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What a Clinical Hematologist Should Know about T Cells?

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

T cell's journey begins from the bone marrow and ends in the peripheral tissues by either fighting the infections or residing in the secondary lymphoid organs as memory T cell. Thymus plays most important role in transforming a docile T cell precursor into a warrior. T cell is one of the most important cells in health and disease. Various diseases originate from qualitative or quantitative defects in T cells leading to various inherited and acquired diseases. This simple and short review is focused on the basic understanding and clinical hematologist's perspective of T cells.

Keywords: T cells; thymus; T cell receptor; autoimmune diseases; severe combined immunodeficiency; hematopoietic stem cell transplant; graft-versus-host disease; leukemia; lymphoma; aging; CAR-T cell; checkpoint inhibitors.

1. INTRODUCTION

T cells can be considered as the backbone of our immune system. Any defect in the T cells can paralyze the immune system leading to profound morbidity and mortality. T cells have a special need for the thymus for their development and there is a mutual cross-talk between the thymic epithelial cells and the maturing T cells, and any defect in either of these can impair normal T cell maturation [1]. The defective T cells thus produced are not only inefficient in combating the infections but also lead to development of autoimmune diseases. Inherited T cell defects

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can cause severe combined immunodeficiency syndromes and related disorders, and acquired T cell defects can lead to autoimmune diseases and various malignancies [2,3]. A balance between effector T cells and regulatory T cells is also very important for normal functioning of adaptive immune system and the imbalance is linked to various infections, autoimmune diseases and cancers. T cell functions have been manipulated in several ways to utilize their services for fighting against infections and cancers, either as in-vitro activation and transfer of adoptive T cells, or as cell engineering to modify antigen receptor, or as checkpoint inhibitors to augment T cell activation [4]. The role played by T cells, both in hematopoietic stem cell engraftment and post transplant immune-reconstitution, and in development of graft-versus-host disease determines the outcome of the transplant [5]. T cells are also prone to mutations leading to development of T cell malignancies. With aging the T cells undergo senescence and thus elderly people are predisposed to increased risk of infections and poor response to vaccines [6]. This review article highlights the basics of T cell development and function, and the role T cells play in our day-to-day life in health and disease.

2. DEVELOPMENT OF T CELLS AND ROLE OF THYMUS

T cell is one of the most important cells of our body as it is not only involved in the defense system of the body against the pathogens and cancers but also in the success of the stem cell based therapies. T cells start their journey from their home i.e. bone marrow where they are generated as precursor T cells from hematopoietic stem cells [7]. Thymus secretes certain chemokines to attract these precursor T cells towards itself. Notch-1 is necessary for intrathymic T cell development [8]. In the thymus they undergo further development and maturation (their army training school) and exit the thymus as fully trained (but not yet exposed to foreign antigen) naïve T cells (as newly commissioned cells). In the thymus there are two training camps (Fig. 1). The first one is the thymic cortex where positive selection occurs and cells with appropriate T cell receptors (TCRs, which can bind to antigen bound MHC) are selected whereas those with defective TCRs are deleted [9]. The antigen binds to the TCR via MHC molecule of the antigen presenting cells (APCs). The T cells without CD3 are called triple negative cells, as they don't have CD3, CD4 and CD8. Once they acquire CD3 they become double negative thymocytes (DN, CD4-, CD8-). In the cortex TCR develops along with CD3 and both are transferred to cell surface as TCR-CD3 complex. CD3 is essential for transferring the signals of TCR to cytoplasmic downstream elements. The DN T cells then acquire both CD4 and CD8 and become double positive (CD4+, CD8+) T cells in the cortex. The TCRs present on the surface of one T cell are usually all identical [10]. A set of cells with the same TCRs defines a T cell clonotype, and the set of T cell clonotypes in the body can be thought of as a repertoire of T cells [11]. The second selection camp is the thymic medulla. Here the T cells are exposed to the epithelial cells of medulla, which express a very special gene called AIRE (autoimmune regulatory gene) [12)]. In the late 1990s it was found that the thymus has an extraordinary capacity to express and present proteins from all over the body [13], which is due to the expression of the AIRE gene by the epithelial cells that allow them to express, process and present proteins to the developing T cells in the thymus that are ordinarily found in respective organs only. The characteristic feature of this gene is that it represents the tissue-specific-antigens of the whole of the host body which the T cells would encounter once they leave the thymus [14]. Developing T cells that bind tightly to these organ-specific proteins in the context of MHC molecules undergo negative selection (i.e. they undergo apoptosis). These tissue-specific-antigens are the antigens of different organs, which the T cells have to recognize as self-antigens and are taught not to react against them. If these developing T cells fail to undergo this training of identification of self-antigens in the medulla, they will react against body's own tissue-antigens and will lead to autoimmunity, which will be self-destructive. For example, the developing T cells are exposed to cardiac muscle antigens in the thymic medulla (without these T cells being directly taken to heart), and are trained not to respond to these antigens after exiting the thymus, otherwise autoimmune myocarditis would result. If the T cells show increased affinity to the self-antigens in the thymus (e.g., to cardiac antigens), then these T cells are not able to exit the thymus and are killed by apoptosis. The foreign or non-self antigens are not expressed in these thymic epithelial cells and so these T cells are able to fight against foreign antigens. This deletion of auto-reactive T cells (negative selection) results in development of central tolerance. This is one of the most remarkable features of thymic

