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Review

The role of TGF-β superfamily during T cell development: new insights

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Abstract

Members of the transforming growth factor beta (TGF-β) superfamily are soluble factors that regulate a variety of functional responses including proliferation, differentiation, apoptosis and cell cycle, among others, depending not only on the cell type and its differentiation state, but also on the milieu of cytokines present. All three members of this superfamily: TGF-βs, bone morphogenetic proteins (BMPs) and Activins, have been shown to be expressed in the thymus suggesting their potential role as regulators of the T lymphocyte differentiation process. Although initial reports described the role of TGF-β in controlling specific checkpoints during thymocyte development, recent data has provided new evidence on the role of BMPs and Activins in this process. This review provides new insights on the function of members of the TGF-β superfamily at different stages of thymocyte development.

Keywords: TGF beta superfamily; BMP; Activin; Inhibin; Signaling; Thymocyte; Development

1. Introduction

T cell development is a highly regulated process. It has been demonstrated that both cellular interactions as well as soluble factors play a key role during thymocyte differentiation. Although several reports adressing the role of soluble factors in T cell function and homeostasis have shown the potential role of the superfamily of transformed growth factor β in the regulation of immune responses, little is known regarding the influence of these mediators during T cell development. TGF-β superfamily comprises multiple factors with a widespread expression, which are able to regulate a variety of cellular responses depending on the cell type and its maturation stage. In this review we will focus on the potential role of TGF-β superfamily members as critical regulators in T cell differentiation and maturation.

2. T cell development

The thymus is a primary lymphoid organ in which thymocyte development and repertoire selection of mature T lymphocytes occurs [1]. Thymocyte differentiation is a highly regulated process dependent not only on interactions between early T cell precursors with stromal cells but also on the presence of soluble molecules such as chemokines, cytokines and growth factors. The thymus is a bilobed organ composed by stromal and thymocyte subpopulations that interact with each other, defining discrete anatomical microenviroments within the thymus, known as subcapsular, cortical and medullary regions [2]. At early embryonic stages (E10–11) fetal liver lymphoid progenitors seed the thymic epithelial rudiment derived from the third pharyngeal pouch [3–6]. After birth, the thymus is continually seeded by bone marrow-derived lymphoid progenitors reaching the thymus through the blood stream and entering at the cortico-medullary junction [7]. In the thymus three different subpopulations of thymocytes are found based on coreceptor expression: double negative (DN, $CD4^-$ $CD8^-$), double positive (DP, $CD4^+$ $CD8^+$) and single positive (SP, $CD4^+$ or $CD8^+$). Immature DN cells, have been further subdivided into four populations based on the expression of CD44 [8] and CD25 [9]; DN1: $CD44^+$ $CD25^-$; DN2: $CD44^+$ $CD25^+$; DN3: $CD44^-$ $CD25^+$ and DN4: $CD44^-$ $CD25^-$ (reviewed in [10]). At DN3, the first developmental checkpoint (also known as β selection) occurs at the cortical region of the thymus. At this stage, functionally rearranged TCR (T Cell Receptor) β gene pairs with a surro-

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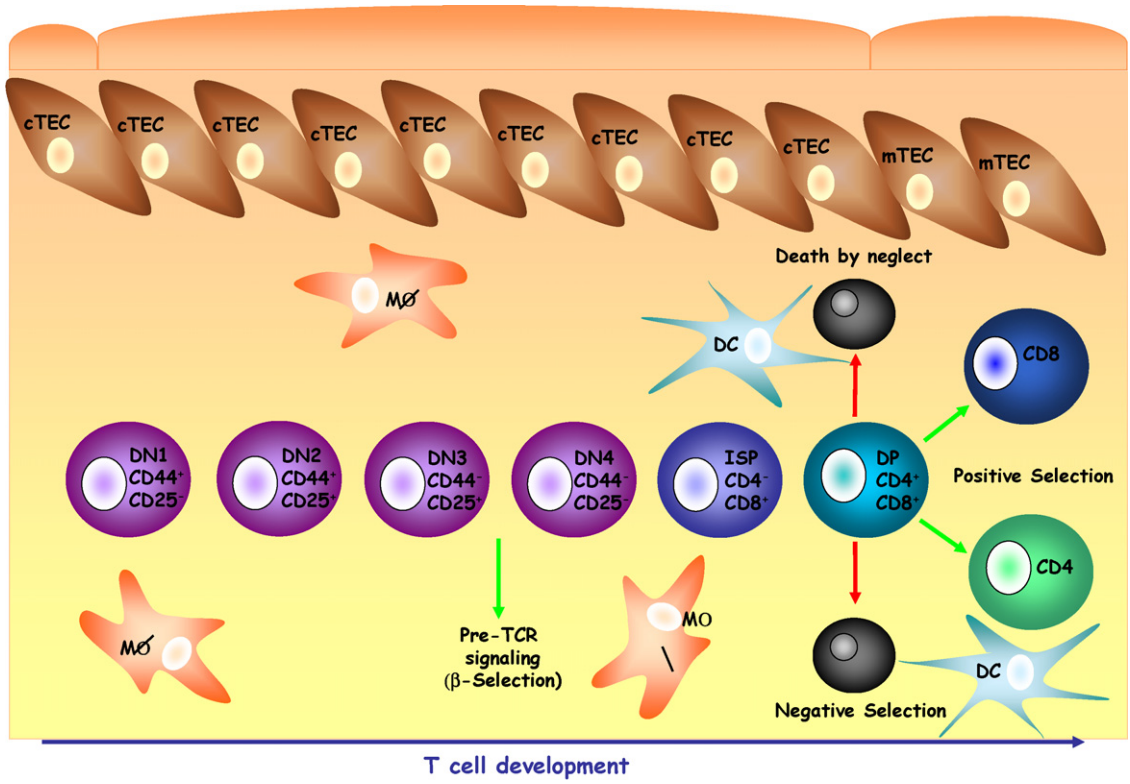

