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T CELL: ORIGIN, FUNCTIONS AND FATE

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Multi-potential hematopoietic stem cells in adult marrow give rise to all hematopoietic lineages. Some of these purified stem cells are believed to be transferred to thymus. Thymus is believed to produce originators of immunologically competent cells during embryogenesis, many of which migrate to other sites after birth [1]. Thus, thymus is believed to be the birth place of a functioning T cell migrating from marrow. The resident cells in bone marrow continue to differentiate to give rise to other subset of lymphocytes, the B lymphocytes (B cell) responsible for humoral immunity. The cells that migrate from bone marrow to thymus on education visa are called T cells. Thymus derived cells can also produce antibodies, but only in the presence of B cells. Immunological potential of bone marrow cells is enhanced in presence of thymocytes.

T and B cell existence is responsible for several adaptive immune mechanisms like carrier effect, memory, tolerance, autoimmunity and genetically determined unresponsive states. T cells were subsequently described by Medawar to have cell mediated immunity and further subdivided into subsets based on cell surface markers and secreted products/ interleukins (IL) [2]. B lymphocytes are committed to single antigen specificity, however their precursors have multipotential antibody specificity. In contrast, T cells could never be shown to bind to antigen although they could inactivate a radiolabelled antigen, and had single specificity. Zinkernagel and Doherty's discovery of MHC restriction of T cell reactivities explained how T cells recognized an antigen [3].

T-CELL DEVELOPMENT IN THYMUS

Earliest thymocytes express CD 4. They differentiate to CD 4^- CD 8^- (double negative-DN) stage, identified as progenitors[4]. This group includes a minor population of T cell receptor (TCR) a b and TCR gd without progenitor activity, and a major population of TCR CD 4^- CD 8^- (triple negative-TN) cells which are able to repopulate the thymus. TN cells are further classified into early, intermediate and late stages. Early TN cells are CD 44^+, CD 25^-, low affinity p55 chain of IL2 receptor, HSA intermediate cells. The intermediate stage TN cells are CD 44^-, CD 25^+, HSA high cells which do not home to thymus. Although they bind to IL-2, the receptor ligand complex is not internalized and these cells do not proliferate. The late TN cells are CD 4^{trace} and/ or CD 8+ with high HSA. There are two other types of TN cells: immature CD 4^+ CD 8^-, high HSA, TCR^- cells and immature CD 4^- CD 8^+, high HSA, TCR^- cells that are devoid of T cell function.

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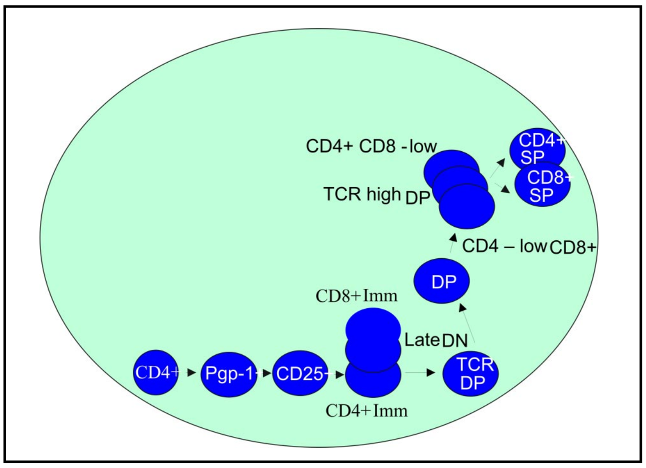

Figure 1 Pathway of Intrathymic T cell development.

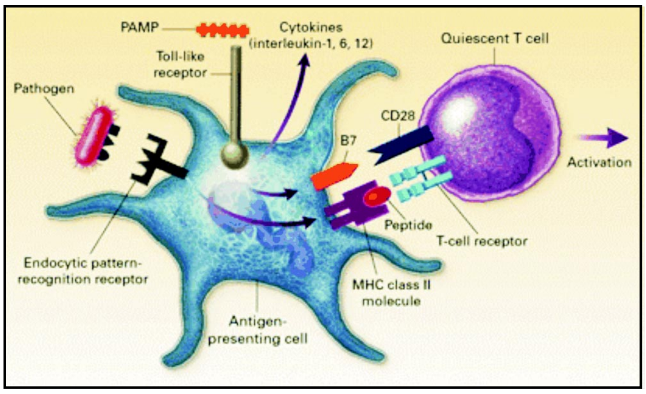

Figure 2 Positive and Negative Selection in Thymus.