medullary epithelial cells, who have the provision of training the T cells about all the human body antigens at one place, rather than the T cells wandering from tissue to tissue to identify self-antigens, which is not practically possible for T cells. So, the T cells are given training of whole body's antigenicity at one common place i.e., the medullary camp of the thymus and this results in development of disciplined self-tolerant T cells. After these two selections, the so-called naïve T cells (the cells newly commissioned in the army) are ready to face the antigens invading the body. These cells retain only either CD4 or CD8 after down-regulating one of the CD markers, and thus become single positive T cells which give them the lineage specificity [1]. The CD2, CD3, CD5 and CD7 are pan T cell markers. The CD4 and CD8 are lineage specific T cell markers. The naïve T cells move to lymph nodes where they are presented the antigen attached to MHC brought by the APCs (dendritic cells and macrophages) from the periphery. CD4 T cells identify the antigen presented by MHC II and CD8 T cells identify the antigen presented by MHC I. Once antigen is presented to TCR of the naïve T cell by the MHC of the APC, the signal is mediated downstream via CD3, and this leads to naïve T cell proliferation and differentiation into effector T cells, and secretion of cytokines, e.g. interleukin-2 (IL-2), interferon-γ (IFN-γ) and tumor necrosis factor (TNF-α), which have autocrine and paracrine effects on T cells and other cells involved in the innate and adaptive immunity. A T cell response typically peaks at 7–15 days after initial antigen stimulation. For a productive response, this peak corresponds roughly to the eradication of the pathogen. Over the next few days, 90–95% of antigen-specific T cells die off, leaving behind a pool of memory cells (cells retaining the memory of the encountered antigen) [15]. Once formed, subsets of memory cells can survive for decades (the half-life of memory T cells is about 8–15 years), providing protection from that particular pathogen and responding rapidly on re-exposure to the same antigen [15]. This principle has also been used in development of vaccines. Moreover, because of their ability to kill viruses, T cells have been stimulated *in-vitro* against particular viruses and transferred into the infected host in the form of adoptive T cell therapy (called living drugs). T cells engineered against specific targets on cancer cells form the basis of chimeric antigen receptor T cell therapy (CAR-T), and have been used in the treatment of leukemias and lymphomas.

Another important subset of T cells is regulatory T cells (T-regs) [16], which develop both in thymus (natural T-regs) and periphery (peripheral T-regs) [17,18]. Once effector T cells have completed their function, T-regs dampen the effector T cell mediated inflammation to protect the normal tissue from injury. Peripheral tolerance refers to the tolerance induction outside the thymus and the mechanisms involved include anergy, deletion, or suppression of T cells by T-regs. Balance between conventional T cells and T-regs maintain the homeostasis. If conventional T cells outnumber T-regs then there is a risk of normal tissue injury, and if T-regs outnumber conventional T cells then the infection will flare and malignant cells will escape by evading T cell mediated immune surveillance [19]. The normal ratio of conventional T cells and T-regs is about 10:1 [20].

3. DEVELOPMENT OF TCR

The TCR is formed by the product of variable (V), diversity (D) and joining (J) (VDJ) genes recombination and requires recombinase-activating genes (RAG 1 and 2) [21]. RAG genes break the DNA containing the VDJ genes at specific points to construct the TCR. RAG genes along-with Artemis gene are also involved in the joining of the VDJ gene segments that form the final VDJ segment destined to become TCR [21]. Genetic recombination refers to the rearrangement of DNA sequences by the breakage and rejoining of specific chromosome segments. This breakage and recombination is a random process and allows recombination of different genes each time, by various permutations and combinations, resulting in generation of different genetic material and hence different proteins (TCRs), leading to development of million types of TCRs. This enormous variability among TCRs to identify any possible existing microbial agent is termed as broadening of T cell repertoire.

The loops formed from extrachromosomal DNA excision circles that are generated following TCR gene rearrangements in the thymus are called T cell receptor excision circles (TRECs), and are indicator of thymic output of naïve T cells.

