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Review on T-Cell Development and its Action

[1]Fuad Adem and [2]Garoma Desa

[1]Jimma University, Jimma, Ethiopia
[2]National Institute for Control and Eradication of Tsetse Fly and Trypanosomiasis,
Kaliti Tsetse Fly Mass Rearing and Irradiation Centre, P.O. Box: 19917, Addis Ababa, Ethiopia

Abstract: T-cell, or T lymphocyte, is a type of lymphocyte that plays a central role in cell-mediated immunity. The immune system is the body's defense in opposition to infection and is made up of a network of cells and organs that defend the body from foreign substances called "antigens." Antigens stimulate the activation of the immune system to target foreign material and kill infected cells. They are called T cells because they mature in the thymus from thymocytes. Hematopoiesis is the term used to describe the overall blood cell development process. This developmental pathway starts with hematopoietic stem cells (HSC). Lymphocytes are a key part of a complex immune system and are the cells that respond to foreign organisms and they help to fight against infection and cancer. Most lymphocytes are found in the lymph nodes, the spleen, a few other lymphatic organs and the lymphatic channels and some of them enter the bloodstream. A T-cell, or T lymphocyte, is a type of lymphocyte (a subtype of white blood cell) that plays a central role in cell-mediated immunity. T cells can be distinguished from other lymphocytes, such as B cells and natural killer cells, by the presence of a T-cell receptor on the cell surface. They are called T-cells because they mature in the thymus from thymocytes and although some of them mature in the tonsils. T lymphocytes (T-cells), B lymphocytes (B cells) and natural killer (NK) cells are the three major types of lymphocytes. For detail information, further study is necessary to highlight the Thymus, its development, organogenesis and signaling path ways in specific and to review the T-Cell development and its action in general.

Key words: Action · Development · Hematopoiesis · Review · Thymus · T- Cells

INTRODUCTION

Hematopoiesis is the term used to describe the overall blood cell development process. This developmental pathway starts with hematopoietic stem cells (HSC), which are defined as cells able to both replicate themselves and generate progeny cells that can ultimately develop into more than ten different lineages. For B and T lymphocytes, it is important to study the stages involved in the development of the clonal antigen-specific receptors. The initial approach to identify HSC has been to sort cells based on their cell surface markers and then test the ability of the sorted cell populations to repopulate immune-deficient murine recipients [1]. From HSC, the next step in the development of T and B lymphocytes is the presence of multi-potential progenitor cells (MPP), which are characterized as Lin - $CD45^{lo}$ CD34 + CD38 + CD45RA - CD90 - Ki67 +MPP have lost self-renewal potential but still retain the capacity to differentiate down multiple lineage pathways [2].

Bone marrow and Thymus are the central or primary lymphatic organs, as these are the sites where new, "naive" B- and T cells originate and rearrange their receptors. In the bone marrow, hematopoietic stem cells give rise to lymphoid progenitor cells. Lymphoid progenitors migrate to the thymus (located on top of the heart), where they undergo complex quality assurance procedures that allow only a small fraction of these thymocytes to leave the thymus as mature and naive T-cells. Mature, naive B- and T-cells, as well as precursors of APC from the bone marrow emigrate from the central lymphatic organs. Lymphocytes travel mainly via the bloodstream. APC leave the bloodstream to widely roam

Corresponding Author: Garoma Desa, National Institute for Control and Eradication of Tsetse Fly and Trypanosomosis, Kaliti Tsetse Fly Mass Rearing and Irradiation Centre, P.O. Box: 19917, Addis Ababa, Ethiopia. E-mail: garomadesa@yahoo.com.

tissues. Eventually, all types of cells meet again at the peripheral lymphatic organs: lymph nodes, GALT/ Peyer plaques and tonsils, BALT and spleen [1].

T lymphocytes, which are distinguished from other leukocytes by their expression of either the αβ or the γδ type of T cell receptor (TCR), are essential for regulating immune responses in addition to their cytotoxic functions. Although all lymphocyte progenitors are initially generated in the bone marrow, the thymus is the sole organ that supports development of T lymphocytes, whereas development of other leukocytes continues mainly in bone marrow. There are several types of mature T cells and the generation of distinct T-cell subsets takes place first in thymus, which is followed by differentiation of naive T cells into effecter T cells upon encountering antigens in the peripheral lymphoid organs. The thymus is thus a place where multipotent hematopoietic progenitors go through several cell-fate decision processes to prepare them to become T-cell subsets. There are three major types of lymphocytes: T lymphocytes (T cells), B lymphocytes (B cells) and natural killer (NK) cells. With these facts in mind, the objective of this paper is to review the T- Cell development and its action.

