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Chapter 1

Lymphoid Hematopoiesis and Lymphocytes Differentiation and Maturation

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Additional information is available at the end of the chapter

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Abstract

Lymphocytes belong to the lymphoid lineage and are considered as divergent from other blood cells lineages as those from the myeloid or erythroid lineage. Lymphoid hematopoiesis is not trivial, because although lymphocytes are found in the bloodstream and their precursor originates in the bone marrow, they mainly belong to the separate lymphatic system, which interacts with the blood circulation. We will discuss B cell differentiation in the bone marrow and the later stages of maturation in secondary lymphoid tissues, besides the B cell profiles in interfollicular, perifollicular, and follicular areas. In addition, we will also discuss T-cell precursor and natural killer cells derivation in the marrow. Furthermore, we will also discuss T-cell precursor migration to thymus, differentiation, rearrangement, thymic selection, involved transcription factors, and, finally, T-cell profiles and subsets in secondary lymphoid organs. We will provide flow cytometry plots showing strategies to identify and characterize NK, T and B lymphocytes and their subsets in circulation. Furthermore, we will provide illustrations to help the reader to understand and visualize the information provide over the chapter. Furthermore, the comprehension about lymphocytes and their contribution to the immune response will favor their application in developmental hematology and immunology. These topics are very important for the continuous development of knowledge.

Keywords: hematopoiesis, B cells, T cells, differentiation

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1. Introduction

Lymphocytes belong to the lymphoid lineage and are considered as divergent from other blood cells lineages as those from the myeloid or erythroid lineage. Lymphoid hematopoiesis is not trivial, because although lymphocytes are found in the bloodstream and their precursor originates in the bone marrow, they mostly belong to the separate lymphatic system, which interacts with the blood circulation. Lymphoid and myeloid lineages are separated at the progenitor level; the common lymphoid progenitors (CLPs) can differentiate into all types of lymphocytes but lack the myeloid potential under physiological conditions, although some myeloid-related genes can be detected in CLPs depending on experimental conditions [1, 2].

After transplanting a single hematopoietic stem cell (HSC) into an irradiated mouse, long-term reconstitution of both lymphoid and myeloid compartments was achieved demonstrating that the HSC is the common predecessor of all blood cells [3–5].

Hematopoiesis studies, mainly in the fetal liver indicated that the difference between the lymphoid and myeloid lineages may not be as simple as imagined. Nevertheless, a corresponding adult common myeloid progenitor (CMP) has been recognized in a fetal liver, but the presence of a lymphoid-committed progenitor (CLPs) has not yet been demonstrated [6, 7].

The bi-directional T and B cell derivation from a single cell was not found in the fetal liver progenitors at clonal levels, but T cell and granulocytes and macrophages (GM) or B cell and GM progenitor ability of differentiation were present [8]. Regarding these findings, it has been wondered whether these differences observed in fetal and adult hematopoiesis are due to different intrinsic mechanisms in fetal and adult progenitors or due to the liver and bone marrow environmental differences.

Several hematopoietic and lymphoid progenitors, such as multipotent progenitors (MPPs) and CLPs, are mobilized from bone marrow and initiate T-cell development in the thymus [9]. MPPs CCR9+ are the major bone marrow population that transit to the thymus. Once the hematopoietic progenitor cell home to the thymus, B cell development potential is immediately turned off by stimulation through Notch, while B cell differentiation will be regulated by several transcription factors in the bone marrow.

Next, we will discuss B lymphocyte differentiation in the bone marrow and later their stages of maturation in secondary lymphoid tissues and profiles in interfollicular, perifollicular and follicular areas. In addition, we will also discuss T-cell precursor and natural killer cell derivation in the marrow. Furthermore, we will also discuss T-cell precursor migration to thymus, differentiation, rearrangement, thymic selection, involved transcription factors, and, finally, T-cell profiles and subsets in secondary lymphoid organs.

1.1. B Lymphocytes

1.1.1. B Lymphocytes ontogeny

Lymphocytes are cells from the adaptive immune system and are derived from hematopoietic progenitor cells. These cells are first produced in the yolk sac, next, they are formed

in the liver during the fetal phase and lastly in the bone marrow [10]. B cell development is dependent of several specific cytokines and contact with a favorable microenvironment [11, 12].

The hematopoietic progenitor cell differentiates into a CLP and depending on stimuli they will give rise to a T or a B lymphocyte [13]. B cell differentiation from a CLP is regulated by several factors such as E-box binding protein 2A (E2A), early B cell factor-1 (EBF1), purine box factor 1 (PU.1), Ikaros, paired box protein-5 (Pax5) and CXCL12. These factors are resulting from the interaction of interleukin 7 (IL-7) and their receptor CD127 (IL-7Rα) existent in the B lymphocyte. Together, these factors are crucial for the hematopoietic progenitor cell commitment to B lymphocyte differentiation and gene rearrangement to the immunoglobulin heavy chain [14–21].

The first cell committed to B-lymphoid differentiation is the pro-B cell. The presence of stromal cells and IL-7 also favors the B lymphocyte differentiation. These cells begin to express $CD45^{dim}$, CD22, CD34, terminal deoxynucleotidyl transferase (TdT) and $CD38^{high}$ [19]. The Pax5 factor activates the CD19 expression, one of the most premature B lymphocyte antigens [18, 22]. In the next step of differentiation, these cells express $CD10^{high}$, $CD38^{high}$, CD34, CD79a, TdT and start being called pre-B I [19, 20]. Immunoglobulin (Ig) gene recombination in the heavy chain locus starts in this phase. The heavy chain gene is present in segments that code for the variable (V), diversity (D), joining (J), and constant (C) regions [23, 24]. Gene recombination is initiated by recombinase activating gene proteins RAG1 and RAG2; these proteins have the ability to bind and cleave DNA at specific recombination signal sequences called RSSs.

These RSSs surround each genic segment V, D and J. During recombination, D and J gene segments are drawn closer, excluding the intermediary DNA, and this DJ segment is joined to a V segment originating VDJ rearranged exon. Pre-B I cells also express TdT, which is responsible for catalyzing the random addition of junctional (N) nucleotides [24, 25]. The VDJ rearrangement is now adjacent to the constant Cμ region and creates an active gene which codes for the heavy chain, whose synthesis originates the μ intracytoplasmic chain (IgM) and from now these cells become termed pre-B II [19].

During pre-B II cells, they gain heterogeneous CD20 expression and lack the expression of CD34 and TdT [19, 20, 26]. Besides, B lymphocyte expresses a complex known as a pre-B cell receptor (pre-BCR) that is formed by the heavy chain μ (Igμ) associated to a light chain (λ5 and pre-B V) joined to a heterodimer Igα (CD79a) and Igβ (CD79b) [27]. If the pre-BCR is able to bind to the bone marrow microenvironment, the *immune-receptor tyrosine*-based *activation motif* (ITAMs) domains of Igα and Igβ are phosphorylated and their signaling rescues these cells from apoptosis. This positive selection confirms that the Igμ chain generated is functional, and the pre-B II cells detected with Igμ not functional are deleted [19]. The signals generated by the pre-BCR also stimulated the pre-B II differentiation and are responsible for their proliferation in the bone marrow, inhibiting the heavy chain recombination and stimulating the light chain recombination [28, 29]. The light chain rearrangement comprises the junction of a V with a J segment forming a VJ exon associated with an Igμ chain. This association activates the translation of kappa and lambda proteins leading to a formation of

a complete IgM molecule [30, 31]. The B cell that expresses an IgM molecule on the cell membrane is denominated immature B cell [19].

Immature B lymphocytes begin to express some immunophenotypic markers of still naïve but mature B lymphocytes; among these characteristics we can quote the CD20 expression, enhanced expression of CD45, CD10^{dim} and CD38^{high}, low expression of CD21, CD5 (homogeneous), and high levels of CD81 [19, 26].

