Immunological tolerance :Unresponsiveness of the adaptive immune system to antigens, as a result of inactivation or death of antigen-specific lymphocytes, induced by exposure to the antigens. Tolerance to self antigens is a normal feature of the adaptive immune system, but tolerance to foreign antigens may be induced under certain conditions of antigen exposure.

Factors induction Immune Tolerance :

1.The stage of differentiation of lymphocytes.
2.The site of encounter.
3.The nature of cells presenting antigenic epitopes.
4.The number of lymphocytes able to respond.
5.Microinvironment of encounter .

General properties :

1.Immature or developing lymphocytes are more susceptible to tolerance
2.Tolerance to foreign antigens .
3.Tolerance of T lymphocytes .

Divisions of Tolerance.

Central:

1.The cite for T cells is the thymus.
2.The cite for B cells is the bone marrow
3.Mechanism clonal deletion.

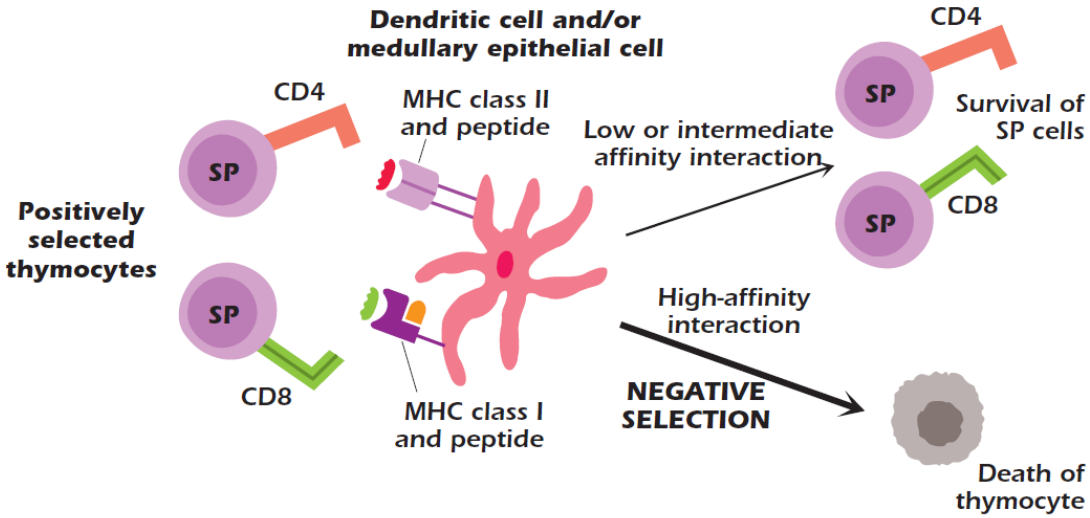
Peripheral :

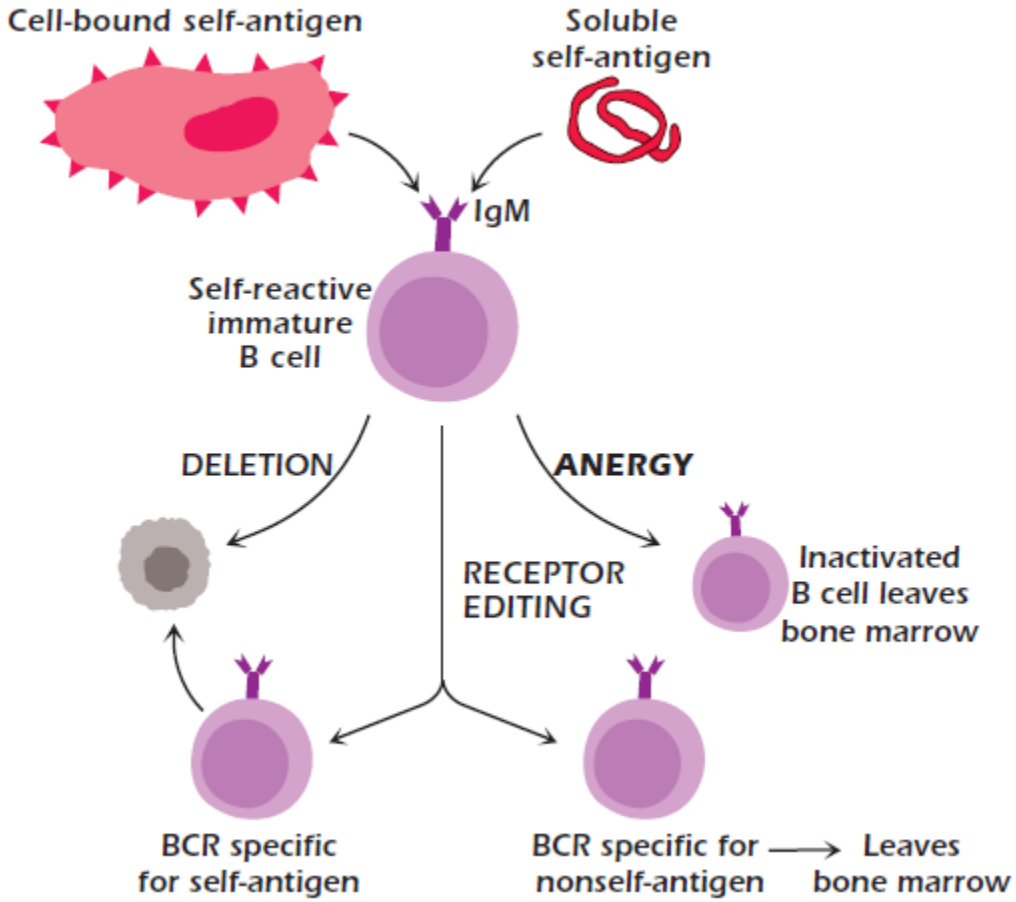
1.The cite in the body.
2.Cells of both T cells & B cells
3.Mechanisms anergy ,cell death and immune deviation