4. CD4/CD8 T CELL RATIO

The normal CD4/CD8 ratio in healthy hosts is about 2 (range 1.5 and 2.5). Normal ratios can invert (<1) through isolated apoptotic or targeted cell death of circulating CD4 cells, expansion of

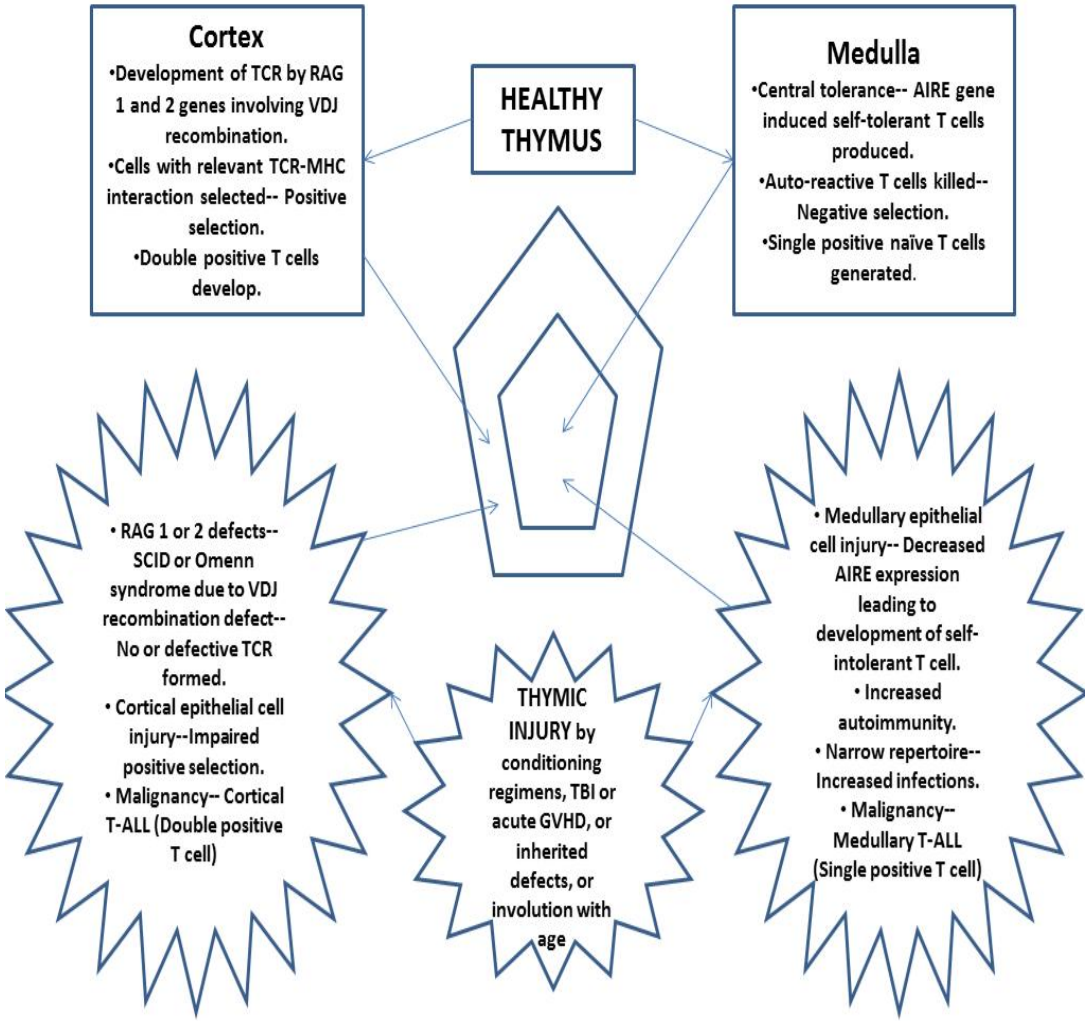

Fig. 1. The thymus consists of an outer cortex and an inner medulla, both of which are involved in the sequential maturation of thymocytes (T cells). Positive selection takes place in cortex and negative selection in the medulla. Defective maturation of the thymocytes either due to inherited defects or due to thymic injury can lead to various diseases as shown in lower part of the figure. Cortical T ALL originates from double positive cortical thymocytes, and medullary or mature T ALL originates from medullary single positive thymocytes. Early T precursor T ALL originates from most primitive double negative thymocytes that have recently emigrated from the bone marrow (not shown here)

CD8 cells, or a combination of both [22]. The prevalence of an inverted CD4/CD8 ratio increases with age and after HSCT (when peripheral expansion of CD8 T cells and decreased thymic output of CD4 T cells results, which normalizes only after thymic recovery). Cytomegalovirus (CMV) infection has a significant impact on the CD4/CD8 ratio through the expansion of CMV specific CD8 cells [23], whereas human immunodeficiency virus (HIV) infect decreases CD4 T cells [24].