These cells undergo a positive and negative selection process before completing their maturation status. During this process, the B lymphocytes that complete, successfully, the gene rearrangement program are positively selected, there are the shut-down of RAG genes and these cells will receive survival signals to proceed in the maturation process [32]. Though, when the B lymphocyte recognizes self-antigens, their receptor is modified, the genes RAG are reactivated and another rearrangement in the light chain V-J is initiated allowing the B cell to develop a non-self-reactive BCR [32–34]. However, if this rearrangement did not succeed this cell undergo through apoptosis in a process known as negative selection. The positively selected cells leave the bone marrow and complete their maturation status in the secondary lymphoid organs.

Mature B lymphocytes lack CD10 and CD38 and express IgD and IgM on their membrane (**Figure 1**) [19]. IgD expression happens when the VDJ segment is trasncribed with Cδ exon instead of Cμ [35]. B lymphocyte differentiation in the bone marrow is heterogeneous and goes through several maturation stages that can be observed by analysis of immunophenotypic characteristics (**Figure 2**).

1.1.2. Mature B lymphocytes

Mature B cells are usually divided into three subgroups known as follicular B cells, marginal zone (MZ) B-cell and B1 cells. The follicular B lymphocytes are the majority of mature B cells and are located in the lymphoid follicle of the lymph node and spleen. These cells will stimulate the T lymphocyte response and this can occur in two different locations, extra-follicular and in the germinal center [36]. B cells in the extra-follicular can be activated by the T-helper

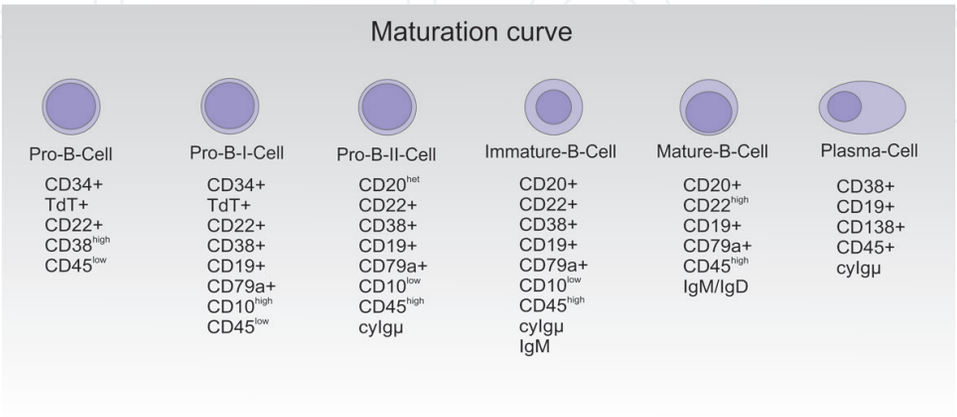


Figure 1. Schematic B cell regular development.

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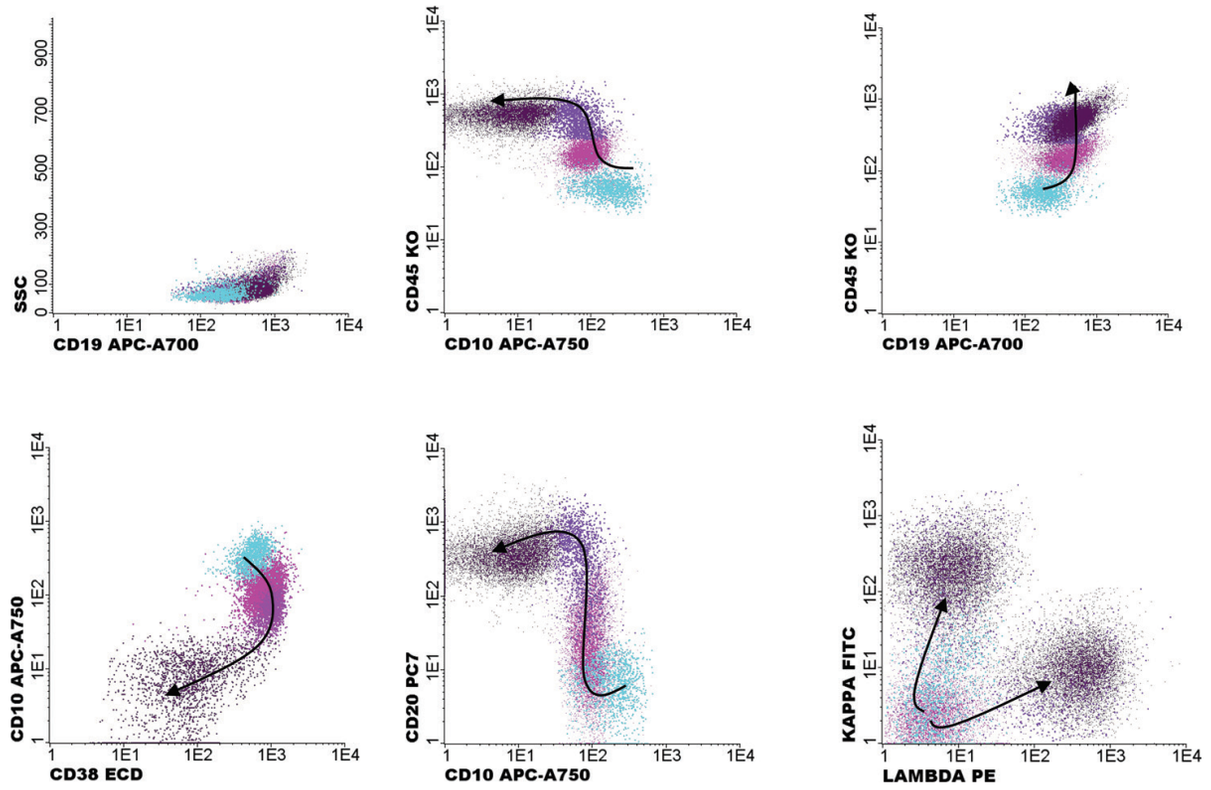


Figure 2. Bone marrow expression profile of B cells in different stages of maturation. The B cells maturation states are represented by the colors displayed in the flow cytometry plots figures: light blue represents immature B cells, purple represents intermediate stage and brown the mature B cells. Analysis performed with the Infinicyt software (Cytognos).

lymphocytes and differentiate into short-lived plasmablasts which secrete antibodies. On the other hand, some activated B cells migrate back to the follicles and under follicular helper T cell (T_{FH}) influence proliferate vigorously to form the germinal centers (GC) [37, 38]. Inside a GC, in the dark zone region, the B cells, now called centroblasts, goes through a rapid cellular division, somatic hypermutation, and isotypes class switching. Centroblasts express CD10 and Bcl-6. Next, these cells migrate to the light zone region and become centrocytes. These centrocytes in the light zone will be in contact with follicular dendritic cells (FDC) and T_{FH} through the interactions between CD23 and CD40L (**Figure 3**). B cells with high affinity for the antigens in this microenvironment will differentiate into plasmablasts (plasma cells) or memory B cells and will express CD27. Plasma cells return to the bone marrow and display well-defined characteristics expressing CD19, CD27, CD38, CD45, CD138 and intracytoplasmic Ig [10, 19, 37–39].

MZ B cells are located in the spleen MZ and are responsible by the T independent-responses (polysaccharides, glycolipids, and nucleic acid). These cells express pan-B markers, lack CD10 and show weak IgD expression [39]. B-1 cells represent another B cell lineage located mainly in the peritonea and mucosa [40]. These cells are also responsive to T cell-independent antigens and can be recognized by the expression of CD27 and CD43, even though this phenotype remains controversial [40, 41].

