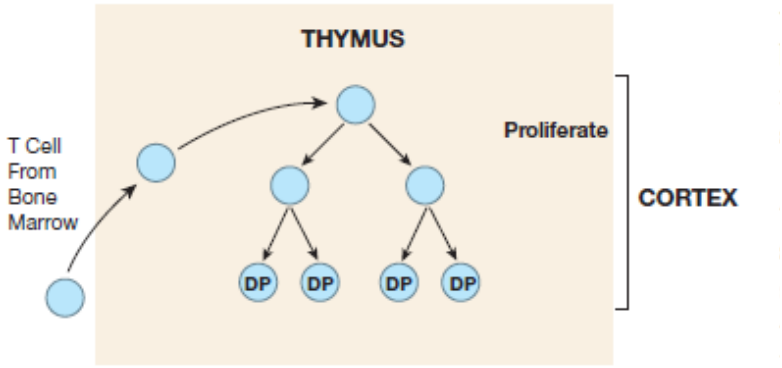
Histologically the thymus is composed of cortex and medulla. Maturation and tolerance occurs in these two parts of the thymus.



T cells originate from the bone marrow and migrate to the thymus. They enter the thymus through blood (like the spleen, the thymus lacks afferent lymphatics).

These T cells that enter the thymus lack TCR, CD4 and CD8. They are called double negative T cells (because there are no co-receptors: no CD4 or CD 8).

Within the cortex, T cells proliferate then they start gene rearrangement and develop TCR as well as BOTH CD$ and CD8 (double positive T cells= DP in the figure below). At this stage they upregulate Fas-L and under-regulate bcl2: so they are ready for apoptosis if they fail the tests of maturation.



Within the cortex, thymic epithelial cells present antigens to these DP T cells, the cell that recognizes the Ag presented by MHC molecule survives, whereas the cell that doesn't recognize, or binds inefficiently with MHC will die by apoptosis this is called **positive selection.**

The aim of positive selection is to keep only T cells that recognize processed presented Ag; we don't want to keep any T that recognizes unpresented Ag.

NOW: These T cells are double positive but once they recognize MHC bound Ag they become single positive (SP), the cell that recognized MHC 1 will downregulate the CD4 and become CD8+ and vice versa. This is called **MHC restriction**, which means each T will only recognize either MHC I or II along with its associated peptide

These SP cells move to the thymic medulla for their second stage of self tolerance training: the **negative selection**, during which T cells that recognize self antigens will be deleted.

Within the medulla two cells will resent a wide range of self antigens to T cells to check for self reactive T cells which will be negatively selected by apoptosis; these two cells are

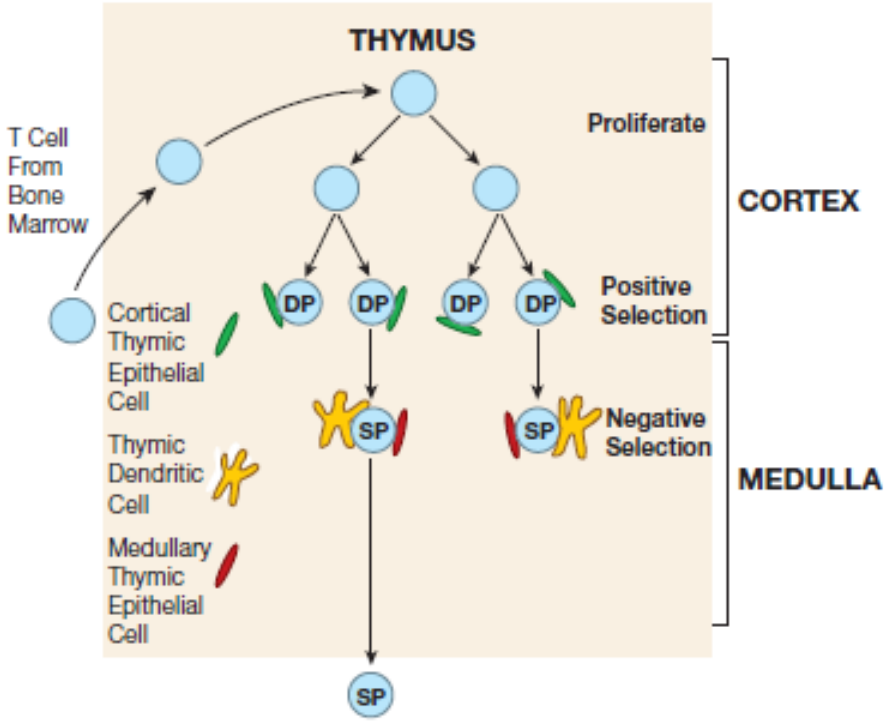
1. **Dendritic cells**, some of which are bone marrow derived, others are mesenchymal in origin. Both migrate to thymus and resent Ag to T cells.