5. T CELLS AND LYMPH NODES

An immune response requires the coordination of a diverse range of cells involved in host's immunity. So, for the T cells to interact with APCs and allow the interactions to result in further proliferation of T cells, a static platform is required as this is not possible in circulation where cells are constantly moving. This problem is solved by concentrating antigens, APCs and antigen-responding cells at one place i.e. in

lymph node [25]. Naïve T cells enter lymph nodes from the blood via specialized vascular regions called high endothelial venules and reach paracortex. If a naïve T cell does not encounter any MHC/peptide complexes, it exits through the efferent lymphatics, which ultimately drain into the thoracic duct and then back into the blood. If a naïve T cell does encounter an APC that expresses an MHC/peptide to which it can bind, it will initiate an activation program. This process of immune surveillance keeps a check on the antigens entering the body. Simultaneously co-stimulation of co-signaling molecules is also necessary for efficient T cell activation and results in the clonal expansion of effector T cells with the selected antigen specificity [26]. Naïve T cells are precursors for effector and memory T cells subsets whose development takes place in lymph nodes. So, the lymph nodes perform several important functions, including pathogen containment, recruitment of naïve T cells from thymus, recruitment of antigen loaded APCs from peripheral tissues (e.g., skin, gut), generation of adaptive immune responses in the form of T cell proliferation and cytokine secretion, suppression of autoreactive cells by T-regs, and providing long term residence to memory T cells [25]. There are about 500 to 600 lymph nodes that are distributed throughout the body to provide region-specific immune responses [26].

Various benign and malignant diseases can originate from the lymph nodes. Autoimmune lymphoproliferative syndrome (ALPS) is an inherited nonmalignant lymphoproliferative disorder characterized by mutations in FAS signaling pathway leading to expansion and accumulation of autoreactive CD4- and CD8- (double negative) T cells in the lymph nodes, leading to splenomegaly, lymphadenopathy, cytopenias, autoimmune disorders, and increased risk of lymphoma [27]. The double negative T cells resulting in ALPS are mature T cells developed probably in lymph nodes from single positive T cells who lose their CD4/CD8. These T cells are different from the immature double negative thymocytes which give rise to early T precursor ALL.

6. T CELLS HELP B CELLS

'T helper cell' was named after it was discovered that T cells help B cells [28]. T cells help B cells in seven different ways by providing support in B cell proliferation, survival, somatic hypermutation, class-switch recombination, plasma cell differentiation, adhesion and attraction [29]. B cells in the germinal centres of lymph nodes depend on CD4 T cells for their development and maintenance, and for the production of plasma cells. T cells help B cells by their cytokines (IL-4, IL-21) or by direct cell-cell contact [29].

7. HOW T CELLS KILL PATHOGENS?

Antibodies do not enter cells, so once a pathogen gains entry into a host cell, antibodies are ineffective at defending the host. To counter the intracellular pathogens T cells are very crucial. They can identify the intracellular pathogens when microbial antigens are presented on the infected cell surface by MHC to the T cells, which is not possible by B cells or antibodies produced by B cells. T cells kill infected cells by either of the three mechanisms; a) releasing cytokines (TNF-α, IFN-γ, IL-2), b) forming pores in infected cells (perforin and granzymes apoptosis pathway), or c) by Fas-FasL signaling pathway (programmed cell death), and similar mechanisms are also involved in the killing of the cancer cells by T cells [30].

8. INHERITED T CELL DEFECTS

The three major steps involved in the T cell development are formation of TCR, positive selection and negative selection. Various diseases can occur if any of these steps involved in the sequential development of T cells in the thymus (Fig. 1), or the execution of their work outside the thymus (in the lymph nodes) are impaired. Complete deficiency of TCR (e.g. due to deficiency of RAG genes) results in severe combined immunodeficiency (SCID), as T cells cannot survive without survival signals received from TCR-CD3 complex (Table 1). Absence of T cells in SCID causes severe infections and is fatal in infancy. Partial mutations in RAG genes also lead to defective TCR formation [31]. The defective TCRs thus formed are unable to identify microbial antigens, thereby predisposing to infections, and also lead to generation of auto-reactive T cells, as their training in thymic medulla is incomplete and cannot differentiate self from non-self (loss of central tolerance). This syndrome resulting from partial mutations in RAG genes is called Omenn syndrome [31]. Deficiency of MHC II leads to defective CD4 T cell production resulting in combined immunodeficiency. Defective development of thymus (DiGeorge Syndrome) also leads to

severe T cell deficiency and increased infections. B cell maturation is also affected in all CD4 T cell defects, as these cells are required for normal functioning of B cells [32]. Mutation in AIRE gene can result in loss of representation of self-antigens by medullary thymic epithelial cells, leading to the development of immunogenicity against self-antigens (Table 1). Any defect in T-reg functioning leads to hyper-inflammatory condition and tissue destruction. FOXP3 is the transcription factor required for the action of T-regs, and mutation in FOXP3 leads to increase in autoimmunity in various organs (IPEX syndrome; immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome) [33].

