TOLERANCE

When lymphocytes encounter specific antigen the result may be :
1)- Activation.
2)- Inactivation (anergy) or elimination i.e. tolerance.
3)- Antigen is ignored.

If immature lymphocytes (in primary lymphoid tissues) encounter specific antigen the result is elimination or inactivation rather than activation, this is known as central tolerance. The antigens present in primary lymphoid tissues are usually self antigens (foreign antigens are trapped in secondary lymphoid tissues where only mature lymphocytes are present), thus central tolerance results in tolerance to self antigens.

Central tolerance of T lymphocytes :
In the cortex of thymus, developing lymphocytes (thymocytes) whose TCR recognize self peptides in conjunction with MHC molecules present on cortical epithelial cells, are given a signal to continue their maturation, this is known as positive selection. Those thymocytes whose TCR does not recognize self peptides on MHC molecules are neglected and die by apoptosis (these are useless since they cannot recognize MHC which will present antigen to them for activation later in the peripheral lymphoid tissues). Positively selected thymocytes move to the cortico-medullary junction where they interact with MHC and self peptides on dendritic cells, macrophages and epithelial cells. Thymocytes whose TCRs exhibit high affinity to self peptides on MHC (potentially self reactive) are given a signal that results in their death by apoptosis, this is known as negative selection. T cells exhibiting low affinity continue to mature and move to the medulla where fully mature T lymphocytes are found before exiting the thymus to the periphery. Thus, self reactive T lymphocytes are eliminated in the thymus leading to self tolerance. AIRE gene in medullary thymic epithelial cells.
Positive selection occurs in double positive (CD4+ CD8+) lymphocytes, while negative selection occurs in double and single positive lymphocytes.
Thymocytes that exhibit medium affinity are believed to develop into regulator T lymphocytes.

Central tolerance of B lymphocytes :
Immature B cells whose BCR specifically recognize antigen (self antigens) in bone marrow undergo deletion by apoptosis
Immature, IgM + multivalent antigen cross-linking leads to apoptosis.
Immature, IgM + soluble antigen leads to reduced expression of sIgM, reduced signaling result anergic cell, pass to periphery as mature cells, but cannot be activated and soon die.
Receptor editing : if the B cell is reactive no further maturation occurs, the kappa gene is inactivated and RAG1 and 2 reappear with consequent lambda chain rearrangement (cell is given another chance) if still autoreactive the cell dies by apoptosis.

Peripheral tolerance :
Antigen binding without costimulator leads to anergy, unable to to produce IL-2, thus unresponsive even if properly stimulated. This applies to abundant antigen in body not encountered in thymus.

Self antigens expressed at too low a level are not recognised by T cells.
RARELY a self antigen is present at sufficient levels to be recognised by T cells but too low to induce anergy, these cells are not activated (lack of costimulation), these cells are said to be in a state of immunological ignorance, and are potential source of auto-immune reaction. This is the weak link.
High dose vs. low dose tolerance.

T reg cells :
Naturally occurring nT reg. cells. Develop in thymus.
Constitute 10 % of peripheral CD4 T cells.
These cells express CD4, CD25 and fox3p markers.
They constitutively express CTLA-4 antigen.
Probably selected in the thymus through intermediate affinity of TCR to MHC-self antigen.
They are activated specifically through TcR, but once activated their action is non-specific.
Terminate immune responses. Protect against autoimmunity.
Work by secreting suppressive cytokines TGF-beta and IL-10.

Induced T regulatory cells iTreg or (TH3 and Tr1) cells are derived from conventional CD4+ CD25- T cells in the periphery under the effect of IL-10 and TGF-beta.
Action through production of IL-10 and TGF-beta.
The individual contribution of nTreg and iTreg cells to tolerance is not known.
TH3 cells are present in GIT mucosa, secrete TGF-beta which promotes IgA switching and also IL-10. It is not clear whether TH3 and iTreg are different entities or not.

Induced Treg develop under effect of TGF beta, interestingly TH17 develop under effect of TGF-beta and IL-6 or IL-21.
Th17 is involved in combating fungal and bacterial infection, but it is involved in the pathology of immune disease e.g. multiple sclerosis, psoriasis, juvenile diabetes, rheumatoid arthritis, Crohn's disease. They secrete IL-17.

Feeding antigen :
TGF-beta producing T cells, for IgA switching. If antigen is given systemically no response.

Immunologically privileged sites : Brain, eye, testis.
Not anatomical, lack of lymphatics, also suppressing cytokines produced in tissue.
Tolerance can be broken : sympathetic ophthalmia, experimental encephalomyelitis through immunisation.
Testis has Fas ligand with T cell leads to apoptosis.

B cell :
1)- Lack of T cell help.
2)- Soluble antigen like Immature cells, anergy is induced (eventually the anergic cell dies within a few days). In the case of particulate antigen or part of a cell surface deletion is induced by cell death.
3)- Somatic hypermutation may lead to autoreactive B cells, encounter with abundant soluble antigen leads to death ? Fas.