TN cells further develop into double positive (DP) cells (CD 4^+ CD 8^+). About 70-80 % of thymocytes are DP. These are further subdivided into TCR a b^{low}, $CD3^-$ TCR a b^- which comprise 30 % of thymocytes, and TCR a b^{high} which constitute 5 % of thymocytes. These are similar to peripheral T cells/ SP thymocytes. The remaining 20 % DP cells are in cycle. DP cells undergo several rounds of division before expression of TCR and only one or two divisions after TCR expression. DP cells then transit through a TCR high DP subsets after or along with development into SP cells. T cells that contain an in-frame TCR b rearrangement undergo full expansion as DP cells, but cannot undergo further maturation to SP cells unless all components of the TCR-MHC interactions are present.

Positive selection

Thymocytes with potential to recognize exogenous antigens in the context of self MHC molecules expressed on thymus epithelium are selected to complete their maturation. This is 'positive selection'. More than 95 % cells are unable to surpass positive selection threshold and hence undergo programmed cell death in thymus itself [5, 6].

Negative selection

T cells respond to foreign antigens while remaining tolerant to cell molecules. T cells use TCR to recognize peptide antigen presented in the groove of self-MHC molecules. TCR must be able to bind to the antigen-MHC complex with a relatively high affinity to be effective, but at the same time this TCR cannot be allowed to respond to self peptide-MHC. T cells that react against self molecules are removed during thymocyte development. This process, called 'negative selection' occurs in thymic medulla [7]. Those cells that surpass a negative selection threshold are tolerized.

Death of useless thymocytes

Majority of thymocytes fail to mature. They may die for three reasons: failure to generate a TCR by gene recombination, expression of a TCR that fails to undergo positive selection or expression of self reactive TCR leading to death by negative selection. Most DP cells are destined to die[4]. There is a hypothesis that most DP cells become DN and undergo apoptotic deletion in liver.

FUNCTIONS OF T CELLS

The primary function of the T cells bearing a b receptors is to recognize the presence of pathogens within the body and activate their disposal directly/ recruiting other immune cells. Inflammatory T cells (T h1) activate macrophages to destroy engulfed bacteria, helper T cells (T h2) activate B cells to secrete antibodies to neutralize, opsonize and induce lysis of extra cellular pathogens [8].

Cytotoxic T cells kill cells infected with cytoplasmic pathogens. Effector functions of T cells are closely linked to the sites in which pathogens are found. Thus T cells must not only recognize the presence of a foreign antigen but also must be able to identify the cellular compartment from which the antigen was derived [7].

T cells with gd ä receptors rapidly leave the thymus and some of them develop outside the thymus, probably in gut. Thymus derived g d T cells migrate throughout the body including the epithelium of the gastrointestinal tract, where they are thought to contribute to mucosal defenses against proteinaceous and non-proteinaceous antigens including those

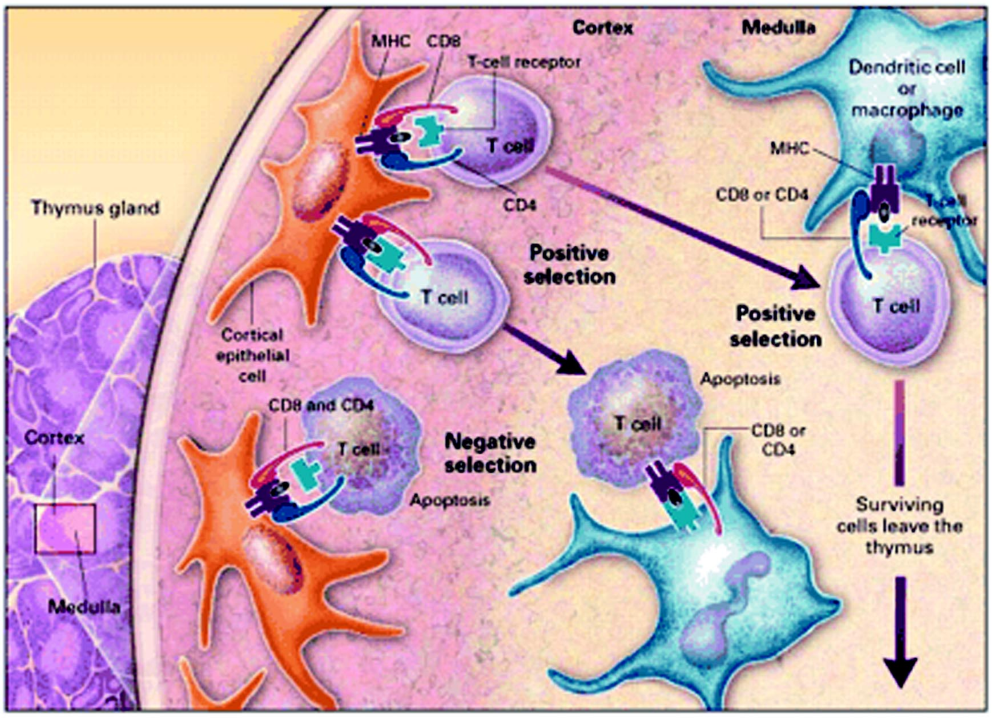

Figure 3 Receptors involved in the intraplay of the Innate and Adaptive Immune systems.