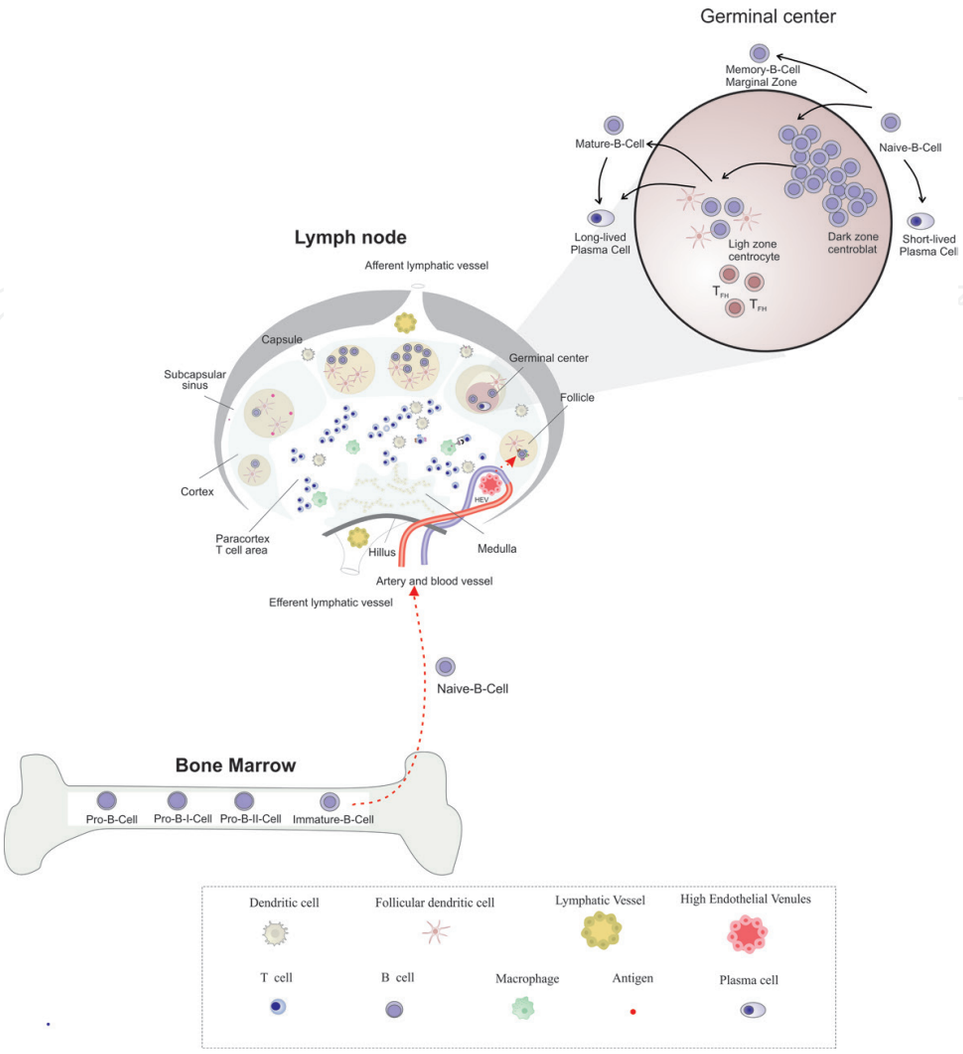


Figure 3. Schematic representation of B cell maturation in bone marrow and their differentiation in the lymph node [19, 35].

1.2. T Lymphocytes

1.2.1. T Lymphocytes ontogeny

Currently, we will discuss the origin and differentiation of T and natural killer (NK) cells, as well the migration of T cell precursors from the bone marrow to the thymus. In addition, we will discuss stages of T cells maturation and immunological development such as differentiation and proliferation, T cell receptor (TCR) genic rearrangement, thymic positive and negative selection and T cells with different phenotypes. These steps summarize the requisites for T cells to become immunologically competent and populate the peripheral lymphoid tissues.

It is well known and scientifically accepted that all blood cells are derived from a hematopoietic stem cell (HSC), defined as pluripotent and capable of self-renewal. HSCs express the CD34 antigen and account only for 0.1% of the all bone marrow nucleated cells. The first phase of HSC differentiation is the cell commitment to specific lineages. The lymphoid lineage

commitment is dependent on several environmental factors such as stromal cells signaling, growth factors, cytokines, and kinases (Janus-JAK), tyrosine kinases (Kit-L) and surface molecules such as Notch-1. Notch-1 is very important since their collaboration with GATA-3 will contribute to the T lymphocytes lineage commitment, mainly to the αβ receptor T cells [21]. Radtke et al. have shown that the deletion of Notch-1 in murine models resulted in the T lymphocytes impaired development in the thymus [42].

The interleukins (IL) are also fundamental for HSC differentiation into lymphoid precursors and the key ILs involved in this process are IL-1, IL-2, IL-3, IL6, and IL-7. IL-7 is produced by the bone marrow stromal cells and by the thymic epithelial cells, and IL-7 plays a role in T cell development, proliferation and survival of lymphoid precursors. The IL-7 receptor is composed of two chains, IL-7Rα, and the gamma common (γc), the last is shared by several cytokines receptors such as IL-2, IL-4, IL-9, IL15 and IL-21. Alterations in the genes that codify IL-7Rα or the γc result in an immunodeficiency X-linked named severe combined immunodeficiency (SCID), which is characterized by the significant reduction or absence of T lymphocytes and NK cells, revealing the roles of IL-7 in humans [43–46].

Lymphoid progenitors can be characterized phenotypically by the expression of CD7 and CD34. Some studies define the lymphoid progenitors by the CD7 expression since this antigen has a lower expression in myeloid cells and is not expressed in other cell lineages [47].

A key event on T lymphocyte development is the gene rearrangement that is responsible for the generation of a diverse antigen receptor repertoire. The genes involved in the T cell receptor (TCR) rearrangement are present in the germ cell lineage and are located in the chromosomes 7 and 14. As seen in B lymphocytes, the heavy chain genes are present in the segments that code for the variable (V), diversity (D), joining (J) and constant (C) regions, and this recombination is known as V(D)J. In humans and mice, the γδ T cells have a limited repertoire of V and J segments that are involved in the TCR genic rearrangement [48, 49]. In humans, the δ-locus is clustered inside the α-locus, and there are only three true Vδ, they are Vδ1, Vδ2, and Vδ3. The human Vγ repertoire is situated in the γ-locus with 12 Vγ genes, of which only seven are identified as functional, since Vγ1, Vγ5P, Vγ6, Vγ7, and Vγ10 are considered pseudogenes. The difference between the low diversity in γ-δ loci and the high diversity of the α-β loci suggest that the γδ TCRs low diversity accompanies their recognition of preserved self-proteins with low variability.

The TCR V(D)J recombination is very similar to the B lymphocytes BCR recombination, involving also the enzymes Rag-1 and Rag-2, endonuclease *Artemis* and terminal deoxynucleotidyl transferase (TdT), Ku70, Ku80, DNA-dependent protein kinase (DNA-PK) and *XRCC4-DNA ligase IV.* Functional defects on these enzymes can result in immune deficiency such as SCID that can be derived of Rag-1 or Rag-2 mutations [50–52]. The higher TCR diversity generated during V(D)J recombination is a result of two combined mechanisms of diversity that involve random combination of gene segments and junctional diversity that results from the nucleotides addition or removal, complementary or not, within the junctions between V(D)J segments. These mechanisms of diversity can generate around of 10^7 different T lymphocyte clones. Each clone represents a unique TCR, the number of T cells clones is not higher as expected, but can be explained by the large number of T cells depleted during the thymic selection [51, 53].

1.2.2. Thymocytes and thymic selection

Different from B lymphocytes, the precursors of T lymphocytes migrate from the bone marrow to the thymus to complete their maturation status and undergo the positive and negative selections. The thymus colonization by immature lymphocytes, also known as thymocytes, enrolls chemokines, mainly CC-chemokine ligand 21 (CCL21) and CCL25, and their respective receptors CCR7 and CCR9 [54]. The thymic maturation is very important and only 1–3% of thymocytes that enter in the thymus survive the selection steps and gain the circulation [55–57].