Fig. 1. Thymocyte development. In the thymus three major thymocyte subpopulations can be found based on the expression of CD4 and CD8 coreceptors: double negative (DN, $CD4^-$ $CD8^-$), double positive (DP, $CD4^+$ $CD8^+$) and single positive (SP, $CD4^+$ or $CD8^+$). At DN3 stage pre-TCR signaling promotes α chain rearrangement, cell proliferation and allows thymocytes to initiate coreceptor expression. At the DP stage, a high percentage of thymocytes which are unable to recognize self ligands on the context of self MHC die by neglect, while antigen recognition through the αβ TCR leads to positive selection of those thymocytes able to recognize peptide/MHC complexes with low/intermediate affinity on cortical epithelial cells. At the same time, lineage commitment of positively selected thymocytes occurs, and they become mature $CD4^+$ or $CD8^+$ single positive thymocytes, ready to exit the thymus and migrate to periphery where they will get activated to become effector $CD4^+$ "helper" or $CD8^+$ "cytotoxic" T lymphocytes. When thymocytes reach the cortical-medullary junction, negative selection will induce deletion of those thymocytes whose TCRs have high avidity for peptide/MHC complexes expressed on the surface of dendritic cells or medullary epithelial cells, leading to apoptosis. cTEC: cortical thymic epithelial cell; mTEC: medullary thymic epithelial cell; MØ: macrophage; DC: dendritic cell.

gate α chain or pre-Tα, forming an immature receptor known as pre-TCR, which will be expressed on the surface of DN3 thymocytes [11]. Signaling through the pre-TCR prevents further TCR β rearrangements (allelic exclusion), induces proliferation, and eventually leads to coreceptor expression and TCR α chain rearrangement (reviewed in [12]). The αβ TCR expression at the DP stage allows the thymocytes to be positively or negatively selected in response to endogenous peptides expressed on MHC-bearing stromal cells. Based on aspects inherent to the TCR recognition such as avidity for the ligand (endogenous peptide/MHC complexes), most of thymocytes express TCRs with no measurable reactivity and die by neglect [13,14] while thymocytes with TCRs with low to moderate avidity are positively selected and allowed to mature into $CD4^+$ or $CD8^+$ SP cells (lineage commitment). Positive selection ocurrs in the cortical region of the thymus and is dependent on antigens expressed by cortical epithelial cells [15] (reviewed in [16]). On the other hand, negative selection takes place in the cortico-medullary junction and is mediated by medullar epithelial cells and bone marrow derived dendritic cells, expressing the ligand together with costimulatory molecules, which ensures the deletion of selected thymocytes with strong affinities for their selecting peptide-MHC and constitutes the basic mechanism of central tolerance induction [17,18] (reviewed in [19]). Those thymocytes surviving selection, mature in the medulla to finally exit the thymus and migrate to secondary lymphoid organs, where they become activated, and thus enabled to exert their functional phenotype: "helper" for $CD4^+$ or "cytotoxic" for $CD8^+$ [20] (Fig. 1).

As has been extensively reported, thymocyte development is a tightly regulated process in which different stromal cells including epithelial cells, macrophages and dendritic cells, support interactions and signals required for the proper development of T cell precursors [21]. An example of this tight interaction is the developmentally regulated migration necessary for the developing thymocyte, in which differential expression of soluble factors by stromal cells such as chemokines provides a signal for thymic precursors undergoing differentiation in order to migrate and relocate within specific compartments in the thymus (reviewed in [22,23]). Nevertheless, there is also evidence suggesting that thymocytes themselves contribute to the growth and maintenance of the stromal compartment (reviewed in [24]). Recently, numerous studies have shown that different molecules such as cytokines and chemokines are important mediators in the differentiation program of thymocytes and, although several studies have revealed a relevant role of growth