Tolerance

Is the failure of the immune system to respond to an epitope in an aggressive way.

Self tolerance results from the inactivation or destructionof lymphocytes bearing BCR or TCR that recognize and bind self epitope. Inactivation or destruction mar occur during early development (central tolerance) or may be imposed on lymphocyte in periphery (peripheral tolerance).

Central tolerance:

Occur during early differentiation of B cells in the bone marrow and T cell in the thymus. Normally, both B and T cells that bind self epitopes at early stages of development meet an apoptotic death (negative selection), thus eliminating large numbers of potentially self reactive cells before they enter the circulation.

Peripheral tolerance:

Several mechanisms control or eliminate autoreactive B and T cells after they exit the bone marrow and thymus:

1. Anergy: binding of TCR to an appropriate pMHC I or pMHC II on the surface of APC provides the 1^{st} signal for activation, but the T cell must receive the 2^{nd} signal from APC for activation to proceed. Receipt of the 1^{st} signal in the absence of the 2^{nd} signal causes naïve T cell to enter a state of inactivity known as anergy. B cells can also undergo anergy. Naïve B cells can be anergized if their surface immunoglobulins bind to self antigens in the absence of the additional necessary T cell signals.
2. Suppression: tolerance to self epitopes can be induced by regulatory cells (e.g $CD4^{+ve}$ $CD25^{+ve}$ T cells).

Loss of Tolerance:

Despite the various mechanisms that prevent responses to self epitopes, autoimmunity still occurs. This may happens through different possibilities:

1. Molecular mimicry
2. Epitope spreading
3. Loss of suppression
4. Sequestered antigens
5. Neoantigens.