Thymus and its Development in Vertebrates: The thymus, as the central hematopoietic site for making T cells which act as major players of the adaptive immune system in vertebrates, has been studied extensively since the 1960s by Miller and many others [3]. Thymus is comprised of two main components, the thymic epithelial cells (TECs) and the lymphoid thymocytes (T-cells). Together with the surrounding mesenchymal cells, thymic epithelial cells, originally derived from the third pharyngeal endodermal pouch (anterior foregut), form an epithelial micro environmental niche (the outer cortex and the inner medulla) that supports T cell differentiation. Several lines of evidence suggest that the medullary and cortical TECs originate from one common germ layer in the third pharyngeal pouch endoderm and then undergo a series of differentiation and proliferation steps to form the functional TECs [4-6].

The first phase in TEC development occurs during early embryonic gestation in a thymocyte-independent manner and the second thymocyte- dependent phase initiates in later phases of gestation while the thymus continues to develop and produce the compartmentalized structures which are finally organized after birth [7]. Once specified into the T lymphocyte lineage, immature T cells undergo a successive and dynamic differentiation, including positive selection for T cell receptors (TCRs) in the cortex and negative selection to remove the self-immune responsive cells in the medulla. The postnatal thymus consists of three cell types, i.e., hematopoietic-derived cells (CD45+), Foxn1dependent cells including medullary and cortical TECs (Keratin+CD45) and Foxn1-independent cells including mesenchymal cells, endothelial Cells and fibroblasts (Keratin CD45) [5].

Thymus Development in Vertebrates

Thymus Organogenesis in Zebra Fish: The zebra fish (Danio rerio) has recently become an important genetic model organism for the study of thymus and T cell development since blood development and the adaptive immune system are highly conserved throughout vertebrate evolution and there are many advantages to zebra fish model. Zebra fish embryos are transparent at early stages with external fertilization and rapid development, which allows the visualization of hematopoietic stem cell (HSC), colonization and homing of lymphoid progenitors to the thymus in vivo. In zebra fish, the thymic anlage arises from the pharyngeal endoderm, which develops from the epithelium between the third and fourth brachial arches and can be detected around 48 hrs post fertilization by whole-mount RNA in situ hybridization (WISH) using a foxn1 probe. By 1-2 weeks of age, the thymic epithelial cells are arranged into two distinct regions, the cortex and the medulla, both of which persist into adulthood [8, 9].

Signaling Pathways Involved in Thymus Organogenesis: The thymic micro environment mainly composed of the thymic epithelial cells and other stromal cells must be tightly controlled by extrinsic and intrinsic signals to support T cell differentiation and maturation. Several signaling pathways have been implicated in thymus and TEC development.

Bone Morphogenetic Proteins (BMPs) Signaling: BMPs belong to the transforming growth factor (TGF- β) super family and are known to be involved in cell-fate determination and patterning of the embryo, early thymus and parathyroid morphogenesis and maintenance of a normal thymic micro environment [10, 11].

Wingless Related Integration (Wnt) Signaling: Wnt (wingless related integration) genes encode small secreted proteins that are required for cell-fate specification, progenitor-cell proliferation and asymmetric cell division [12]. There are three different Wnt pathways: the

canonical Wnt / β-catenin cascade, the non-canonical planar cell polarity (PCP) pathway and the Wnt /Ca2+ pathway. Among them, the canonical

Wnt / β-catenin pathway is best characterized during thymus development [13].

T-Cell Development: A T cell, or T lymphocyte, is a type of lymphocyte (a subtype of white blood cell) that plays a central role in cell-mediated immunity. T cells can be distinguished from other lymphocytes, such as B cells and natural killer cells, by the presence of a T-cell receptor on the cell surface. They are called T cells because they mature in the thymus from thymocytes [14] although some of them mature in the tonsils [15]. Differently from other hematopoietic lineages, development of T-cells from pluri-potent hematopoietic stem cells takes place in the thymus. This means that T lymphocyte precursor cells must be able to migrate from the bone marrow through the blood to the thymus. T cell development in postnatal life is a prolonged developmental process in which bone-derived multi-potent hematopoietic progenitor cells seed the thymus (thymus seeding progenitors, TSPs) to become gradually reprogrammed into fully mature and functional T lymphocytes. Experimental data indicates that the interaction between the chemokine receptors, CCR9 and CCR7, expressed on precursor cells and the thymic-produced chemokines, CCL25 and CCL19-CCL21, is essential to the process of directing these cells toward the thymus. However, the expression of these receptors does not appear to play a role in the differentiation of the thymocytes [16].

