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Review Article

Transcriptional Control of T-Cell Development: A Review

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Abstract

T-lymphocytes are types of lymphocytes that play a central role in cell-mediated immunity and consist of several subtypes with distinct functions. The thymus is a specialized primary lymphoid organ of the immune system, where T-lymphocytes mature. A naïve T-cell is a T-cell that has differentiated in the bone marrow, and successfully undergone the positive and negative process of central selection in the thymus. There are several developmental checkpoints during T-cell development, where regulation by a combination of transcription factors imprints specific functional properties on precursors. The transcription factors GATA-binding protein 3 and RUNT-related transcription factor are involved at various stages in the differentiation of double-negative thymocytes and in b-selection, as are transcription factors from the notch signaling pathway; other transcription factors such as B-cell lymphoma/leukemia11b, myeloblastosis viral oncogene homolog and inhibitor of DNA binding 3 are involved at specific stages. Differentiation of T-cells into helper versus cytotoxic cells involves antagonistic interplay between Runx and Th inducing POZ-Kruppel factor. A wide range of well-defined transcription factors, including signal transducer and activator of transcriptions are known to shape Th1/Th2 differentiation. In this review, we briefly discuss how T-cell characteristics are acquired and become divergent from the point of view of transcriptional regulation.

Keywords: T-lymphocyte; T-cell development; transcription factors

Introduction

T-lymphocytes, which are distinguished from other leukocytes by their expression of either the αβ or the γδ type of TCR (T-cell receptor), are essential for regulating immune responses in addition to their cytotoxic functions. Because of the vast majority of thymocytes and peripheral T-cells express the αβ T-cell receptor rather than the γδ T-cell receptor, in this review are denoted by αβ receptor. Progenitor T-cells from the early sites of hematopoietic begins to migrate to the thymus at about day 11 of gestation in mice and in the eighth or ninth week of gestation in humans. 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 effectors T-cells upon encountering antigens in the peripheral lymphoid organs. Transcription factors are nuclear proteins that bind specific gene sequences and (alone or in complexes with other proteins) activate or repress transcription of DNA to mRNA. T-cell maturation involves rearrangements of the germ-line TCR genes and the expression of various membrane markers. T-cell development involves progenitor homing, lineage specification, and commitment and requires a complex interplay among key transcription factors. In this review I will discuss briefly the progress of a transcriptional control of T-cell development with special focus on the early thymocyte differentiation, the helper versus cytotoxic lineage choice in the thymus and the differentiation of $CD4^+$ T cells into T_h1 and T_h2 cells.

Transcriptional Control of Early Thymocytes Differentiation

Migration of stem cells to the thymus early in development and maturation in to thymocytes (T-cells). Developing T-cells, known as thymocytes, proliferate and differentiate along developmental pathways. T-cell development is initiated in the thymic subpopulation that lacks the cell surface expression of both CD4 and CD8 glycoprotein, thus called DN(double-negative) thymocytes.

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The T lineage becomes then double-positive thymocytes (DP; $CD4^+CD8^+$) subsequently, becomes single-positive (SP; $CD4^+CD8^-$ or $CD4^-CD8^+$) thymocytes.

The thymocytes differentiation process within the DN population is divided into four stages according to the expression of CD25 and CD44, starting from DN1 ($CD44^+CD25^-$), followed by DN2 ($CD44^+CD25^+$), DN3 ($CD44^-CD25^+$) and DN4 ($CD44^-CD25^-$) [1].

Even though these co-receptors are not expressed during the DN early stages, the differentiation program is progressing and is marked by changes in the expression of such cell surface molecules as c-Kit, CD44, and CD25. The initial thymocyte population displays c-Kit, the receptor for stem cell growth factor, and CD44, an adhesion molecule involved in homing; CD25, the β chain of the IL-2 receptor, also appears on early stage DN cells. During this period, the cells are proliferating. But the TCR genes remain un rearranged. Then the cells stop expressing c-Kit, markedly reduce CD44 expression, turn on expression of the recombinase genes RAG-1(Recombination Activation Gene 1) and RAG-2 and begin to rearrange their TCR genes [2].

The earliest known T-cell progenitors that seed the thymus are called ETP (early T-cell progenitors) which are characterized by the lack of lineage-specific markers. ETP are the equivalent of the DN1a subset plus the DN1b subset. ETP can be further divided by the expression of Flt3 (fms-like tyrosine kinase receptor 3) [3]. The proto-oncogene *c-Myb* participates in T-cell development in the thymus and mature T cell proliferation. *c-myb* is required for the development of thymocytes at the DN3 stage, for survival and proliferation of double-positive thymocytes, for differentiation of single-positive CD4 and CD8 T cells, and for the proliferative responses of mature T-cells [4].