The main reason self-specific B cells do not respond is due to lack of T cell help

The mechanisms of clonal deletion and anergy do stop some self-specific B cells from developing or functioning However many self-antigens are not expressed in the bone marrow and therefore mature self-antigen specific B cells do leave the bone marrow and enter the lymphoid system. In . So why do they not go on to become antibody-producing plasma cells? The answer is a lack of self-antigen specific helper T cells. For B cells to be able to differentiate into plasma cells they require help from CD4 T cells. B cells bind antigen through the Ig on their cell surface and take up the antigen. They then process the antigen and express antigen peptides on class II MHC on the cell surface . This peptide/MHC complex is recognised by helper T cells which then provide signals to the B cell that stimulate it to divide and differentiate into a plasma cell. If the B cell is specific for foreign antigen there will be CD4 T cells specific for that foreign antigen. However, if the B cell is specific for self-antigen, even if it can process the antigen and present self-peptide on

its class II MHC there will be no self-specific CD4 T cells present and therefore the B cell will not get the signals to become a plasma cell. In fact, in the absence of these T cell signals the B cell will die by apoptosis.





Self-tolerance in T lymphocytes – selecting for recognition of self-MHC but not self-antigen

The development of T cells poses some additional problems not seen with B cells. Since B cells recognise free antigen there is a simple distinction to be made with every developing B cell and that is whether the Ig it expresses is specific for self-antigen or foreign antigen. T cells recognise antigen in an MHC-restricted manner. Some of the TCR binds to MHC and some binds to the peptide . Because the rearrangement of TCR genes is random, T cells can be produced with four potential types of specificity in terms of MHC and antigenic peptide. The TCR could be specific for:

1. Foreign antigenic peptide + self-MHC.
2. Self-antigenic peptide + self-MHC.
3. Foreign antigenic peptide + foreign MHC.
4. Self-antigenic peptide + foreign MHC.

Of the four specificity patterns, only cells that are specific for foreign antigenic peptide plus self-MHC I will be useful at recognising antigens derived from pathogens. Cells with specificity for self-antigenic peptide plus self-MHC II are potentially damaging and could cause an immune response against the body's own antigens. Cells that can only recognise antigen in association with foreign MHC will be useless in that particular individual because they cannot recognize antigen peptide in association with the individual's own MHC. While these cells would not be harmful to the individual, if they were not got rid of they would clog up the immune system with lots of useless cells. Therefore during T cell development there is the requirement (i) to select T cells that are self-MHC-restricted, a process called positive selection, and (ii) to prevent the production of potentially damaging T cells with specificity for self-antigenic peptide and self-MHC, called negative selection. These are accomplished by special mechanisms that operate during T cell development in the thymus.

How do we maintain tolerance to self-antigens not expressed in the thymus?

Tregs are vital in preventing autoimmune disease they are not in themselves sufficient. This is because not all self-antigens are expressed in the thymus.

The self-antigens that thymic dendritic or medullary epithelial cells express on their MHC must either be made in the thymus or travel to the thymus in the bloodstream. most self-antigens would not be expressed in the thymus because they are proteins that are made only in specific tissues or organs and are not secreted and therefore do not enter the bloodstream. An example of this would be the thyroid-stimulating hormone receptor, which is only expressed on the surface of thyroid epithelial cells. The self-antigens that are

expressed outside the thymus have been called peripheral antigens. Recent evidence has indicated that thymic medullary epithelial cells may express proteins that would normally be regarded as tissue-specific extra-thymic proteins. One of the first demonstrations of this was that of insulin expression in the thymus; previously it was thought that insulin was only produced by the b cells in the islets of Langerhans of the pancreas. As a consequence of this they suffer from a number of autoimmune disorders. Therefore there may be more self-proteins expressed in the thymus than was previously thought. This means that T cells specific for these self-antigens will be produced in the thymus and enter into the bloodstream and lymphoid system. It is therefore important to have mechanisms that stop these self-reactive T cells from being activated and mounting an immune response against self-antigens. Tolerance induced in T cells that have left the thymus and entered the lymphoid system is known as peripheral tolerance and there are a number of different mechanisms.