Early T-cell progenitors enter the thymus at the cortico-medullary junction, where they encounter instructive signals inducing cell growth and proliferation mainly through stimuli such as interleukin-7 (IL-7) and stem cell factor (SCF) [17]. During thymopoiesis, T cell progenitors derived from the bone marrow, move through blood vessels and enter the cortical-medullary junction (CM junction) of the thymus. In zebra fish embryos, the first definitive HSCs are derived from the ventral wall of the dorsal aorta (VDA) and then migrate to the caudal hematopoietic tissue (CHT), eventually homing to the thymus and the kidney [18].

After immigration, T cell progenitors begin to differentiate, expand and eventually mature in the thymus. In mice, several developmental stages of thymocyte differentiation can be distinguished through cell surface markers. Thymocytes are primarily subdivided into double negative (DN), double positive (DP) and single positive (SP) subsets in relation to the expression of the molecules CD4 and CD8. However, CD4 and CD8 have not been identified in zebra fish making it difficult to investigate the late stage of T cell development in this model [19].

Emigration of T-Cells: After residence in the medulla for about 12 days, the mature T cells begin to emigrate out of the thymus. This emigration is regulated by a novel pertussis toxin-sensitive signaling pathway involving a G-protein. S1P1, which is a widely distributed G protein-coupled receptor (GPCR), is up-regulated in mature thymocytes and plays a critical role in the egress of T cells into the periphery [21, 22].

Activation of T-Cell: Activation of $CD4^+$ T cells occurs through the simultaneous engagement of the T-cell receptor and a co-stimulatory molecule (like CD28, or ICOS) on the T cell by the major histocompatibility complex (MHC II) peptide and co-stimulatory molecules on the APC. Both are required for production of an effective immune response; in the absence of co-stimulation, T cell receptor signaling alone results in energy. Optimal $CD8^+$ T cell response relies on $CD4^+$ signaling. $CD4^+$ cells are useful in the initial antigenic activation of naïve CD8 T cells and sustaining memory $CD8^+$ T cells in the aftermath of an acute infection. Therefore, activation of $CD4^+$ T cells can be beneficial to the action of $CD8^+$ T cells [23].

The first signal is provided by binding of the T cell receptor to its cognate peptide presented on MHC II on an APC. MHC II is restricted to the so-called professional antigen-presenting cells, like dendritic cells, B cells and macrophages. The peptides presented to $CD8^+$ T cells by MHC class I molecules are 8-13 amino acids in length; the peptides presented to $CD4^+$cells by MHC class II molecules are longer, usually 12–25 amino acids in length, as the ends of the binding cleft of the MHC class II molecules are open [24].

The second signal comes from co-stimulation, in which surface receptors on the APC are induced by a relatively small number of stimuli, usually products of pathogens, but sometimes breakdown products of cells, such as necrotic-bodies or heat shock proteins. The only co stimulatory receptor expressed constitutively by naïve T cells is CD28, so co-stimulation for these cells comes from the CD80 and CD86 proteins, which together constitute the B7 protein, (B7.1 and B7.2, respectively) on the APC. Other receptors are expressed upon activation of the T cell, such as OX40 and ICOS, but these largely depend upon CD28 for their expression.