9. ACQUIRED T CELL DEFECTS

Acquired defects in T cell development also lead to T cell deficiency. The two most common causes of acquired T cell defects are HIV infection, and use of high dose chemotherapy and HSCT. HIV typically damages CD4 T cells, increasing the risk of opportunistic infections and secondary malignancies [24]. Decrease in absolute CD4 T cells has historically served as biomarker for HIV's immune suppression and response to treatment. Conditioning chemotherapy and radiotherapy used for allogeneic HSCT and the high dose chemotherapy used in autologous HSCT damages the bone marrow, thymus and lymph nodes, thus impairing the normal development and function of T cells, and post HSCT inverts CD4/CD8 ratio, which recovers only after thymic recovery (Fig. 2).

10. T CELLS AND ALLOGENEIC HSCT

T cells play an important role in allogeneic HSCT. Both the host and donor T cells have clinical implications in HSCT. The T cells of the host need to be ablated (lympho-ablation) so that they do not reject the donor stem cells, whereas the donor T cells are needed for early engraftment and T cell reconstitution post HSCT, and to mediate graft versus leukemia (GVL) effect, though at the cost of graft-versus-host disease (GVHD). Graft rejection is an immunological phenomenon where the host T cells recognize the donor hematopoietic stem cells as foreign and mediate T-cell attack on the donor cells [34]. The two arms of conditioning regimens are myelo-ablation (creating space in bone marrow by ablating myeloid cells) and lympho-ablation (ablating T cells which mediate graft rejection) [35]. Lympho-ablation is more important than myelo-ablation for engraftment as graft rejection is mainly mediated by host T-cells, and agents which are more lympho-ablative are more effective in preventing the graft rejection, and same principle lies behind the success of reduced intensity and non myelo-ablative conditioning regimens [35]. Donor T cells are capable to create marrow space for the graft to home [36]. Improved conditioning regimens (adding lympho-ablative agents like fludarabine, antithymocyte globulin or cyclophosphamide) before transplant, have led to significant decrease in graft rejection [37]. Conditioning chemotherapy is not needed for HSCT for patients with SCID, because of the significant lack of host T cells which mediate graft rejection [38].

Table 1. Inherited diseases affecting T cell development in the thymus

Disease	Pathogenesis	Defect	Manifestations
SCID	Complete RAG deficiency in thymocytes	TCR not formed as VDJ recombination does not occur	Fatal infections in infancy
Omenn syndrome	Partial RAG deficiency in thymocytes	TCR formed but defective	Infections, autoimmunity
IPEX syndrome	FOXP3 mutation in thymocytes	T-reg defect	Autoimmunity
APECED disease	AIRE gene mutation in medullary epithelial cells	T cell defect with impaired self tolerance	Autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy
DiGeorge Syndrome	22q11. 2 deletion	Abnormalities of the third and fourth pharyngeal pouches	Thymic hypoplasia, lymphopenia, cardiac defects

11. T CELL RECONSTITUTION AFTER HSCT

T cell reconstitution following allogeneic T cell replete HSCT occurs by two major pathways [39]. Firstly, the thymic-independent pathway in which peripheral clonal expansion of donor-derived mature T cells from the graft takes place, and the second pathway is the thymic-dependent pathway, which is a long-term process of de-novo generation of naïve T cells in the thymus from hematopoietic stem cells (Fig. 2).

12. T CELLS AND AUTOLOGOUS HSCT

In autologous HSCT for autoimmune diseases, the re-infusion of hematopoietic stem cells is not only to shorten the myeloid aplasia but also is therapeutic as the naïve T cells which generate from the auto-graft are trained and reprogrammed in the thymus to become self-tolerant [40]. Moreover, autologous HSCT induces the restoration of T-regs from severely reduced numbers before auto-HSCT to normal levels after auto-HSCT [41].