Initially, the T cell precursor migrates to the corticomedullary region of the thymus, then inside the cortex and the double negative cells (DN) CD4-CD8- (**Figures 4** and **5**) [58]. The DN cells in development receive Notch-1 and IL-7 mediates signals, usually derived from the cortical thymic epithelial cells (cTECs) [59, 60]. Most thymocytes rearrange the V(D)J genes efficiently to express TCR $\alpha\beta$ from DN3, at this stage, the TCR was not tested for their specificity and is termed pre-TCR$\alpha\beta$, which is associated with the protein complex CD3/ζ for the signal transduction [61]. Following maturation, thymocytes begin to express CD4 and CD8 co-receptors, initially expressing CD8, and then expressing CD4 to form the thymocyte double positives (DP) CD4+CD8+ (**Figures 4** and **5**). This DP population is present in the thymic cortex, expresses TCR$\alpha\beta$ and consists of most lymphocytes inside the thymus of young individuals [62].

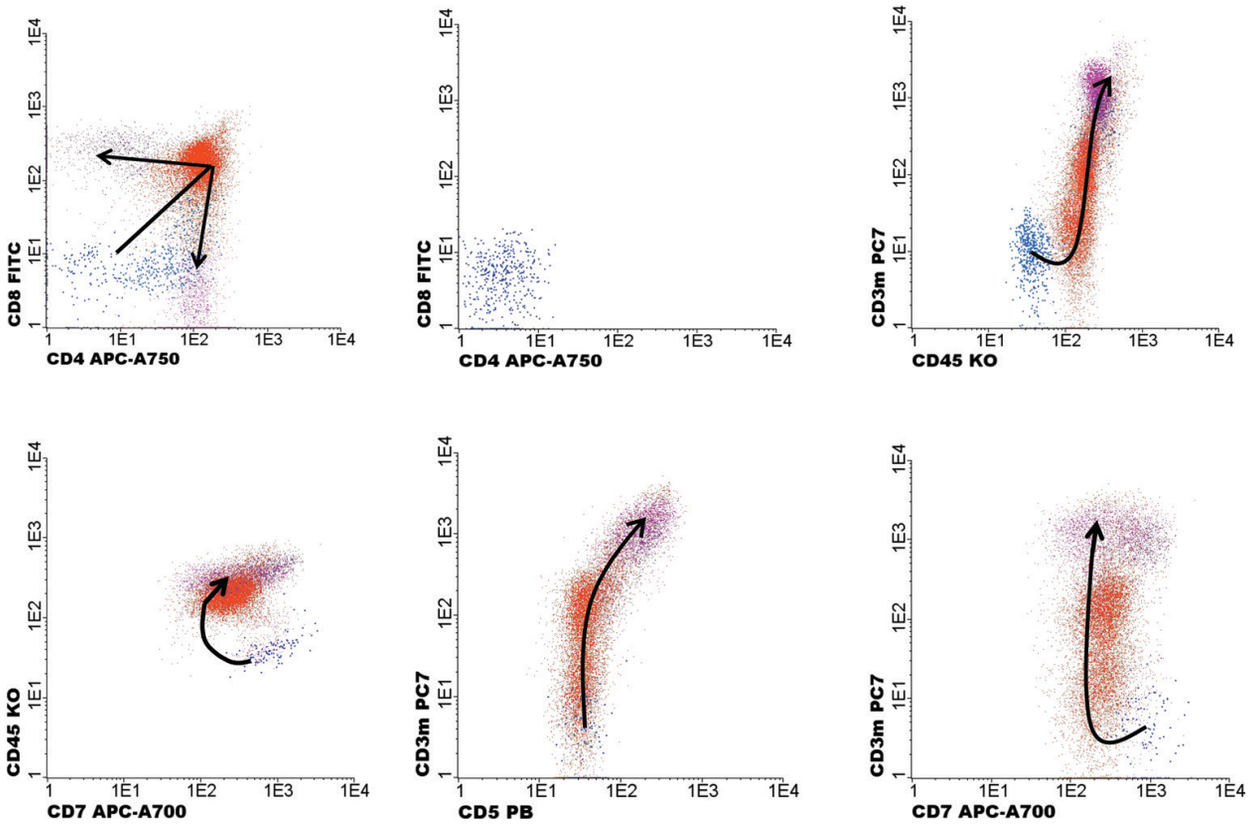


Figure 4. Thymus expression profile of T cells in different stages of maturation. The maturation states are represented by the colors displayed in the flow cytometry plots figures: dark blue represents immature double negative T cells, orange represents double positive cells in intermediate stage and purple represents the single positive mature T cells. Analysis performed with Infinicyt software (Cytognos).

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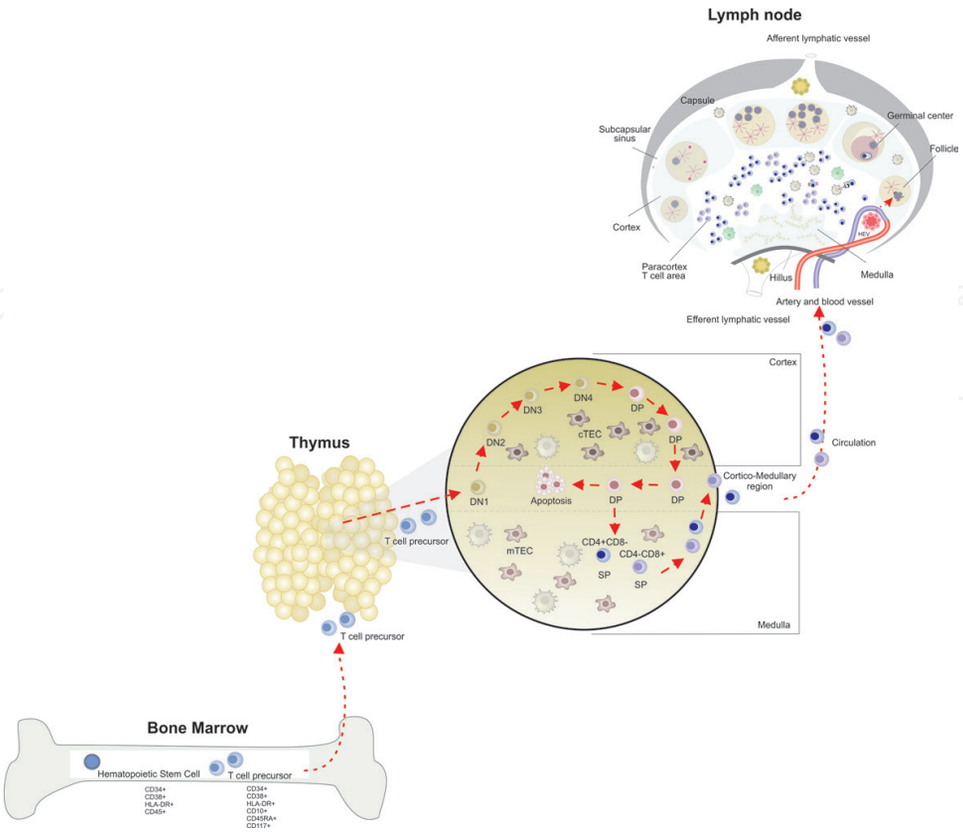


Figure 5. Schematic representation of T lymphocytes thymic selection [54, 59–63].