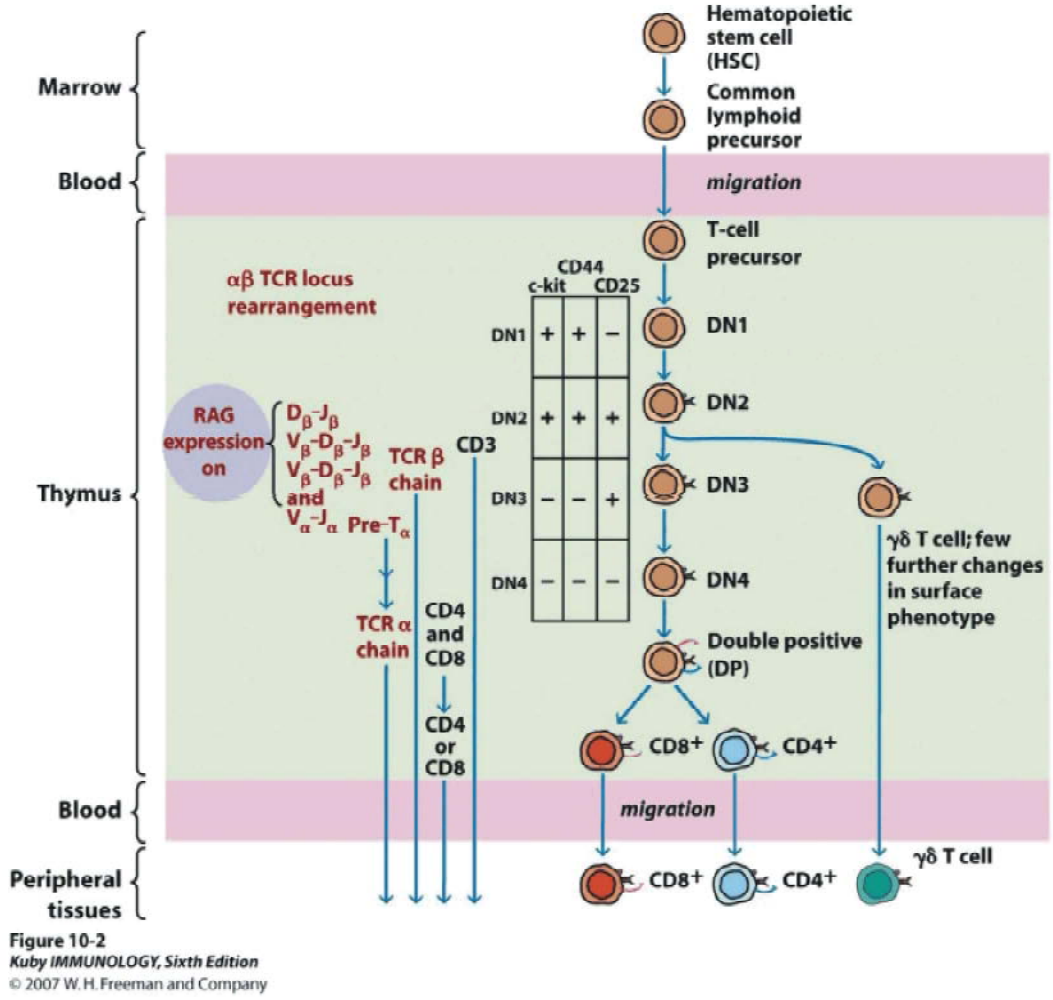

Fig. 1: Tcell maturation
Source: [20]

The second signal licenses the T cell to respond to an antigen. Without it, the T cell becomes energic and it becomes more difficult for it to activate in future. This mechanism prevents inappropriate responses to self, as self-peptides will not usually be presented with suitable co-stimulation. Once a T cell has been appropriately activated (i.e. has received signal one and signal two) it alters its cell surface expression of a variety of proteins. Markers of T cell activation include CD69, CD71 and CD25 (also a marker for Treg cells) and HLA-DR (a marker of human T cell activation). CTLA-4 expression is also up-regulated on activated T cells, which in turn outcompetes CD28 for binding to the B7 proteins. This is a checkpoint mechanism to prevent over activation of the T cell. Activated T cells also change their cell surface glycosylation profile [25].

Transcription Factors: Gene regulatory networks (GRNs) describing key regulatory players during T cell development have been reviewed quite well recently [26]. Many transcription factors have been identified that are important for T cell development in mammals, involving cell fate specification, differentiation, survival, expansion, negative or positive selection and migration [26, 27]. The earliest known T-cell progenitors that seed the thymus are called early T-cell progenitors (ETP), which are characterized by the lack of lineage-specific markers (these 'Lin$^-$' cells lack lymphocyte markers such as CD3 as well as markers for other lineages) although they do express markers such as c-kit and Sca-1. ETP are the equivalent of the DN1a subset plus the DN1b subset [28]. Notch1 helps ETPs to get over multi-potential and adopt T cell identity. TCF-1, a high mobility group (HMG)

box-containing transcription factor, is positively up-regulated by Notch1 in the very early T cell progenitors and plays a significant role in early T cell development. TCF-1 hematopoietic progenitors fail to acquire T cell fate when co-cultured with OP9- DL1 stromal cells [29, 30].

Selection of Useful T-Cells: Progenitors of mature T cells in the thymus are called thymocytes. Arriving from the bone marrow, progenitor cells rearrange their T cell receptors (TCR) and proceed to mature in an interaction process with thymic epithelial cells that is thought to involve three aspects: β-selection, positive and negative selection. β -selection is the first checkpoint, where the T cells that are able to form a functional pre-TCR with an invariant alpha chain and a functional beta chain are allowed to continue development in the thymus. Next, positive selection checks that T cells have successfully rearranged their TCRα locus and are capable of recognizing peptide-MHC complexes with appropriate affinity. Negative selection in the medulla then obliterates T cells that bind too strongly to self-antigens expressed on MHC molecules. These selection processes allow for tolerance of self by the immune system [31].

Beta Selection: Common lymphoid precursor cells that migrate to the thymus become known as T-cell precursors (or thymocytes) and do not express a T cell receptor. Broadly speaking, the double negative (DN) stage is focused on producing a functional β-chain whereas the double positive (DP) stage is focused on producing a functional α-chain, ultimately producing a functional αβ T cell receptor. As the developing thymocyte progresses through the four DN stages (DN1, DN2, DN3 and DN4), the T cell expresses an invariant α-chain but rearranges the β-chain locus. If the rearranged β-chain successfully pairs with the invariant α-chain, signals are produced which cease rearrangement of the β-chain (and silence the alternate allele) and result in proliferation of the cell. Although these signals require this pre-TCR at the cell surface, they are independent of ligand binding to the pre-TCR. These thymocytes will then express both CD4 and CD8 and progress to the double positive (DP) stage where selection of the α-chain takes place [32].