13. T CELLS IN THYMIC DAMAGE

The thymus requires continuous input of hematopoietic progenitors to maintain T cell development [8]. Many chemotherapeutic agents used in conditioning regimens and drugs used in post transplant immunosuppression as well as acute GVHD have been shown to deplete thymocytes (T cells) [42], and thymic stromal cells [43]. Thymic regenerative capacity in humans decreases with age, suggesting that thymic-independent pathways of T cell regeneration may predominate during adulthood [44]. Therefore, T-cell populations can be regenerated in hosts in the absence of a thymus via a process that has been termed peripheral expansion [44]. This involves the mitotic division of mature T cells, however, it is generally unable to restore TCR repertoire diversity, which is a thymic dependent process (mediated by VDJ recombination). Mature T cell proliferation loses the T cell receptor diversity development and has limited repertoire broadening, leading to increased incidence of infections and autoimmunity. Therefore, thymic-dependent pathways are needed for complete restoration of T cell immune competence [45]. Functional immune reconstitution after T cell depleted HSCT can adequately develop in children and young adults from the thymic output of naïve T cells, but not in older adults (with thymic involution) who rely predominately on the peripheral expansion of memory T cells [46].

14. T CELLS AND GVHD

The donor graft transfused in allogeneic HSCT contains chiefly two types of cells with significant clinical relevance (Fig. 2). The first ones are allo-reactive donor T cells present in the T cell-replete graft. These are the mature T cells which when infused into the host undergo activation and proliferation and can result in allogeneic reactions termed acute graft versus host disease (GVHD). These allo-reactive donor T cells can also mediate thymic damage by causing acute GVHD of the thymus [47]. Damaged thymus is not able to produce normal self-tolerant naïve T cells from stem cells/precursor T cells (Fig. 2), and the impaired T cells thus produced are either self-reactive (impaired self-tolerance) or have impaired activity against pathogens (impaired T cell reconstitution), or both [48]. The second type of cells present in the donor graft are the CD34 positive hematopoietic stem cells which home in the bone marrow and produce progenitor T cells which then migrate to thymus for further development, where they undergo positive and negative selection, before exiting the thymus as naïve T cells, as discussed earlier. Thymic injury incurred during HSCT impairs T cell development particularly because of the damage to the AIRE-expressing medullary-epithelial cells [47]. If the T cells have defective maturation in the medulla and are not exposed effectively to AIRE-expressing self-tissue-specific antigens on epithelial cells, they will react with self-tissues in periphery and will generate autoimmunity [49]. These defective T cells thus generated fail to differentiate self from non-self and lead to chronic GVHD which has manifestations like autoimmune diseases [50]. Mild chronic GVHD has been shown to improve overall survival in hematological malignancies [51], probably by GVL effect.

15. T CELLS AND AUTOIMMUNE DISEASES

Aplastic anemia is a T cell immune-mediated disease that involves destruction of hematopoietic progenitor/stem cells [52], and treatment with cyclosporine and anti-thymocyte globulin (ATG) leads to hematological recovery in a significant number of patients. T-regs

impairment also plays a critical role in the pathophysiology of aplastic anemia [53]. Defect in T-regs has also been implicated in the development of autoimmune gastritis, thyroiditis, type 1 diabetes and inflammatory bowel disease [54].