2. **Medullary thymic epithelial cells (** mTEC). These present self antigens which are abundant in the thymus but also use two strategies to increase the diversity of Ag presented:

First strategy: they use autophagy to create self antigens .. note: this is also used by cortical thymic epithelial cells.

Second strategy: they contain a transcription factor (Aire) which upregulates expression of tissue specific Ag (example heart or kidney have specific Ag not found in other tissues, so autophagy alone will not create them)

SO: by these two strategies a very wide range of self Ag will be created and any T that recognizes any self antigen will be deleted by apoptosis.



Note that each day in the thymus of a young person, about 60 million double-positive cells are tested, but only about 2 million single-positive cells exit the thymus and these tests take about two weeks!

These cells that exit the thymus are MHC restricted , single positive and the majority of them are self tolerant. However, not all self Ag are presented in the thymus … so some self reactive T cells will escape and go to lymphatic tissues and secondary lymphoid organs.

This means we need further steps to delete those self reactive T that escaped. This is done in the secondary lymphoid tissues and is called **peripheral tolerance** (as opposed to **central tolerance in the thymus)**

Before leaving the subject of central tolerance, a puzzling question is : how is it possible that the T cell that recognized a self Ag in the cortex survived and this same one that recognized the same Ag in the medulla died?

The answer lies in the signaling pathways of the TCR. If you remember we said in a previous lecture that TCR have several signaling pathways with different outcomes: survival, death, anergy or activation!

It is thought that T cells in the cortex bind the Ag presented on the MHC molecule lightly, which results in survival signaling, whereas this cell binds the MHC- Ag complex tightly in the medulla resulting in a death signaling pathay. How this difference in binding happens? Probably due to changes in the surrounding envireonment, chemical mediators, co stimulation available .. etc

PERIPHERAL TOLERANCE OF T CELLS

Peripheral tolerance occurs via several mechanisms

1. Naïve T cells circulate within lymphatics, away from tissue antigens, so they are not in direct contact with tissues and even if there are self reactive T cells, this **circulation** prevents them from coming in contact with their cognate Ag.

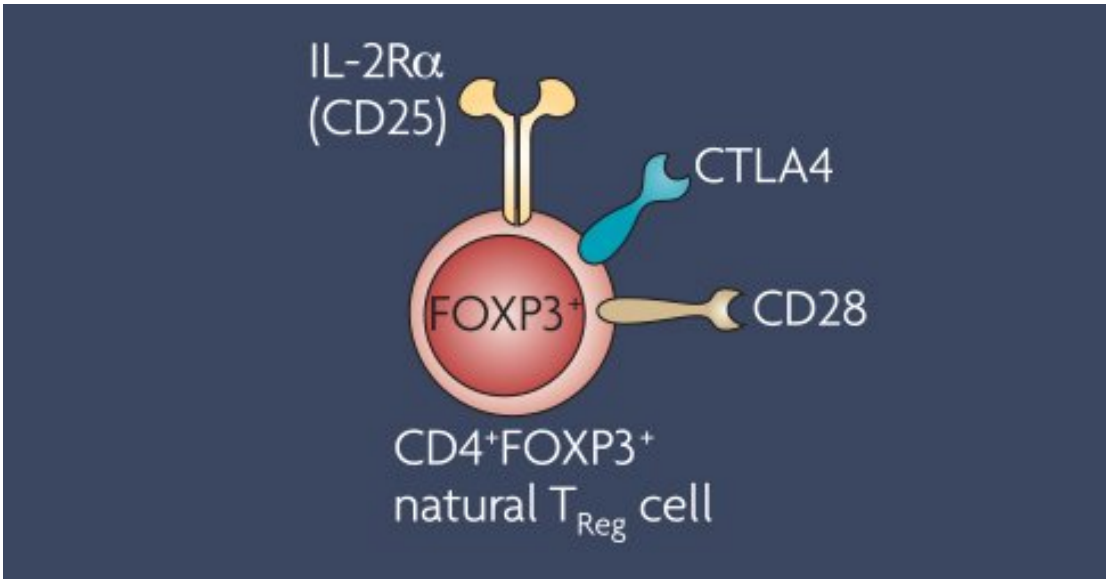
2. Some self reactive T recognize Ag present normally in little amounts not enough to elicit an immunologic reaction (remember, recognizing the cognate Ag is not enough to stimulate the T cell, you need receptor cross linking and co stimulation.. so if the Ag concentration is low no reaction will happen) so as if this T cell is ignoring this Ag… this is called **tolerance by ignorance**