Positive Selection: Positive selection "selects for" T cells capable of interacting with MHC. Positive selection involves the production of a signal by double-positive precursors that express either MHC Class I or II restricted receptors [33]. Double-positive thymocytes ($CD4^+/CD8^+$) move deep into the thymic cortex, where they are presented with self-antigens. These self-antigens are expressed by thymic cortical epithelial cells on MHC molecules on the surface of cortical epithelial cells. Only those thymocytes that interact with MHC-I or MHC-II appropriately will receive a vital "survival signal". This process ensures that the selected T-cells will have an MHC affinity that can serve useful functions in the body.

A thymocyte's fate is determined during positive selection. Double-positive cells ($CD4^+/CD8^+$) that interact well with MHC class II molecules will eventually become $CD4^+$ cells, whereas thymocytes that interact well with MHC class I molecules mature into $CD8^+$ cells. A T cell becomes a $CD4^+$ cell by down-regulating expression of its CD8 cell surface receptors. If the cell does not lose its signal, it will continue down-regulating CD8 and become a $CD4^+$, single positive cell. Generally, a T cell is only useful if its TCR can be activated by our own MHC. Positive selection therefore results in self-MHC-restriction: all thymocytes surviving this step are able to recognize at least one of our own MHC molecules [34].

Negative Selection: Negative selection removes thymocytes that are capable of strongly binding with "self" MHC peptides. Among all the thymocytes that are positively selected for recognizing our own MHC to a greater or lesser extent, some are bound to recognize some combination of MHC molecule and presented self-peptide just perfectly. These are objectionable, as they are auto- reactive and dangerous. Auto-reactive T cell clones are therefore eliminated by negative selection. The goal of this entire process is to select T cells that are able to work with our own MHC. Thymocytes that survive positive selection migrate towards the boundary of the cortex and medulla in the thymus. While in the medulla, they are again presented with a self-antigen presented on the MHC complex of medullary thymic epithelial cells (mTECs) [35].

Differentiation of T-Cells: All T cells originate from haematopoietic stem cells in the bone marrow. The progenitors of T cells, the thymic settling precursors (TSPs) are derived from HSCs. There are two waves of hematopoiesis in vertebrates, the primitive and the definitive. Only the definitive wave gives rise to HSCs

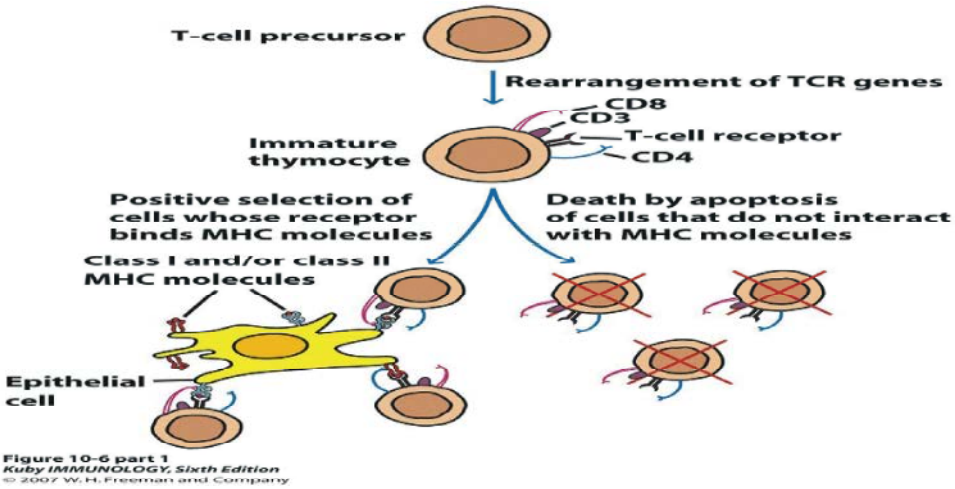

Fig. 2: Positive Selection of Thymocytes in the Thymus
Source: [20]