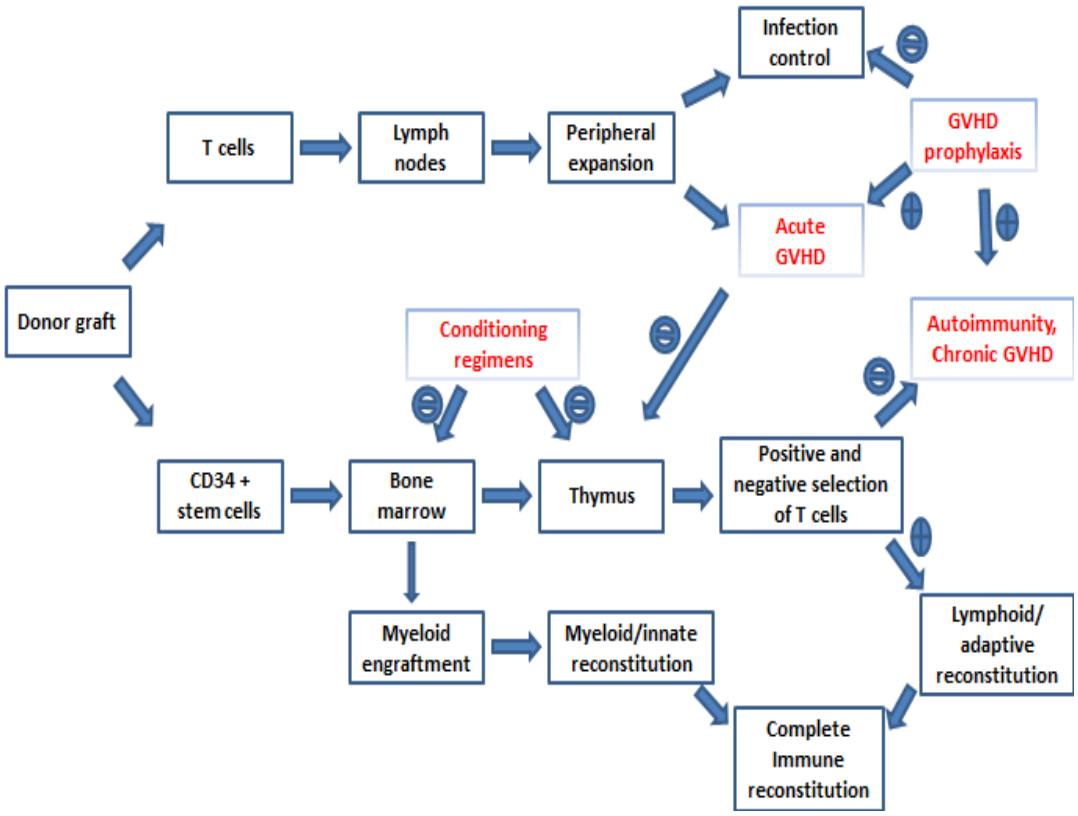

Fig. 2. Donor graft contains two main types of cells-- T cells and the CD34+ hematopoietic stem cells. The allo-reactive T cells undergo peripheral expansion in the host and can lead to acute GVHD. The CD34+ stem cells home to bone marrow and engraft. Myeloid engraftment occurs early and leads to reconstitution of innate immunity within 2-3 weeks. The precursor T cells move to thymus for further maturation, where they undergo positive and negative selection, finally producing naïve T cells, which lead to T cell reconstitution, which may take 6-12 months. Damage to bone marrow or thymus by conditioning regimens or acute GVHD can lead to impaired T cell production (thymic medullary epithelial cell damage decreases AIRE gene expression and thus reduced exposure of T cells to self-antigens during their training, which then mediate self-intolerance) that can lead to autoimmunity and chronic GVHD. This is how acute GVHD can lead to chronic GVHD. Medications used for GVHD prophylaxis and treatment, can lead to prolonged immune suppression by suppressing the T and B (not shown here) cells of adaptive immunity. (Circles with minus indicate negative impact and circles with plus indicate positive impact)

Table 2. T cell acute lymphoblastic leukemia (T ALL)

Type of T ALL	Cell of origin	Organ of origin/ Localization
Early T precursor ALL	CD4-, CD8-, Double negative	Recent immigrants from the bone marrow to thymus
Cortical T ALL	CD4+, CD8+, Double positive	Thymic Cortex
Medullary T ALL	CD4-/CD8+ or CD4+/CD8- Single positive	Thymic Medulla

16. T CELL MALIGNANCIES

Uncontrolled proliferation of T cells or loss of apoptosis signals can lead to generation of T cell leukemia and lymphoma. This malignant transformation could be due to the dysregulation of signaling pathways controlling T cell development, differentiation, and maturation or due to the virus induced T cell mutations [3]. Malignancies arising from the precursor T cells in bone marrow or thymus (both being primary lymphoid organs) result in T-acute lymphoblastic leukemia (T-ALL)/T-lymphoblastic lymphoma (T-LBL) (Table 2). Based on the cell of origin, and depending upon the type of antigens (CD4 or CD8) expressed by CD3 bearing T cells (Fig. 1), during different stages of their development in the thymus, patients with T-ALL can be classified into three categories: a) Immature T cell ALL (CD4-, CD8-, double negative, early T precursor), b) Maturing T cell ALL (cortical) (CD4+, CD8+, double positive), and c) Mature T cell ALL (medullary) (CD4-, CD8+ or CD4+, CD8-, single positive) [55]. Early T precursor ALL (ETP-ALL) arises from very immature T cells when they still retain stem cell and myeloid markers termed myeloid-lymphoid progenitors [56]. ETP-ALL carries a poor prognosis. T cell lymphomas have the features of post-thymic T lymphocytes and can arise from secondary lymphoid organs like lymph node (nodal) or extranodal tissues (skin or sinuses) [57]. The most common subtypes of mature T cell lymphomas originating in the lymph nodes are peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS), anaplastic large cell lymphoma (ALCL) and angioimmunoblastic T-cell lymphoma (AITL) (Table 3). PTCL is often associated with clonal rearrangements of the TCR genes. Primary cutaneous T-cell lymphoma originates from mature skin-resident memory T cells. Adult T-cell leukemia originates from mature CD4 T cells.