Notch signaling pathway is the first for the generation of ETP which is signaling by master-like protein. Inhibition of Notch signaling using dominant-negative mastermind-like caused loss of ETP and its progeny but didn't affect LSK ($Lin^-Sca\text{-}1c\text{-}Kit^+$) [5]. Recently; TCF-1(T-cell factor 1, also known as TCF-7) is critical downstream factor of Notch1. TCF-1-deficient T-cell progenitors show marked reduction ETP.TCF-1 expression is low in LMPP (Lymphoid primed multi potent progenitor) or common lymphoid progenitor but induced in ETP. TCF-1 expression is induced by Notch signaling via direct regulation [6]. Over-expression of TCF-1 elicits T lineage cells even in the absence of Notch signaling, inducing T cell-specific transcription factors including Gata3 (GATA-binding protein 3) and Bcl11b (B-cell lymphoma/leukemia 11b).

Loss of function of the transcription factor Gata3 causes severe inhibition of ETP development, but not that of the presumed immediate progenitors. GATA-3 is required for the cell-autonomous development of the earliest characterized thymic T cell progenitors. It is also important for ETP to become DN2 thymocytes [7]. E2A and HEB are members of the bHLH (basic helix–loop–helix) transcription factor family and play an important role in early T-cell development. Loss of E2A activity results in a partial block at the earliest stage of T lineage development [8]. Runx (RUNT-related transcription factor complexes), which are composed of a Runx protein and an obligate non-DNA-binding partner Cbfβ (core-binding factor β), are essential for early thymocyte development [9].

The DN2 (double-negative 2) stage can be subdivided into GFP^-(Green fluorescent protein) and GFP^+ populations, representing functionally different developmental stages in that the GFP^-DN2, but not GFP^+DN2, cells retain dendritic cell potential. The GFP^+DN2 cells were found to undergo several rounds of proliferation before the initiation of TCRβ rearrangement. Early and late DN2 stages can be distinguishing by the expression of a pLck–green fluorescent protein transgene since GFP^- DN2 (early-DN2) cells can produce DC and macrophage, whereas GFP^+ DN2 (late-DN2) cells produce only T-cells [10]. Recently; a transcriptional factor Bcl11b is essential to fully commit the T lineage and providing molecular evidence for branching point at the DN2. The expression of Bcl11b in hematopoietic cells is limited to the T lineage and rises in DN2 thymocytes [11]. As soon as T lineage properties acquiring, αβ T-cell precursors at the DN3 stage have to pass another developmental checkpoint known as β-selection, where the expression of a functional TCRβ chain is examined [12,13].

The simultaneous deletion of E2A and HEB in developing thymocytes leads to a severe developmental block before pre-TCR expression and a dramatic reduction of Pre-Tα expression Impairment of E2A and HEB function by expression of dominant-negative HEB protein causes a defect of VDJ rearrangement, thereby causing developmental arrest at DN3 [14]. E2A is necessary to maintain integrity of β- checkpoint. The lack of E2A results in development of T-cell malignancies, and inactivation of E2A is a common feature of a wide variety of human T-cell proliferative disorders. bHLH transcription factor regulates expansion of thymocyte that passes β-selection; in the absence of E2A or HEB, DN3 cells exhibit premature hyper proliferative activities [15].

The Knockout of either Notch1 or of RBP-J (recombining binding protein for immunoglobulin Jκ region), which acts as an essential transcription factor downstream of the Notch pathway, causes accumulation of DN3 cells, with defective V-to-DJ rearrangement in the case of Notch1 inactivation. Recently; E2A and notch pathways converge at DN3. Activation of the Notch1 gene is downstream of E2A [16]. At the DN3 stage, a bHLH protein cooperates with Notch1 to prevent uncontrolled proliferation and promote TCRβ chain rearrangement. Once cells are signaled through their pre-TCR complexes, Id3 (inhibitor of DNA binding 3) suppresses bHLH protein activity, a mechanism that ensures allelic exclusion [17].

Transcriptional Control of the Helper versus Cytotoxic Lineage Choice

As thymocytes passing through β-selection it start to express the TCR α chain and the CD4 and CD8 co-receptors. These double positive thymocytes comprise the largest cell population in the thymus. Each DP thymocytes is subjected to another selection process, known as positive selection, in this case the quality of

its αβ TCR is examined according to its affinity for self-peptide presented on MHC molecules [18].