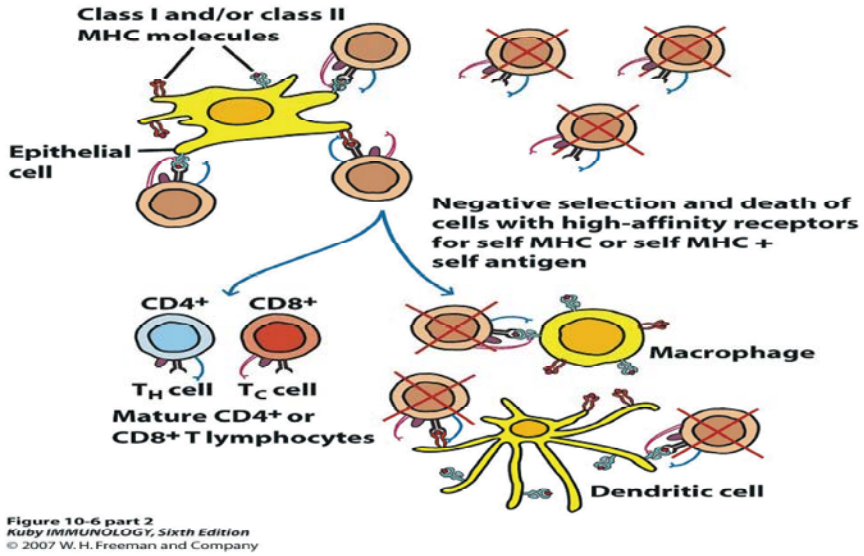

Fig. 3: Negative selection of thymocyte in thymus
Source: [20]

which can differentiate into T cells and many other cell types [18]. Haematopoietic progenitors (lymphoid progenitor cells) from haematopoietic stem cells populate the thymus and expand by cell division to generate a large population of immature thymocytes. The earliest thymocytes express neither CD4 nor CD8 and are therefore classed as double-negative ($CD4^-CD8^-$) cells. As they progress through their development, they become double-positive thymocytes ($CD4^+CD8^+$) and finally mature to single-positive ($CD4^+CD8^-$ or $CD4^-CD8^+$) thymocytes that are then released from the thymus to peripheral tissues [36].

About 98% of thymocytes die during the development processes in the thymus by failing either positive selection or negative selection, whereas the other 2% survive and leave the thymus to become mature immune-competent T cells. Increasing evidence indicates microRNAs, which are small non-coding regulatory RNAs, could impact the clonal selection process during thymic development. For example, miR-181a was found to play a role in the positive selection of T lymphocytes [37].

CD4 and CD8 T cells leave the thymus and enter the circulation as resting cells in the G0 stage of the cell cycle. There are about twice as many CD4 T cells as CD8 T cells

in the periphery. T cells that have not yet encountered antigen (naive T cells) are characterized by condensed chromatin, very little cytoplasm and little transcriptional activity. Naïve T cells continually re-circulate between the blood and lymph systems. During recirculation, naive T cells reside in secondary lymphoid tissues such as lymph nodes. If a naive cell does not encounter antigen in a lymph node, it exits through the efferent lymphatics, ultimately draining into the thoracic duct and rejoining the blood. It is estimated that each naive T cell re-circulates from the blood to the lymph nodes and back again every 12–24 hours. Because only about 1 in 105 naive T cells is specific for any given antigen, this large-scale recirculation increases the chances that a naive T cell will encounter appropriate antigen [38].

T- Helper Cells: The effecter responses of CD4 + T lymphocytes, known as "T-helper cells, " primarily consist of the production of cytokines. CD4 + T lymphocytes can produce a wide variety of cytokines, but usually do not produce them all at once. Instead, CD4 + T cells produce a discrete set of cytokines that is determined by the combination of cytokines already present in the environment when T cell activation occurs. CD4 + T cells are divided into categories based on the cytokines they produce: T-helper 1 (Th1) cells, T-helper 2 (Th2) cells, T-helper 3 (Th3) cells and T-helper 17 (Th17 cells) [39].

TH1-cells coordinate the immune response against intracellular pathogens by additional cytokines. They push their own proliferation by IL-2. Naive T cells express only the β and γ chain (low affinity) of the IL-2 receptor. IL-2 feedback loop is necessary for clonal expansion. IL-3 and GM-CSF stimulate the bone marrow to produce additional phagocytes. CCL2 (monocyte chemotactic protein) attracts additional macrophages to the site of infection. TNFα activates nearby epithelial cells, indicating a "bus stop" for monocytes approaching in the blood. The early presence of TGF- β directs CD4 + cells to produce Th3 cytokines, TGF-β and IL-10, which facilitate the production of IgA in mucosal tissues. When both TGF- β and IL-6 are present early in the immune response, CD4 + T cells are directed toward the Th17 phenotype resulting in the production of IL-17 and are often found in inflammatory conditions [40].

Cytotoxic T-Cells: CD8 + T cells (cytolytic) can produce Th1 cytokines when activated; the primary method these cells use to eliminate intracellular pathogens is by lysing the pathogen-infected cells. The lysis of these infected cells is accomplished through exocytosis of cytolytic granules. Main components of these granules include serine proteases called granzymes and perforin, a protein that forms holes in the cell membrane [41].