In the cortex, the TCRs from DP thymocytes interact with peptides via major histocompatibility complex (MHC) molecules expressed by the cTECs and dendritic cells and go through steps of positive and negative selections, thymocytes that interacting properly (low avidity interaction) are positively selected and receive survival signals (**Figure 5**). Thymocytes that fail in this interaction or interact with high avidity are selected negatively by the mechanism of apoptosis (death by neglect). This process is important so that thymocytes that continue their development are able to recognize foreign antigens but not self-antigens, thus avoiding autoimmunity. Interestingly, approximately 90% of DP thymocytes express ineffective TCRs and do not pass through cortex checkpoints and end dying due to the absence of positive selection (**Figure 5**) [54, 61, 63]. The positively selected DP thymocytes migrate to the thymus medulla, guided primarily by the expression of CCR7 and the chemoattraction of CCL19 and CCL21 produced by the medullar thymic epithelial cells (mTECs) and are induced initiate differentiation for CD4+CD8- or CD8+CD4-positive single (SP) thymocytes (**Figure 4**) per the MHC molecule involved (MHC class II for SP CD4+and MHC class I for SP CD8+) (**Figure 5**) [64].

The thymocytes that have escaped negative selection by cTECs and are self-reactive to tissue-specific antigens expressed by mTECs are also depleted [65, 66]. TThe expression of tissue-specific antigens by mTECs is controlled by the transcriptional factor autoimmune regulator (AIRE) and AIRE deficiency results in the disease, in humans, called autoimmune polyendocrinopathy – candidiasis - ectodermal dystrophy (APECED) [67, 68]. Interestingly, some thymocytes CD4+ that recognize self-antigens with high avidity into the thymus may develop

in a CD4+ population of peripheral regulatory lymphocytes, which have the function of controlling and preventing autoimmune reactions.

Phenotypically, SP thymocytes express CD62 L and CD69 and also acquire the functional capacity of mature T lymphocytes, but are still naïve, not having yet experienced antigens during an adaptive immune response [69, 70]. Expression of sphingosine-1-phosphate receptor 1 (S1P1), one of the S1P receptors, is required for the outflow of the mature T lymphocytes from the thymus and in addition to S1P1, CCR7, CCL19 and CXCL12 also participate in this process [71]. This stage of differentiation and maturation in the thymus lasts approximately 12 days and is critical for the establishment of central tolerance [56]. Finally, immunologically competent lymphocytes leave the thymus and become part of the pool of mature and naive peripheral T lymphocytes, which remain in the cell cycle interphase for extended periods until they encounter with specific antigens presented by antigen-presenting cells (APCs) via MHC in secondary lymphoid organs (**Figure 5**).

1.2.3. Mature T lymphocytes

Once lymphocytes have left the thymus, they are carried in the blood to the peripheral lymphoid tissues such as lymph nodes, where the cells organize themselves to facilitate the encounter with antigenic particles and consequent lymphocytic activation. Immune cell-cell interactions are usually rolling interfaces that undergo continuous architectural change. The contact between T and B lymphocytes and the antigen-presenting cells (APCs) favors the information exchange among the cells, contributing to the assembly, type, and scope of immune responses [72].

Now, we will describe different classes of lymphocytes based on transcription factors expression and their cytokine secretion profile, associated to their differentiation status, functional profile and plasticity. It is important to highlight that each lymphocyte has a unique antigen receptor that is generated by somatic recombination and recognizes a different foreign component, and thus collectively, lymphocytes provide an almost limitless defense against a wide range of antigens. Recent evidences have demonstrated that a lymphocyte can produce daughter cells with different fates that carry out different functions. Based on these indications, it seems as if a single lymphocyte typically produces a diversity of functional daughter cells and manages to renew itself [73–76]. Successful immune responses often require more than one type of differentiated cell fate. Kelso and collaborators had already demonstrated in 1995 that biased T helper (Th) Th2 responses contained traces of Th1-type cytokines expression [77].

Activated $CD4^+$ T cells differentiate into immune suppressive regulatory T (Treg) cells or inflammatory T effector cells, such as T helper Th1, Th2, Th9, Th17, Th22 and follicular helper T (Tfh), each one with distinct characteristic metabolic programs (**Figure 5**). These different $CD4^+$ subsets play a critical role in the immune and effector response functions of T cells [78]. In response to distinct antigen challenge and extracellular cytokines signals, each $CD4^+$ T cell subset has distinct abilities in producing cytokine and chemokine receptors and expressing

polarizing transcription factors, along with their association with specific forms of immune defense. New tools and techniques have revealed the capacity of polarized cells change their phenotype and repolarize towards mixed or alternative fates. The same cytokines that drive the polarization of each T helper cell subset during initial priming also drive the plasticity of established T helper cell subsets [79, 80].

1.2.3.1. CD4 Cell subsets

Since the establishment of the Th1-Th2 dogma in the 1980s [81, 82], different lineages of effector T cells have been identified that not only promote but also suppress immune responses.

Th1 cells are defined based on the production of pro-inflammatory cytokines such as interferon (IFN)-γ, and tumor necrosis factor (TNF)-α or TNF-β to stimulate innate and T cell immune responses. These cells are induced by natural killer (NK) and/or dendritic cells, through IFN-γ producing, which activate signal transducer and activator of transcription (STAT) STAT1, resulting in activation of lineage-specific transcription factor encoded by T-box transcription factor—TBX21 (T-bet) [83]. IL-27, a cytokine from IL-12 family, contributes to STAT1 phosphorylation and T-bet activation. T-bet enhances the synthesis of the IL-12 receptor, which activates STAT4 and consequent transcription and production of IFN-γ. Th1-type cytokines are responsible for the death of intracellular antigens and for the autoimmune response maintenance (**Figure 6**) [84, 85].

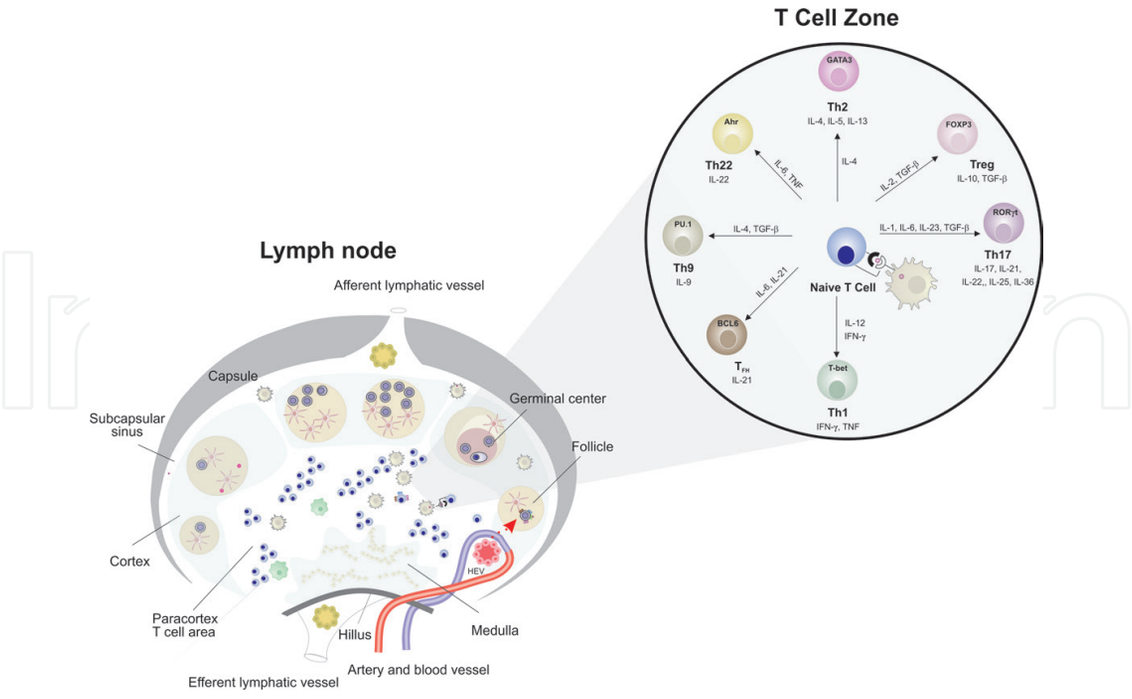


Figure 6. CD4 subsets differentiation, cytokines and transcription factors [78, 84–90, 121].