Tolerance & Auto-immunity

A unique feature of the immune system is the recognition of self from non-self. This unresponsiveness to self is known as immunologic tolerance.
Tolerance is learned, it was believed that tolerance could only be induced during development, but it was later found that adult animals could also be made tolerant.

General properties of immune tolerance :
1)- Tolerance is specific, interaction between antigen and specific receptor results in activation or tolerance depending on the maturational stage of the specific lymphocyte, the nature of the antigenic stimulus and (for T lymphocytes) the nature of the APC.
Tolerance to self antigens is acquired requiring the presence of the antigens to induce it, dizygotic cattle twins have chimeric RBC and are tolerant because the mixture of blood occurred during foetal development.
2)- Immature lymphocytes are more susceptible to tolerance than mature ones, all lymphocytes go through a maturational stage at which antigen recognition leads to their death or inactivation, this is central tolerance.
3)- Tolerance to antigen can be induced in mature lymphocytes if they are exposed to antigen under particular conditions, probably by the absence of second signals (costimulators for T cells, T cell help for B cells and CTL's), this is peripheral tolerance.
4)- Tolerance occurs through deletion and anergy.
5)- Tolerance may also occur despite the presence of mature antigen responsive lymphocytes through inhibition of their growth and differentiation by T reg. cells.
The mechanisms of tolerance are not fully understood.
6)- Immunological ignorance. Probably induced by self antigens that are present in small amounts.

Peripheral tolerance :
Some lymphocytes may escape this central tolerance, these have to be made tolerant peripherally and this is important in the case of antigens that may not be present in the thymus. These cells are probably made tolerant in the periphery through mechanisms similar to peripheral tolerance to foreign proteins i.e. when they encounter antigen under conditions that favour tolerance rather than activation, e.g. the lack of co-stimulators.
Clonal anergy of CD4 cells is best documented with high doses, IV injections, without adjuvants (called high-dose tolerance), oral administration of protein antigens (oral tolerance), and repeated low doses without adjuvants (low-dose tolerance).
This T-cell tolerance can induce B cell tolerance because of the lack of help. But independent peripheral B cell tolerance must occur also with T- independent antigens, although the mechanisms are not fully undrerstood.
This T-cell tolerance may be due to :
1)- Antigen encounter without costimulators from APC, such as B7 that interact with CD28, the T-cell becomes anergic and is incapable to respond upon later stimulation when antigen is presented with proper co-stimulator (because they fail to secrete IL-2).
2)- Helper cells become unresponsive if the antigen is presented by other T-cells that express MHC II molecules; APC's that deliver -ve signals are called veto cells.

Whether T-cell presentation of antigen is of physiological importance is not yet established.

3)- The affinity of antigen recognition by T cells may determine whether activation or tolerance occurs. Higher affinity results in tolerance rather than activation (postulated but not proven).

4)- The microenvironment of the encounter between antigen and lymphocyte may determine whether tolerance or activation occurs, if CD4 cells are exposed to high concentration of IL-2 before or during encounter with antigen these cells undergo apoptosis.

5)- Stimulation of CTLA-4 instead of CD28 by B7 leads to tolerance rather than activation, it is not known why this happens. It is possible that low levels of B7 engage CTLA-4, this may be determined by the nature of the APC, resting APC's having no or little B7.

6)- Repeated activation of CD4 lymphocytes results in the expression of Fas and Fas ligand, which leads to apoptosis. Repeated activation may be due to the presence of abundant self antigens resulting in elimination of self reactive lymphocytes.

Immune deviation :

Thus immune deviation from Th1 to Th2 could be viewed as a means of tolerance.

Regulation of the immune response :

1)- Elimination of antigen which is the necessary first signal for lymphocyte activation.
2)- Cytokines and antibodies have short half-lives.
3)- The effector cells (contrast memory cells) plasma cells and CTL's are short lived and not self renewing.
4)- Memory cells are long lived but are inactive unless stimulated by antigen.

There are also feed-back mechanisms :
Antibody feed-back :
a)- antibodies remove antigen thus removing the stimulus : use of blocking antibodies in Rh incompatibility prevention.
b)- direct inhibition of B-cells by binding to Fc receptors on B cells. Specific immune complexes can cross-link surface Ig and Fc receptors on B cell resulting in B-cell inhibition.
c)- Network hypothesis : this is a theory (not proven), anti-idiotypes (which can be humoral or cell-mediated) against T and B cell receptors i.e. TcR and sIg. The network theory proposes that a steady state is maintained by this network of idiotype and anti-idiotype, introduction of antigen perturbs this balance and leads to detectable immune response.
d)- The expression of CTLA-4 on CD4 cells leads to inhibition.
e)- Appearance of Fas and Fas ligand leads to apoptosis.