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Basics of T Cell Development and Activation

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Mini Review

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Abstract

T cells are defined by their development in the thymus from bone marrow-derived precursors and by heterodimeric receptors allied with the proteins of the CD3 complex. Mature T cells leave thymus and migrate into the peripheral lymphoid organs whereupon encounter with the fragment of foreign antigen proteins which are displayed by major histocompatibility complex (MHC) on the surface of antigen presenting cell (APC), they are activated and differentiate into effectors and memory T cells. The adaptive immune responses by T cells are important to protect the host against various types of pathogens. The present review will focus on the basic mechanism involved in the development and activation of T cells.

Keywords: Activation; Cytokine; Development; Thymus; T cell signaling

Abbreviations: CARs: Chimeric antigen receptors; TCR: T cell receptor; DN: double negative; DP: double positive; SP: single positive; MHC: major histocompatibility complex; ITAMs: immune receptor tyrosine-based activation motifs

Introduction

The immune system comprises highly specialized *cells and organs that aim to abolish or control foreign substances like bacteria, viruses, and parasites.* In mammals, fetal liver is an important site of immune development, contains progenitors of T and B cells. B cell development continues in the bone marrow and T cell development in the thymus throughout our lives [1]. The name T cells are due to their development in the thymus, however, B cells are named due to their early development in the Bursa of Fabricius in birds and bone marrow in mammals [2]. T cells are crucial for the adaptive immune responses which are capable of distinguishing between the body's own cells and unwanted invaders. During lymphocyte maturation in the thymus T cells specific for self-antigens are silenced but several auto reactive T cells specific for organ-specific antigens escaped thymic deletion and have the potential for triggering organ-specific autoimmunity [3,4]. In several autoimmune diseases e.g. Diabetes mellitus, increased lymphocyte apoptosis is responsible for the delayed wound healing [5]. The genetic modification of T cell antigen specificity to target antigens that are expressed by tumors and introducing antibody-like recognition in chimeric antigen receptors (CARs) are most promising approaches used to treat cancer [6].

T Cell Development

T cell development occurs in the thymus is a multistep, highly dynamic complex process beginning with lineage commitment by hematopoietic stem cells followed by T cell receptor (TCR) gene rearrangement, and selection [7]. Highly conserved Notch1 signaling pathway in T cell precursors is required for early T-cell development [8]. In addition to Notch1 several other transcription factors e.g. HES1, TCF1, Gata3, Bcl11b, and cytokines such as IL-7 are required prior to TCR gene rearrangement [9]. The diversity and specificity arise from the rearrangement of multiple V (variable), D (diversity), and J (joining) gene segments by V(D)J recombination using RAG1 and RAG2 recombines and a ubiquitous DNA repair machinery [10].

Bone marrow-derived T cell precursors enter into the thymus where on the basis of TCR gene rearrangement, co receptor expression and expression of cytokine receptors or activation molecules, thymocyte development proceed through a double negative (DN) → double positive (DP) → single positive (SP) stages [11]. DN cells are most immature cells that lacks the expression of both CD4 and CD8 antigens and are further divided into four major populations on the basis of surface expression of c-Kit, CD44 and CD25: c-Kit^{++}CD44^{+}CD25^{-} (early thymic progenitor or DN1), c-Kit^{+}CD44^{+}CD25^{+} (DN2), c-Kit^{-}CD44^{-}CD25^{+}(DN3) and DN4 (c-Kit^{-}CD44^{-}CD25^{-}) [12]. TCR β gene rearrangement begins at DN3 stage whereas TCR α gene rearrangement takes place at DP stage after that fully assembled αβ-TCR is expressed on the cell surface [13]. A minor fraction of T cells possesses immune functions distinct from αβ T cells having alternate receptor referred as γδ TCR are composed of γ and δ chains [14].

