Lec (7)

Assistant Prof. Dr. Ekhlass N. Ali

Immunology

Immune tolerance

Immune or '***immunological tolerance'*** is the process by which the immune system does not attack an antigen. It occurs in three forms: central tolerance, peripheral tolerance and acquired tolerance.
Genetic defects in these processes lead to autoimmunity, such as in the human syndromes SLE

Central tolerance: occurs during lymphocyte development and operates in the thymus and bone marrow. Here, T and B lymphocytes that recognize self antigens are deleted before they develop into fully immunocompetent cells, preventing autoimmunity. This process is most active in fetal life, but continues throughout life as immature lymphocytes are generated.

In mammals the process occurs in the thymus (T cells) and bone marrow (B cells), when maturing lymphocytes are exposed to self antigens. Self antigens are present in both organs due to endogenous expression within the organ and importation of antigen due to circulation from peripheral sites. In the case of T cell central tolerance, additional sources of antigen are made available in the thymus by the action of the transcription factor .

Positive selection occurs first when naive T-cells are exposed to antigens in the thymus. T-cells which have receptors with sufficient affinity for self-MHC molecules are selected. Others that do not undergo **death by neglect** involving apoptosis. This does not occur in B-cells.

Negative selection of T-cells with a very high affinity of self-MHC molecules are induced to anergy, or lineage divergence to form T-regulatory cells.

Peripheral tolerance

Peripheral tolerance is immunological tolerance developed after T and B cells mature and enter the periphery.

Acquired tolerance

Acquired or induced tolerance refers to the immune system's adaptation to external antigens characterized by a specific non-reactivity of the lymphoid tissues to a given antigen that in other circumstances would likely induce cell-mediated or humoral immunity. One of the most important natural kinds of acquired tolerance occurs during pregnancy, where the fetus and the placenta must be tolerated by the maternal immune system. One model for the induction of tolerance during the very early stages of pregnancy is the eutherianfetoembryonic defense system) hypothesis. However, another model suggests that the induction of tolerance primarily requires the participation of regulatory T cells.In adults, tolerance may be induced by repeated administration of very large doses of antigen, or of small doses that are below the threshold required for stimulation of an immune response. Tolerance is most readily induced by soluble antigens administered either intravenously or sublingually. Immunosuppression also facilitates the induction of tolerance.

In clinical practice, acquired immunity is important in organ transplantation, when the body must be forced to accept an organ from another individual. The failure of the body to accept an organ is known as transplant rejection. To prevent rejection, a variety of medicines are used to produce induced tolerance.

One of the most important forms of acquired tolerance is oral tolerance. Oral tolerance, the specific suppression of cellular and/or humoral immune reactivity to an antigen by prior administration of the antigen by the oral route, probably evolved to prevent hypersensitivity reactions to food proteins and bacterial antigens present in the mucosal flora. It is of immense immunological importance, since it is a continuous natural immunologic event driven by exogenous antigen. Due to their privileged access to the internal milieu, antigens that continuously contact the mucosa represent a frontier between foreign and self components,. Failure of oral tolerance is attributed to the development and pathogenesis of several immunologically based diseases, including Inflammatory Bowel Disease (Crohn's Disease and Ulcerative Colitis).