On the one hand, Th2 cells are defined as producers of IL-4, IL-5, and IL-13, which are associated with the production of IgE and eosinophilic responses in atopy. Differentiation of the Th2 subset requires IL-4 produced by Notch ligand activation of dendritic cells, inducing STAT6, which activates GATA-3. This transcription factor activates the production of the Th2 the lineage-specifying cytokines. Th2 cells control immunity to extracellular parasites and all forms of allergic inflammatory responses (**Figure 6**) [85, 86].

In recent years, it became evident that more functional subsets of T helper cells can be induced by various stimuli *in vivo* and *in vitro.* Induction of the Th17 lineage occurs when IL-6, IL-23, and TGF-β are present in the inflammatory milieu without Th1 or Th2 cytokines (**Figure 6**) [87]. Toll-like receptor signaling, leading to MyD88 signaling, is another innate immune signal fostering Th17 differentiation [88]. The cytokine IL-6 promotes STAT3, which induces retinoic orphan receptor (ROR) transcription factors, RORα and RORγT, leading to production of Th17 cytokines IL-17, IL-17F, and IL-22 [89, 90]. Functionally, Th17 cells play a role in host defense against extracellular pathogens by mediating the recruitment of neutrophils and macrophages to infected tissues. Moreover, it has become evident that abnormal regulation of Th17 cells may play a significant role in the pathogenesis of a variety of autoimmune and inflammatory diseases, because these cells can cause tissue injury when aber¬rantly regulated [85].

Another recently reported T helper population includes Th9 cells. This subset of cell undergoes a maturation program similar to Th2 cells, with IL-4 inducing STAT6 activation, and produces the Th2 cytokines IL-9 and IL-10, but unlike Th2 cells, they require TGF-β for maturation (**Figure 6**) [91, 92]. The IL-2-STAT5 signaling including interferon regulatory factor **(IRF)4** expression is critical for Th9 cell differentiation. Additionally, the lineage-specific transcription factor for Th9 development may be the activator protein 1 family transcription factor, BATF, leading to a transcriptional program, which results in increased IL-9 and IL-10 production [85, 91, 93]. There is a requirement as well for TGF-β-induced SMAD proteins and the SMAD-independent induction the transcription factor PU.1 in the generation of IL-9-secreting T cells. Although the GATA3 expression is lower in Th9 cells than Th2 cells, STAT6 is an important target gene involved in Th9 differentiation. These cells can exacerbate the immune response by enhancing antibody production and increasing immune cell infiltration and activity within the respiratory tract, contributing to asthmatic disease. In addition, IL-9 mediates anti-parasitic activity by altering epithelial cell function, increasing immune cell infiltration into infected locations, and augmenting leukocyte immune function. Besides that, the production of IL-9 by Th9 cells impairs tissue repair process during colitis, in contrast, can limit tumor growth by stimulating lymphocyte antitumor activity (**Figure 6**).

Th22 cells are promoted by IL-6 and TNF-α, which induces STAT3, and expression of the aryl hydrocarbon receptor [94]. Th22 cells have a specific profile of Th1 and Th17-associated genes, such as IFN-γ, IL17a, T-bet and RORγt [95]. In addition the counterpart maturation between Th17 and Th22 subsets, numerous phenotypic markers are expressed in both cell populations, including CCR6, CCR4, dipeptidyl peptidase IV, CD26, and CD90. But, differently from Th17, the Th22 cells expresses CCR10 and represents a distinct subtype of T cells that is involved in

the epidermis immunity. IL-22, a cytokine from the IL-10 family, is not exclusively produced by the Th22 cells, then also by Th1 and Th17 cells (**Figure 6**) [85, 96].

A subset of human $CD4^+$ T cells that specifically express IL-22 has been identified in the skin where the synthesis of active vitamin D enhances IL-22 expression, contributing to skin homeostasis, but also to the pathogenesis of skin disease, observed in psoriasis patients [97, 98].

Follicular helper CD4+T (Tfh) cells were first found in human tonsils, but now it is clear that are localized in the B-cell follicle and germinal center (GC) and is specialized in facilitating B-cell responses, enhancing immunoglobulin production [98, 99]. Tfh cells require a strong TCR signal for induction, which is also required for Treg responses [85, 100]. Tfh specification requires activation of the inducible co-stimulator (ICOS), a CD28-related co-stimulatory signal provided by activated dendritic cells or B cells, which initiates transcription of MAF, one transcription factor that induces IL-21 activation. The OX-40/CD134 co-stimulatory signal ligation is necessary to down-regulates CTLA-4, a dominant suppressor molecule of T cell activation (**Figure 6**) [101]. IL-6 and STAT3 are required for Tfh development like Th17 cells, yet Tfh cells can be generated in the absence of Th17 cytokines, IL-17, IL-17F, or TGF-β [102].

In order to understand how Tfh cells are identified, first is necessary to comprehend T and B cells migration for their interaction sites, which usually takes place in secondary lymphoid organs such as lymph nodes (LNs). Naive T cells migrate to the T cell zone in LNs responding to CCL19 and CCL21 gradients. After dendritic cells antigen stimulation, Tfh cells up-regulate CXCR5, down-regulate CCR7 and migrate to the interfollicular regions within LNs, where they interact with activated B cells. These interactions result in antibody production by the short-lived plasmablasts, which take place in extrafollicular regions or in the germinal center. In both regions, Tfh cells support B-cell maturation, class switch and affinity selection, via cytokines secretion or by expressing surface molecules. The germinal center responses drive memory B cell and plasma cell development. Then, Tfh cells are characterized according to patterns of receptor expression that enables their movements, as well as the expression of other surface proteins associated with migratory processes [103–107].

Regulatory T-cells (Treg) represent a heterogeneous population of CD4+T-cells characterized by suppressive capacity, which can be generated in the thymus, termed natural Tregs (nTregs) or adaptive regulatory T cells, induced in the periphery, involved in maintaining oral tolerance (Th3 cells), and T regulatory type 1 cells (Tr1 cells), stimulated by IFN-α secreted by neighboring plasmacytoid dendritic cells (pDCs). According to the literature, the nTregs need a strong TCR signal for their development. They are formed by low co-stimulation, so the T cell antigen recognition without a robust second signal provide by the CD28 family members leads to tolerance [85, 108]. Differentiation of induced Tregs, Th3 cells, and Tr1 cells happens in the periphery and needs high TGF-β concentrations and absence of pro-inflammatory cytokines [109]. Cell-cell interaction and IL-10 secretion are essential for the Treg suppressor function, mediated by the transcription factor Foxp3 through STAT5 activation (**Figure 6**), and simultaneous RORγt down regulation, which is the Th17 transcription factor [85, 110, 111].