Positive selection for thymocytes bearing receptors capable of binding self-MHC(major histocomatibility complex) molecules, which results in MHC restriction. Cells that fail positive selection are eliminated within the thymus by apoptosis. Negative selection that eliminates thymocytes bearing high-affinity receptors for self-MHC molecules alone or self-antigen presented by self-MHC, which results in self-tolerance [2]. DP thymocytes expressing a αβ TCR that recognizes peptide on MHC class I differentiate into a $CD4^-CD8^+$ SP thymocyte that is committed to the cytotoxic lineage, whereas a DP thymocyte selected by MHC class II becomes a $CD4^+CD8^-$ thymocyte committed to the helper lineage [18].

This is realized by two different models that shows, multiple interactions between the TCR, $CD8^+$ or $CD4^+$ cor-eceptors, and class I or class II MHC molecules instruct the cells to differentiate into either $CD8^+$ or $CD4^+$ single positive cells, respectively. Class I MHC–specific TCR together with the CD8 co-receptor would generate a signal that is different from the signal induced by a class II MHC specific TCR together with the CD4 co-receptor. CD4 or CD8 expression is switched off randomly with no relation to the specificity of the TCR.

Only those thymocytes whose TCR and remaining co receptor recognize the same class of MHC molecule will mature [2]. Since lineage-specific expression of genes are encoding CD4 or CD8 co-receptors, the mechanism regulating CD4 or CD8 gene expression would share common molecules with the mechanism regulating the helper versus cytotoxic lineage choice. Expression of the CD4 gene is repressed in cytotoxic-lineage cells by an intronic transcriptional silencer, referred to as the CD4 silencer. Expression of the Zbtb7b gene, encoding the transcription factor ThPOK (Th inducingPOZ-Kruppel factor) is negatively regulating by the ThPOK silencer, whose activity requires biding of the Runx complex and MAZR [19].

ThPOK not only activates the helper program but also suppresses cytotoxic features such as Cd8 and Runx3 expression. Antagonistic interplay between ThPOK and Runx3 is thus central in the transcription factor network that governs the helper versus cytotoxic lineage choice. An antagonistic function of ThPOK for both the *CD4* silencer and the *ThPOK* silencer stabilizes ThPOK and CD4 expression [20]. Different Runx proteins regulate the Cd4 silencer activity at different developmental stages: Runx1 at the DN stage and Runx3 at the $CD4^-CD8^+$ SP stage. Runx complexes bind to the enhancer regions in the Cd8 locus. Runx complexes are involved in CD8 gene activation during differentiation to $CD4^-CD8^+$ SP thymocytes. Runx complexes are the first essential regulators for CD4/CD8 expression during cytotoxic-lineage differentiation [21].

Runx1 regulates the transitions of developing thymocytes from the $CD4^-CD8^-$ double-negative stage to the $CD4^+CD8^+$ double-positive (DP) stage and from the DP stage to the mature single-positive stage. Runx1 and Runx3 deficiencies causes marked reductions in mature thymocytes and T cells of the $CD4^+$ helper and $CD8^+$ cytotoxic T-cell lineages, respectively. Inactivation of both Runx1 and Runx3 at the DP stages results in a severe block in development of $CD8^+$ mature thymocytes [18]. Runx complex associates with the Zbtb7b locus at two regions ,which correspond to two regulatory regions, DRE(distal regulatory element) and PRE (proximal regulatory element), which can identify through the analysis of DNase I hypersensitive sites, which is essential to confer helper lineage-specific expression of a reporter transgene drives by other regulatory regions from the Zbtb7b gene (16).On the other hand PRE, possesses a transcriptional enhancer activity , which is essential to up-regulate development of $CD4^+$ T_h cells [22].

The antagonistic regulation of ThPOK and Zbtb7b is central in transcription factor network that governs helper versus cytotoxic lineage choice. MAZR (MAZ-related factor) is a negative regulator for CD8 expression. MAZR deficiency causes a partial re-direction of MHC class I-selected cells. Loss of MAZR function can leads to de-repression of the Zbtb7b gene. Binding of MAZR to the DRE, MAZR is thus a functional unit in protein complexes that regulate DRE silencer activity [19]. Myb (myeloblastosis viral oncogene homolog) is another transcription factor involving in promoting CD4 lineage development. When Myb is binding to the Gata3 locus, Myb may be a direct upstream molecule for Gata3 expression [4]. TOX (thymocyte selection-associated high-mobility group box transcription factor) is a molecule whose expression is up-regulates upon receiving positive selection signals. Over-expression of Tox by transgenesis promotes cytotoxic lineage development; however, Tox deficiency results in a lack of $CD4^+$ T-cells and a lack of ThPOK expression [23].