Perforin facilitates entry of granzymes into the cell cytoplasm where they are able to induce programmed cell death (apoptosis) in the target cell. Once CD8 + T cells receive sufficient activating signals, they begin producing granzymes and perforin and packaging these proteins into granules. When an activated and armed CD8 + T cell encounters a cell expressing the same antigen as that which triggered its initial activation, cytolytic granules are mobilized to the point of contact and triggered to exocytose stored contents into the extracellular environment next to the target cell. Once clearance of an infectious pathogen has been accomplished, activated CD8 T cells are reduced in number via a process called activation-induced cell death. Yet, even after this contraction, the number of memory CD8 T cells specific for the pathogen remains elevated. High levels of granzyme A have been observed in these resting memory CD8 T cell populations. Five granzymes can be found in human cytolytic granules: A, B, H, K and M [42].

These are produced and present in varying amounts depending on cell type. Out of these five types, granzymes A and B have been most extensively studied. Granzyme B induces target cell apoptosis through cleavage of caspases that trigger the apoptotic pathway. Granzyme A may also induce apoptosis via an alternative pathway, it also contributes to inflammation by cleaving and thereby activating, assemblies of proteins called inflammasomes. Inflammasome activation triggers the cleavage of IL-1β and IL-18 pro forms, which in turn leads to the production of active cytokines that induce inflammatory responses [43].

Genetic Control of T-Cell Development in Mammals

Signaling Pathways in T-Cell Development: The thymus is a delicate niche that provides all the signals required for the survival, proliferation, differentiation, apoptosis and maturation of T cells. Here we summarize some critical signals that are indispensable for T cell development.

Notch: The notch was first cloned from Drosophila in the 1980s [44]. In zebra fish, according to the Uniprot database, 4 Notch receptors (Notch1a, 1b, 2 and 3) and 8Notch ligands (Dla, Dlb, Dlc, Dld, Dll4, Jag1a, Jag1b and Jag2) have been identified. When activated, the Notch is cleaved by a c-secretase mediated complex that releases the intracellular domain of Notch (NICD), which can

translocate into the nucleus and form a transcription activation complex with the DNA-binding protein CSL and Mastermind (Bray, 2006). The Notch 1 signaling pathway is critical in the thymus for early T-cell fate specification and thymocyte development [45].

Early in T cell development, the expression level of notch1 increases from the DN1 to DN3 stage. Notch1 provide important signals for the differentiation, survival, proliferation and metabolism of T cells [45]. Notch receptors are synthesized as a 300 kDa precursor that is fucosylated in the endoplasmic reticulum and is cleaved at the S1 site in the trans-Golgi network by a furine-like convertase. In fact, constitutive activation of Notch1 pathways in HSCs and/or CLPs (common lymphoid progenitors) results in the ectopic development of DP T cells in the bone marrow or in vitro [46]. In addition to its role in T cell commitment, a low level of Nocth1 signal can promote β-selection. Notch1 promotes survival of pre-T cells at the β-selection checkpoint by regulating cellular metabolism through the PI3K-AKT pathway [47].

Wingless Related Integration (Wnt): Wnt signaling plays an important role in normal hematopoiesis and it often becomes de-regulated in malignancies of the hematological system [48]. Briefly, the Wnt signaling cascade is often discerned into canonical or Wnt / β-catenin pathways and the non-canonical pathways. In the canonical Wnt pathway, in the absence of Wnt ligands, cytoplasmic levels of β-catenin are kept very low due to its constitutively phosphorylation and degradation through the action of a protein complex. This so called destruction complex is composed of two negative regulatory kinases, GSK3β and casein kinase 1 (CK1) and at least two anchor proteins, Axin1 or Axin2 and adenomatous polyposis coli (APC) protein [49].

Wnt signaling is required for normal thymocyte development, both at the pro-T-cell stage and at later stages of thymocyte differentiation. Of the three different Wnt pathways, the canonical and the Wnt /Ca2+ pathway have been reported to affect T cell differentiation and proliferation [12, 30]. During the DN to DP stage, Wnt signaling provides a signal for T cell proliferation and facilitates β -selection. However, over expression of the inhibitor for β -catenin and TCF-1 which disrupts β-catenin-TCF interactions, blocked T cells at the transition of DN to DP [50]. In contrast, conditional stabilization of β-catenin in immature thymocytes results in the generation of SPT cells that lacked the αβ TCR and develops in the absence of pre-TCR, but these T cells show reduced proliferation and survival capacity [51].

Conditional stabilization of β-catenin promotes negative selection while TCF-1 deficiency can inhibit negative selection. The β-catenin /TCF-1 cascade affects this process by modulating the intracellular strength of TCR signaling, leading to altered expression of mediators of thymocyte survival [52].