Human T cells can be divided into functionally distinct subsets. Two primary categories are naïve T cells (TN) that have not been exposed to antigen and those that are antigen-experienced (memory). Naive T cells are usually characterized by the expression of CD45RA+, CD62L+ and CCR7+. CD45RA and CD45RO are high and low molecular weight protein derived from the CD45 gene splice variant, distinctly, with CD45RO being mainly expressed by memory cells. CD45RO+ cells are rarely found in neonates and gradually increased with age. The analysis of homing receptors revealed that T cells are heterogeneous and in particular naïve T cells express high levels of the lymph-node homing receptor CD62 L (L-selectin). Long-lived memory CD4+ lymphocytes are a hallmark feature of the adaptive immune system in response to pathogens and tumors [112]. The memory T cell compartment is heterogeneous and has been conventionally divided into two subsets on the basis of the lymph node homing molecules CD62 L and CCR7 expression [113]. Central memory T cells (TCM cells) highly express CD45RO+, CD45RA−, CD62L+ and CCR7+, whereas CD45RO+, CD45RA−, CD62L− CCR7− effector memory T cells (TEM cells) are considered to be committed progenitor cells that undergo terminal differentiation after a limited number of divisions (**Figure 7**) [114]. CCR7 and CD62 L are mostly co-expressed on the surface of CD4+ and CD8+T cells, and cells expressing these markers nearly uniformly express CD27 and CD28—but the inverse is not true. CD27 and CD28 are the main co-stimulatory molecules required to induce T cell activation, although memory T cells seem to be less dependent on CD27 and CD28 for their reactivation than naïve T cells [115, 116]. CCR7−/CD62L−, CD28+ cells are found in the peripheral blood of healthy individuals and known as a subset of transitional memory (TM) cells. TM cells seem to be more mature than TCM cells, but not as totally mature as TEM cells [117]. IL-15 administration increases a cell subset that re-expresses CD45RA (named terminal effector cells–TEMRA). The TEMRA cells express senescence markers, such as KLRG-1, CD57, and H2AX phosphorylation, have low functional and proliferative ability, indicating their terminal differentiation [118].

1.2.3.2. $CD8^+$ cytotoxic T lymphocytes (CTLs) subsets

Similar to T $CD4^+$ cells, naïve $CD8^+$ T cells differentiate into effector T cells (CD62L- CD127-) upon TCR engagement with antigen and costimulation by an APC, but the antigen recognition occurs by MHC class I in peripheral lymphatic organs. Additionally, $CD8^+$ T cells also acquire different profiles according to co-stimulatory molecules and cytokines presents in the environmental, contributing to transcription factors induction and specific differentiation into Tc1, Tc2, Tc9, Tc17 or $CD8^+$ T regulatory fate, as we observe in $CD4^+$ T cells [119].

Cytotoxic T lymphocytes (CTLs) also named Tc1 are the best-characterized subset of $CD8^+$ T cells that are responsible for the direct killing of infected, damaged, and dysfunctional cells, including tumor cells. Once differentiated, these cells are IL-2 and IL-12 dependent and highly cytotoxic, rapidly expressing high levels of IFN-γ, TNF-α, perforin, and granzymes, into immunological synapse, following activation [120]. IL-12 promotes expression of T-bet and Id2, and IL-2 down-regulates BCL-6 [121]. The initial activation of $CD8^+$ T cells is related with the up-regulation of CD44 and CD69, killer cell lectin-like receptor G1 (KLRG1) and IL-2 receptor subunit-α (CD25), though the L-selectin (CD62 L), the IL-7 receptor subunit-α (CD127) and CD27 are diminished in comparison with naïve cells [119, 121].

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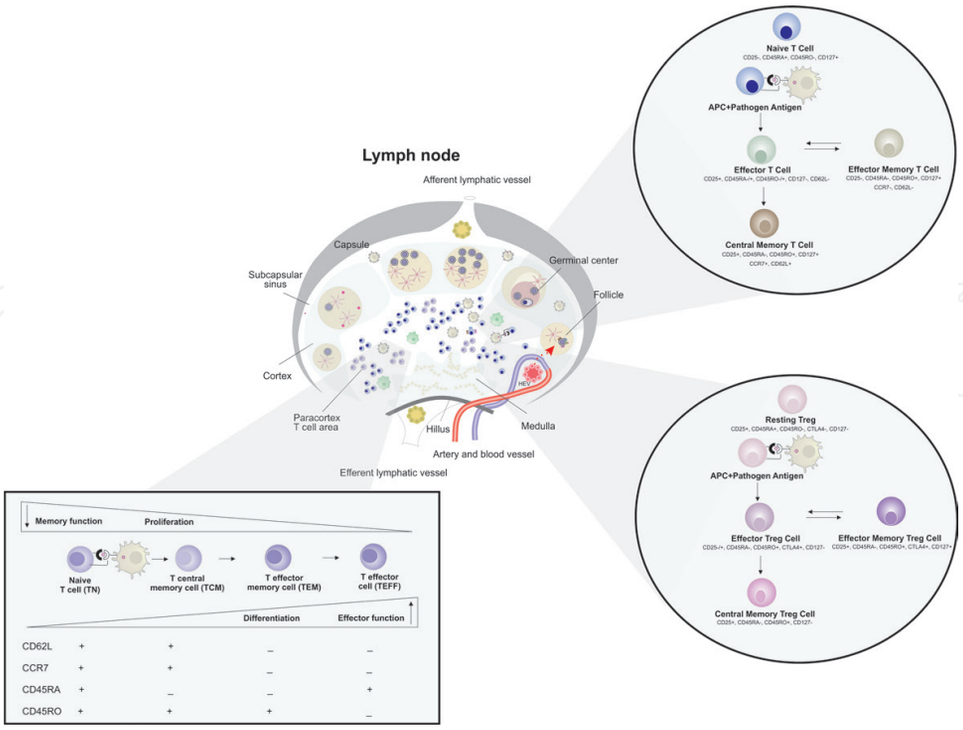


Figure 7. CD4 and CD8 subsets of memory [113, 114, 155].

While most $CD8^+$ T cells die by apoptosis after antigen clearance, there are rare cells that survive as long-lived memory T cells. Memory $CD8^+$ T cells were subdivided into two broad subsets [113, 122], central memory (CD62L+ CD127+ CCR7+) and effector memory (CD162L-CD127+CCR7-), distinguished by the relative expression of two homing molecules, CD62 L and CCR7. T effector memory cells have a phenotype more similar to that of effector cells, characterized by a loss of CCR7 expression and intermediate to no CD62 L expression (**Figure 7**). These cells exhibit rapid effector function, readily differentiating into T effector cells that secrete high amounts of IFN-γ and are highly cytotoxic upon re-exposure to cognate antigen. In contrast, T central memory cells are less differentiated, have increased proliferative potential and greater self-renewal capability, can produce high amounts of IL-2, and acquire effector functions less rapidly [120, 123, 124].

Tc2 cells, similarly to Th2 cells, produce IL-5, IL-13, but the limited extent of IL-4, besides granzymes and perforin, and express the lineage-specific transcription factor GATA3. This profile is associated with propagation of Th2-mediated allergy and probably contributes to rheumatoid arthritis [119, 125].

The differentiation of $CD8^+$ T cells into IL-9 producers (Tc9 cells), in agreement with low expression of granzyme B, occurs mostly in the intestinal epithelium by IL-4 and TGF-β induction, favoring their greater anti-tumor activity. The transcription factors STAT6 and IRF4 are important for IL-9 production while Foxp3 for inhibition [119, 126].

The IL-17-producing $CD8^+$ T (Tc17) cells are differentiated by IL-6 or IL-21 along with TGF-β while IL-23 stabilizes their phenotype. Similar to Th17 cells, they produce IL-17 and IL-21,

express the receptor for IL-23 and the lineage-specific transcription factors IRF-4, RORγt and RORα [127]. Tc17 presents impaired cytotoxic activity because of a low IFN-γ, perforin, and granzyme B production. In contrast, they are able to enhance anti-tumor immunity due to their pro-inflammatory properties, which, on the other hand, may contribute to autoimmune processes [119, 128].

The suppressor $CD8^+$ Treg cells restricted by the non-classical MHC class Ib molecules Qa-1 (mouse) or HLA-E (human) represent a well-defined subpopulation. These cells present $CD44^{hi}$ $CD122^+$ $Ly49^+$ $Foxp3^+$ phenotype and IL-15 is important to their activity [129]. For suppression, these $CD8^+$ Treg cells rely on diverse mechanisms including TGF-β, IL-10, granzymes, perforin and indoleamine 2, 3-dioxygenase (IDO) [129].