3. self reactive T cells that recognize an Ag with moderate concentration can potentially start an immunologic reaction. But some of them don't receive a costimulatory signal and this results in **anergy** (they become inactive)

4. however, some self reactive T cells that recognize an Ag with moderate concentration can receive a costimulatory signal and start a reaction, but these with time will be eliminated by **activation induced cell death** (see previous lecture)

5. An important mechanism in peripheral tolerance is mediated by a t regulatory cell called natural t regulatory T cell **(nTreg)** .. this is different from iTreg described in a previus lecture.

nTreg is a helper T that expresses a gene called FOXp3. These cells originate in the thymus and migrate to peripheral lymphoid organs and eliminate self reactive T cells, probably by inhibiting co stimulatory signals.

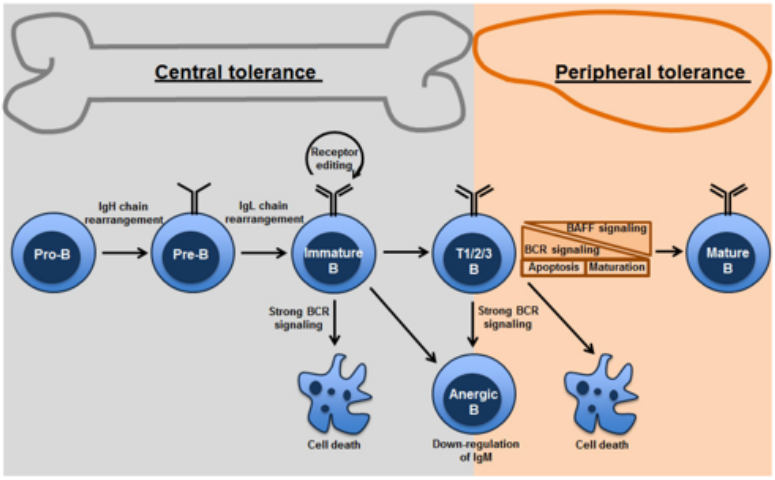


Please note: the role of natural regulatory T cells is to provide protection against T cells which have the potential to react against self antigens and cause autoimmunity, but the main function of inducible regulatory T cells is to keep the immune system from overreacting to foreign invaders

B CELL TOLERANCE

B cells also undergo central tolerance (in the bone marrow) and peripheral tolerance (mainly in lymphoid follicles) where self reactive B cells will die by apoptosis.

The main difference between T and B tolerance is that B cells which are self reactive can be given a second chance to rearrange their receptors via hypermutation (affinity maturation). If this rearrangement (called receptor editing) results in a B cell that recognizes a non- self Ag it will survive, otherwise it will die by apoptosis.



A problem with B cells is that in the lymphoid follicles they can undergo affinity maturation which, in rare cases, might result in recognizing a self Ag. however self tolerance is preserved even if B cells undergo hypermutation for two reasons:

1. The lack of opsonized self antigen required for efficient BCR signaling (self Ag will not be opsonized by complement)

2. The lack of germinal center T helper cells which can provide help for B cells that recognize self Ag.

NATURAL KILLER TOLERANCENK

NK cells are “examined” to be sure that their **inhibitory receptors do recognize at least one of the class I MHC molecules displayed by the cells of the humans they inhabit**. NK cells whose inhibitory receptors do not match up with any of a person’s class I MHC molecules are rendered non-functional. This avoids NK cell-mediated autoimmunity. The mechanisms involved in this type of “positive selection” are not well understood, but this process is believed to take place in the bone marrow.

THANK YOU