The fully assembled αβ-TCR on the DP cell surface undergoes the testing process for their ability to recognize self- MHC–peptide complexes (MHCp) on cortical thymic epithelial cells (cTECs). DP (CD4^{+}/CD8^{+}) thymocytes whose TCR fails to interact with the self-MHCp die in the cortex whereas cells interacting with self-MHCp are rescued from cell death to undergo positive selection, either CD4 single positive (SP, CD4^{+} CD8^{-}) or CD8 SP (CD4^{-} CD8^{+}) lineage. Stimulation of DP thymocytes TCR upon interaction with short peptides presented by MHC I molecule ultimately become CD8^{+} cells whereas thymocytes that interact well with MHC class II molecules mature into CD4^{+} cells [15]. The SP cells now migrate into the medulla to look for the self- peptides on medullary dendritic cells (DCs), including the AIRE (autoimmune regulator gene)-dependent, organ-specific antigens articulated in medullary thymic epithelial cells (mTECs), leading to negative selection which eliminates SP thymocytes with high-affinity TCRs for self-antigens, thus decreasing the risk of generating auto reactive T cells. Some self-reactive thymocytes receiving strong signal during self-MHCp recognition induce a survival program on the place of apoptosis, leading to their differentiation into the unconventional T cell lineage defined as agonist selection [16,17]. On the basis of their role in immune system regulation, agonist-selected unconventional T-cell are categorized into three main cell types; fork head box P3 (Foxp3)$^{+}$ regulatory T (Treg) cells, invariant natural killer T (iNKT) cells and TCRαβ^{+} CD8αα^{+} intestinal intraepithelial lymphocytes (IELs) [18-20].

Upon successful positive and negative selection, SP T cells undergo further maturation to up regulate sphingosine-1-phosphate receptor 1 ($S1P_1$), which is required for the cells to egress from the thymus into the bloodstream [21].

T Cell Activation

Naive T cells leave the thymus and recirculation between the blood and secondary lymphoid tissues (lymph nodes, Peyer's patches, and the spleen) where TCR binds to its cognate peptide presented on major histocompatibility complex (MHC) on an APC to get activated. MHC class I molecule present peptide to CD8^{+} T cells whereas MHC class II molecule present peptides to CD4^{+} cells [22]. Upon binding of α and β heterodimer with the peptide/MHC complex, intracellular signaling machinery gets activated through the invariant components of the TCR: the γ, δ and ε chains (collectively known as the CD3 complex) and the ζ chains [23].

The first molecules to be activated are the Src family protein tyrosine kinases Lck (p56-Lck) and Fyn (p59-Fyn) which phosphorylates immune receptor tyrosine-based activation motifs (ITAMs) and promotes recruitment and activation of ZAP-70 (ζ chain associated protein kinase 70) [24]. Phosphorylation of ZAP-70 promote its kinase activity to activate several target proteins including the key transmembrane adapter protein linker for activation of T cells (LAT) which recruits numerous signaling molecules to form a multiprotein complex, termed the LAT signalosome. Important molecules that constitute this complex include phospholipase C gamma 1 (PLCγ1), growth factor receptor-bound protein 2 (GRB2), GRB2-

related adaptor protein GADS, SLP76 (SH2 domain-containing leukocyte protein of 76 kDa), adhesion- and degranulation-promoting adaptor protein (ADAP), interleukin-2-inducible T cell kinase (Itk), Nck1 and Vav1 [25]. Activation of Itk takes place upon interaction with the LAT-SLP76 complex which further phosphorylates PLCγ1to catalyze second messengers, inositol 1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). DAG activates a number of downstream signaling pathway including Ras and PKCθ. PKCθ participates in activating the NF-κB pathway [26], whereas Ras activates mitogen-associated protein kinase (MAPK) signaling pathways to phosphorylate Erk1 and Erk2 for the activation of transcription factor AP-1 (Jun/Fos) via regulation of Fos expression [27].

IP_3 increases intracellular Ca^{2+} levels in the cytoplasm by stimulating the efflux of Ca^{2+} from the endoplasmic reticulum to activate protein phosphates calcineurin and the Ca^{2+} -calmodulin-dependent kinase (CaMK). Activated calcineurin dephosphorylates nuclear factor of activated T cells (NFAT), leading to their translocation to the nucleus where it joins other transcription factors to promote long-term proliferation of activated T cells [28]. Immunosuppressive drugs, cyclosporine A (CsA) and FK506, inhibit nuclear translocation of NFAT, leading to suppression of cytokine production, T lymphocyte proliferation, and activation to prevent immune-mediated rejection of genetically incompatible transplants [29].

Conclusion

This concise review focuses on the major events takes place during T cell development and activation. The utilization of new genetic tools especially transgenic mouse models and investigative tools, facilitate understanding of T cell development and activation for the improvement of T cell-based therapy e.g. use of Chimeric Antigen Receptor (CAR) T cell therapy for treating cancer. Development of T cells and its activation is a complex molecular process which involved immune checkpoints and interaction between several signaling, adaptors, and co stimulatory molecules. However, there are still a lot of studies requires discovering thelink between many signaling molecules and molecular mechanisms involved in T cell fate determination to identify targeted therapies for human disease.

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