1.3. Natural killer cells (NK)

Natural killer (NK) cells are an important piece of the innate immunity and provide a first-line defense against tumors and viral infections. NK cells were identified in the 1970s by the ability of kill tumor cells without previous activation [130]. The precursor cell able to differentiate towards NK cells was originally identified in the bone marrow, the main organ of hematopoiesis in adult life. However, subsequent experiments revealed that hematopoietic progenitor cell and/or NK cell committed precursors (NKPs) can traffic from bone marrow to peripheral sites, and it is now clear that the NK cell development occurs not only in the bone marrow but also in peripheral lymphoid and non-lymphoid organs [131]. In addition, Yu et al. demonstrated that precursor cells isolated from different sites of tissues can differentiate *in vitro* into mature NK cells [132]. The HSC commitment to NK cells differentiation includes transcription factors such as ID2, PU.1, Ets-1, TOX and NFIL3, and their maturation involves Eomes and Tbet [133–136].

Later studies demonstrated the cytotoxic ability of these cells against virus-infected cells and their participation into early inflammatory response secreting cytokines and chemokines [51, 137]. Particularly, upon activation, NK cells may also sense various bacterial products via toll-like receptors, an event resulting in a significant and rapid increase in their cytolytic activity and cytokine production [138]. Human NK cell function is regulated by several inhibitory and activating receptors. Among the various inhibitory NK cell receptors, an important role is played by Killer Ig-like Receptors (KIRs) that recognize allotypic determinants of HLA-A, -B, -C molecules and by the heterodimer NKG2A specific for the non-classical HLA-E molecule [139]. Regarding the activating NK cell receptors, the examples are NKp46, NKp44, and NKp30 that have been together named Natural Cytotoxicity Receptors (NCRs). The NCRs ligands are only partially known and possibly include pathogen-derived molecules and cellular ligands. In addition to NCR, other activating receptors and co-receptors are involved in NK cell function. These include NKG2D (recognizing MICA/B and ULBPs molecules), DNAM-1 (specific for CD155 and CD112), CD16 (FcRIII), NKp80 (specific for AICL), CD244 (that binds CD48), and NTBA (mediating hemophilic interaction) (**Figure 8**) [140].

Peripheral blood NK cells are not a uniform population. Consequently, two main subsets are identified regarding levels of CD56 expression, $CD56^{dim}$ and $CD56^{bright}$ NK cells [141]. $CD56^{dim}$

NK cells are mainly in peripheral blood and show potent cytolytic activity and fast release of IFN-γ and other cytokines or chemokines upon cell activation through NK receptors. A large fraction of $CD56^{dim}$ co-expresses CD16. $CD56^{bright}$ NK cells represent a smaller population in peripheral blood while they are predominant in tissues and secondary lymphoid organs and are supposed to be responsible for the long-lasting production of chemokines and cytokines [137]. Several soluble factors participate on the NK cells development, and they are listed in **Table 1**.

1.4. Innate lymphoid cells (ILCs)

While NK cells have been known for almost four decades and have been extensively studied, other innate lymphoid cells (ILCs) have been better characterized in recent years. ILCs play a significant role in innate defenses against pathogens in different sites and in lymphoid tissue organization, primarily during fetal life. ILCs are emerging as a family of effectors and regulators of innate immunity and tissue remodeling and express neither somatically recombined

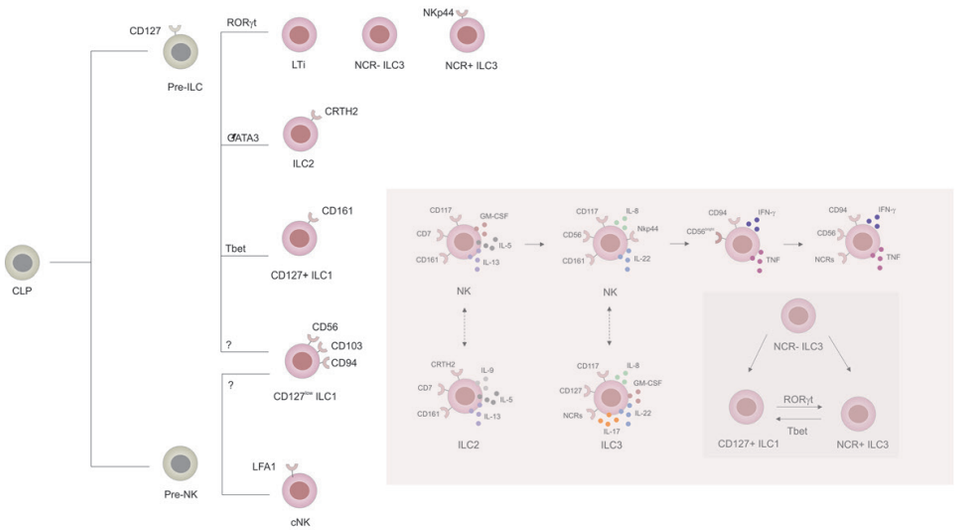


Figure 8. Developmental relationship between NK cells and other ILCs [137, 144, 156].

Cytokine	Role	Reference
IL-15	Central role in the development, maturation, survival, proliferation and differentiation	[142]
IL-7, SCF and Flt3-L	NK cells differentiation	[142]
IL-21	*killer immunoglobulin-like receptors* (KIR) expression on final stage of NK cell differentiation	[143]
IL-8 and MIP-1α	Favor the precursor to differentiate into NK cell, inhibiting the development of myeloid precursors	[144]

Table 1. Soluble factors involved in the NK cell development.

antigen receptors nor phenotypical markers of myeloid cells [145]. These subsets of cells require the transcriptional repressor Id2 and the interleukin 7 (IL-7) for their development, and they generate cytokine secretion patterns that mirror those of helper T cells of the adaptive immune system [146, 147]. ILCs have been classified in three main groups ILC1, ILC2, and ILC3 according to their cytokine profile and to the transcription factors required for their differentiation.

Similar to pro-inflammatory T helper type 1 cells, ILCs of group 1 (ILC1) release IFN-γ and require the transcription factor T-bet for their development, as do NK cells of the innate immune system. ILC1 cells were distinct from natural killer (NK) cells as they lacked perforin, granzyme B and the NK cell markers CD56, CD16 and CD94 (**Figure 8**) [148].

ILCs of group 2, which include natural helper cells and nuocytes, secrete IL-5 and IL-13 and require the transcription factor GATA-3 and thus resemble pro-inflammatory T helper type 2 cells. ILC2s mediate parasite expulsion but also contribute to airway inflammation, emphasizing the functional similarity between these cells and Th2 cells (**Figure 8**) [149–151]. Finally, ILCs of group 3 (ILC3 cells) require the transcription factors RORγt and AhR and include not only mucosal 'NK-22' cells, which secrete IL-22 and thus mimic non-inflammatory cells of the Th22 subset of helper T cells. ILC22 cells include NKp46 (+) and lymphoid tissue inducer (LTi)-like subsets that express the aryl hydrocarbon receptor (AHR). These cells were heterogeneous in their requirement for Notch and their effect on the generation of fetal and mucosal intestinal lymphoid tissues (LTi cells) (**Figure 8**) [152, 153], which produce IL-22 and IL-17 and thus resemble pro-inflammatory cells of the Th17 subset of helper T cells. Interleukin 22 (IL-22)- and IL-17-producing ILCs, which depend on the transcription factor RORγt, express CD127 (IL-7 receptor α-chain) and the natural killer cell marker CD161 [147, 154].

2. Concluding remarks

Herein, we have discussed B lymphocyte differentiation in the bone marrow and their stages of maturation in secondary lymphoid tissues and profiles in interfollicular, perifollicular, and follicular areas. In addition, we also have discussed derivation of T-cell precursors, natural killer cells, and other innate lymphoid cells. Moreover, T-cell precursor migration to thymus, differentiation, rearrangement, thymic selection, transcription factors, their profile and subsets in secondary lymphoid organs are also included. These topics are very important for the comprehension of the complex processes involved in forming a functional, consistently efficient immune response.

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