from mycobacteria and other infectious agents. They also influence antibody production and immunoglobulin class switching by B cells and modify T cell responses. The precise mechanisms of these immunoregulatory mechanisms are undefined so far [9].

Natural killer cells destroy infected and malignant cells. They recognize their targets in one or two ways. They possess Fc receptors that bind IgG (FcgR). These receptors link natural killer cells to IgG- coated target cells, which they kill by process called antibody- dependent cellular cytotoxicity. The second system of immune recognition relies on the killer-activating receptors and killer-inhibitory receptors of these cells. The killer-activating receptors recognize a number of different molecules present on all nucleated cells. If the killer-activating receptors are engaged, a "kill" instruction is issued to the natural killer cell, but the signal is normally overridden by an inhibitory signal sent by killer-inhibitory receptor on recognition of MHC class I molecules [10, 11].

Role of T cells in MHC molecule presentation

Class I MHC molecules are expressed on almost all the nucleated cells where as MHC class II molecules are expressed on B cells, thymic epithelial cells, macrophages and dendritic cells. Recognition of antigen associated with MHC class I molecules results into death of presenting cell, where as recognition of MHC class II associated antigen peptides leads to activation of the presenting cell [8]. T h2 cells recognizing MHC class II antigen are activated and subdivided into two discrete subclasses; naïve T h2 cells are activated by their first contact with antigen-class II complexes and initially secrete a broad range of cytokines like IL 2, 3, 4, 5, 10 and interferon g. Then these cells differentiate into T h1 cells which upon their second encounter with antigen, secrete IL 2, IFN g and TNF; and T h2 cells secrete IL 4, 5, 6 and 10 on second encounter with antigen.

T cell activation

T cell activation refers to immune activation of mature T lymphocytes in peripheral blood, lymphoid system or tissues. The physiological stimulus that activates T cells is a foreign antigen in association with MHC molecules, presented to the T cell by APC. Multiple receptors on the surface of T cell mediate interactions between T cell and APC. The antigen specificity of the response is dictated by TCR. Other receptors playing crucial accessory role are adhesion molecules- CD 2, LFA 1 and their counter ligands, LFA 3 and ICAM- 1. CD 4 and CD 8 molecules contribute to MHC recognition. CD 5 and CD 28 synergize with TCR to initiate T cell activation, their respective ligands CD 72 and B7/ BB 1 are found on B cells. Thus CD 5 and CD 28 are thought to have an accessory role in T-B cell interactions. Activated T cells synthesize and express new receptor molecules like CD 69 and IL 2R, IL 3, GMCSF, IL4 and IL2. Immediate consequence is activation of a protein tyrosine kinase signaling cascade [12] .

Immunoregulation, tolerance and auto-immunity

Clonal deletion of thymocyte can result into a state of immunological unresponsiveness.

Different T cells with distinct lymphokines are mutually antagonistic. There is an inverse relationship between humoral and cellular immune response to foreign proteins/ infectious antigens. Out of IL- 4, 5, 10 secretd by Th2 ; IL 4 and 10 inhibit induction of T h1 responses. IL 2 and IFN ã secreted by T h1 are depleted when IL 4 and 10 are enhanced. The mechanisms controlling the activation of these subsets are unclear. MHC class II genes, types of antigen presenting cells involved and TCR ligand density; all play a decisive role [13, 14].

The dominant tolerogenic mechanisms for T cells appear to be deletion of clones of self reactive cells occurring during intrathymic development. Peripheral tolerogenic mechanisms are believed to be effective through peripheral deletion, anergy or suppression mechanisms. Mature T cells are likely to ignore cells lacking B7/ BB 1/ appropriate ligands for T cell adhesion molecules [15, 16] .

The complexicity of microbial environment has necessitated the pleomorphism of T cell receptor system. This is how the T cell system is critical for survival and the thymus once upon thought to be redundant in adult is uniquely equipped organ which helps in continuation of life!

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