17. DRUGS EFFECTING T CELLS

Other than chemotherapeutic agents and ATG, drugs like steroids and calcineurin inhibitors also lead to immunosuppression and delayed T cell recovery, predisposing to microbial infections. Dexamethasone is more lympholytic than prednisolone [58]. Radiation also has strong lympholytic action and has been used as total body irradiation based conditioning regimen prior to HSCT. Blood products are also irradiated to prevent T cell mediated transfusion-associated GVHD, when host is immunocompromised and is not able to eradicate donor T cells [59].

18. T CELLS AND AGING

With aging the size of thymus decreases (termed thymic involution) resulting in decreased efflux of the naïve T cells and therefore decrease in T cell repertoire, and increase in memory and terminally differentiated T cells, with capability to fight previously exposed microbes only and reduced ability to fight new infections. Thus aging predisposes to increased risk of infections, and decreased response to vaccines [6]. The loss of naïve T cells is due to the decline in the production of new T cells in the thymus and a natural, life-long conversion of naïve T cells into memory cells in the periphery.

Table 3. T cell lymphomas

Type of lymphoma	Cell of origin	Organ of origin/ Localization
Peripheral T cell lymphoma (PTCL), NOS	CD4+ central memory T cell	Lymph node
Angioimmunoblastic T cell lymphoma	CD4+T follicular helper (TFH) cells	Lymph node
Anaplastic large cell lymphoma (ALCL)	CD4+ T cell	Lymph nodes and extranodal sites
Mycosis fungoides	A mature skin-homing CD4+ T cell	Skin
Sezary syndrome	Central memory CD4+ T cells	Lymph node, bone marrow, skin
Adult T cell leukemia/lymphoma (ATLL)	T-regs	Lymph node, peripheral blood
T cell large granular lymphocytic leukemia (T-LGL)	CD8+ T cell	Bone marrow, peripheral blood

19. T CELL BASED THERAPIES

The basic knowledge of T cell development and its ability to fight infections and cancers has been used in clinics for the benefits of humans. Adoptive T cell therapies with; a) Tumor-infiltrating lymphocytes, b) Engineered or gene-modified T cells expressing novel TCRs, and c) Chimeric antigen receptors (CAR), are being used to modify the immune system to recognize tumor cells and destroy them [60]. The first two approaches can only target and eliminate cancer cells when they present their antigens in context with MHC. A major advantage of CARs is their ability to bind to cancer cells even if their antigens aren't presented on the surface via MHC [61]. The CAR-T cell therapy involves separating the T cells from the host, and then using a viral genome, the T cells are genetically engineered to produce receptors on their surface called CARs. These CAR-T cells (e.g. tisagenlecleucel, axicabtagene ciloleucel) are then used to target specific antigens on the cancer cells [62].

20. T CELLS AND IMMUNE-CHECKPOINT BLOCKADE

Other than interacting with tumor cells via TCR (antigen-specific), T cells also require co-signaling molecules (antigen-unspecific) to make contact with the tumor cells, which either activate (co-stimulatory signals) or inhibit (co-inhibitory signals) T cells [63]. These co-signaling molecules (e.g. programmed cell death protein 1 or PD-1, and cytotoxic T-lymphocyte-associated protein 4 or CTLA-4) are called checkpoints as they limit the T cell signaling. Since tumors originate from within the body, T cells may fail to recognize them as non-self and activation of co-inhibitory signals prevents T cell activation and lysis of cancer cells. This is one of the ways by which cancer cells escape immune-surveillance. If the interaction of these co-inhibitory signals is blocked then T cells will get activated and will kill the cancer cells [4]. Several PD-L1/PD-1 checkpoint inhibitors have been developed for cancer immunotherapy, including anti-PD-1 (e.g. pembrolizumab, nivolumab) and anti-PD-L1 (e.g. atezolizumab, durvalumab), and have shown affectivity in many hematological and non-hematological malignancies [64].

21. CONCLUSION

T cells originate in the bone marrow, mature in thymus and reside in the lymph nodes. Any inherited or acquired defects can lead to T cells deficiency and increased risk of infections and autoimmunity. They also play an important role in graft rejection, and can cause acute and chronic GVHD. Malignant transformation of T cells can result in leukemia or lymphoma depending upon the stage and site of T cell maturation at the time of mutation. Naïve T cell production decreases with aging. T cells have been manipulated in many ways to harness their cytotoxic properties for the benefit of humans. This short review gives a deep insight into the journey of T cells, their training in the thymus to work as warriors in the periphery, their ability to protect the human body from infections and cancers, and their utilization for fighting against diseases. To understand the new advances in the T cell therapy it is very important to understand the basics of T cell's development and function, which this review article tries to explain.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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