IL-7R/JAK/STAT Pathway: Interleukin 7 (IL-7) is an essential cytokine for normal T-cell development and homeostasis that promotes cell survival and cell cycle progression. Upon ligand binding, the IL-7 receptor chain (IL-7Rα; CD127) and the common chain (γc; CD132) dimerize and induce the trans-phosphorylation of JAK3 and JAK1. Activated JAKs phosphorylate the cytoplasmic tail of the receptor allowing the recruitment and phosphorylation of STAT5 (signal transducer and activator of transcription 5), which in turn dimerizes and translocate into the nucleus to regulate the transcription of target genes such as B-cell CLL/lymphoma2 (BCL-2) family members [53]. Besides JAK/STAT pathway, IL-7 can also mediate anti-apoptotic and proliferative signals via PI3K/AKT and RAS/MAPK. The expression of IL-7R is strictly regulated, as IL-7 is crucial at different stages of T-cell development for survival and maturation of specific cellular subsets in the thymus, as well as for the homeostasis of mature naïve and memory T-cells in the periphery [54].

Cell Death and T-Cell Populations: Cell death is an important feature of development in all multi-cellular organisms. During fetal life it is used to mold and sculpt, removing unnecessary cells to provide shape and form. It also is an important feature of lymphocyte homeostasis, returning T- and B-cell populations to their appropriate levels after bursts of antigen-induced proliferation. Although the induction of apoptosis involves different signals depending on the cell types involved, the actual death of the cell is a highly conserved process amongst vertebrates and invertebrates. For example, T cells may be induced to die by many different signals, including the withdrawal of growth factor, treatment with glucocorticoids, or TCR signaling. Each of these signals engages unique signaling pathways, but in all cases, the actual execution of the cell involves the activation of a specialized set of proteases known as caspases [55].

The role of these proteases was first revealed by studies of developmentally programmed cell deaths in the nematode *C. elegans*, where the death of cells was shown to be totally dependent upon the activity of a gene that

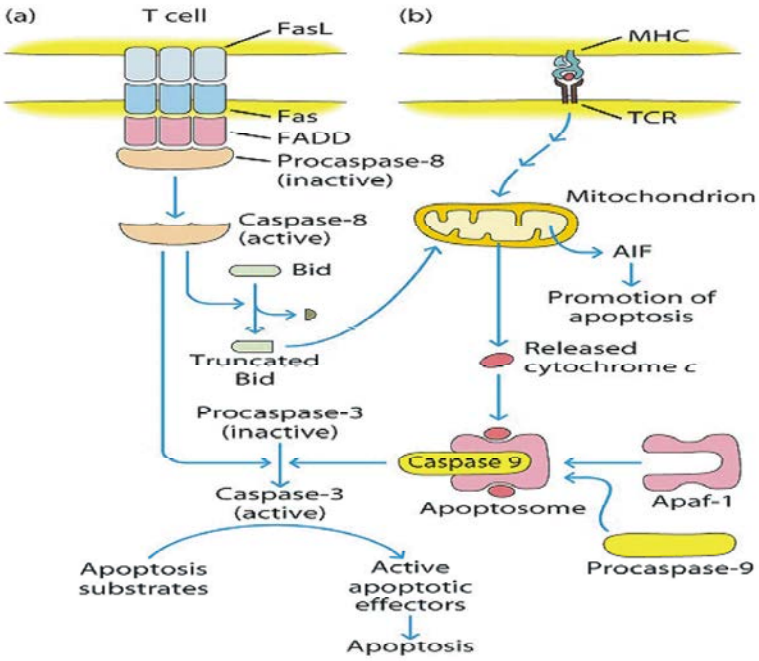

Fig. 4: Two pathways to Apotosis in T Cells
Source: [20]

encoded a cysteine protease with specificity for aspartic acid residues. Cells protect themselves from apoptotic death under normal circumstances by keeping caspases in an inactive form within a cell [55].

CONCLUSION AND RECOMMENDATIONS

The immune system is the body's defense against infection and is made up of a network of cells and organs that defend the body from foreign substances called "antigens." Antigens stimulate the activation of the immune system to target foreign material and kill infected cells. T cells, which develop in the thymus, are key players in cell-mediated immunity. A T cell, or T lymphocyte, is a type of lymphocyte that plays a central role in cell-mediated immunity. They are called T cells because they mature in the thymus from thymocytes. Lymphocytes are a key part of a complex immune system and are the cells that respond to foreign organisms and they help to fight against infection and cancer. Most lymphocytes are found in the lymph nodes, the spleen, a few other lymphatic organs and the lymphatic channels and some of them enter the bloodstream.

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