Transcriptional Control of T_h1 and T_h2 Cells Differentiation

The immune response to different pathogens is modified by the differentiation of $CD4^+$ T_h cells into different effector types. After encountering antigen, and depending on the microenvironment (including the balance of cytokine stimulation), naive $CD4^+$ T cells differentiate into distinct effector T cells [24]. Currently; there are varieties of $CD4^+$ T-cell subsets and transcription factors that are involving in development of each subset. However, separation of effectors $CD4^+$ T-cell subsets initiates with the identification of two subsets, T_h1 and T_h2 cells. The Th1 subset is responsible for many cell-mediated functions (e.g., delayed-type hypersensitivity and activation of TC cells). The Th2 subset stimulates eosinophil activation and differentiation, provides help to B cells, and promotes the production of relatively large amounts of IgM, IgE, and noncomplement-activating IgG isotypes [2].

T_h1 differentiation is linked to activation of the transcription factors STAT 1 (signal transducer and activator of transcription 1) and STAT4 downstream of IFN-γ and IL-12 signaling, respectively. Together with the transcription factors [such as NFAT(nuclear factor of activated T- cell, AP-1(adaptor-related protein complex 1 and nuclear factor κB (NF-κB)] that are activated by TCR engagement, STAT1 induces the expression of the master transcriptional factor of the T_h1 subset, T-bet [also known as Tbx21 (T-box transcription factor 21) [25].

STAT4 and T-bet act coordinately to induce the expression of Runx3, which functions coordinately with T-bet to produce large amounts of IFN-γ production in T_h1 cells .Unlike T-bet, however, transduction of Runx3 cannot potentiate IFN-γ production in T_h2 cells. T-bet and Runx3 are inhibiting T_h2 programming both by antagonizing Gata3 activity and by direct repression of the IL-4 gene through activating a silencer element in the IL-4 locus [26].

T_h2 development promots by the cytokine IL-4, which signals via activation of STAT6 after engagement of the IL-4R. IL-4 signals enhance Il4 transcription in cooperation with NFAT, AP-1 and NF-κB. These signals also amplify expression level of a master regulator of T_h2 differentiation, Gata3 is known to activate its own expression as well as to drive epigenetic changes at the T_h2 cytokine cluster, which contains the Il4, Il5 and Il13 genes. Gata3 have antagonistic ability against the T_h1 program by inhibiting responsiveness to IL-12 and IFN-γ [27]. Recently; T_h2 cytokine loci undergo alterations of higher order chromatin structures including changes in DNA methylation and histone modifications. NFAT1 is likely to play an important role in regulating chromatin structures during the initiation and re-activation processes as it binds to promoters of all IL-4, IL-5 and IL-13 genes and enhancer elements in the IL-4 locus [28].

Tregs play an important role in the preservation of self tolerance and modulation of overall immune response against tumor cells. Th17 cells are highly relevant to the onset and propagation of local chronic inflammation, in part by producing inflammatory cytokines. Notably, there is a close relationship between Treg and Th17 cells. FOXP3+CD4+CD25+ Treg (Regulatory T-cells) and IL-17 producing helper T cells (Th17) are critical subsets of T cells which play essential roles in immune homeostasis. The FOXP3 (Forkhead family transcription factor) is predominantly expressed in Treg cells, where the FOXP3 ensemble is essential for Treg cell development and function. As FOXP3 is to Treg cells, the ROR (orphan retinoic acid nuclear receptor) family transcription factor RORγt is essential for Th17 development and function [29].

Conclusions and Recommendation

T-cell development becomes interesting for immunologists because it has key role in regulating acquired immune responses and its usefulness for studying cell differentiation. With advances in genetic and bioinformatics technology, transcription factors that play a vital role in regulating T-cell development are already available; however, it remains hard to express how these factors control genetic programming towards a particular lineage during the commitment process and how the given integrity is maintained. For example, although ThPOK is important for preventing expression of cytotoxic-lineage related genes, such as Runx3 and Cd8, ThPOK target genes that are necessary to install helper function are characterizing poorly. Epigenetic mechanisms contribute to retain cell identity through imprinting gene expression patterns during the commitment process.

Future studies will aim to understand how a genetic program activated by a combinatorial activity of transcription factors is stabilized by epigenetic machineries in a locus- and stage-specific manner while leaving some developmental potency for further differentiation upon encounter to a novel microenvironment.

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