**Editorial**                                                                 **Open Access**

# Signal Transduction Mechanisms in T lymphocytes – Introduction

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Multicellular organisms are strictly dependent on the ability of individual cells to communicate with each other and cooperate properly to coordinate functions during embryogenesis and throughout the entire life span. A major mechanism of cellular communication is mediated by cell surface receptors that deliver signals across the plasma membrane following their engagement with cognate ligands. Since all cells express a large variety of surface receptors they can respond to many different signals provided by peptide hormones, growth factors, neurotransmitters and antigens, as well as surface molecules on neighboring cells or components of the extracellular matrix.

Studies over the past two decades yielded a multitude of evidence to substantiate a concept in which both constitutive and transient protein-protein interactions, mediated by a relatively small number of evolutionary conserved protein modules, provide the underlying framework through which signaling pathways operate. Spatially and temporally regulated protein-protein interactions that occur at the ligand-occupied receptor site promote the assembly of multi-molecular complexes where posttranslational modifications regulate molecular interactions and protein functions.

One of the most extensively studied receptors is the T cell antigen-specific receptor (TCR). T lymphocytes, which are the major players in cell-mediated immunity, are non-active under steady state conditions but undergo activation following the simultaneous engagement of their TCR [1] and co-stimulatory receptors [2-4]. The first signal is provided by TCR binding to a specific peptide antigen presented on major histocompatibility complex (MHC) molecules on the surface of an antigen-presenting cell (APC). This signal activates an array of enzymes essential for signal delivery across the cell membrane [5-8]. A second signal, obtained through a co-stimulatory receptor, is antigen nonspecific. It is provided by the interaction of a T cell co-stimulatory molecule, such as CD28, with one of its corresponding ligands on the surface of APC, the CD80 and CD86 proteins (also termed B7.1 and B7.2, respectively). CD28 is the only co-stimulatory receptor expressed constitutively by naïve T cells, while receptors such as OX40 and inducible T-cell co-stimulator (ICOS; CD278) are transiently expressed following cell activation and are largely dependent upon the expression of CD28. Both signals are required for production of an effective immune response in the absence of co-stimulation; TCR signaling alone results in non-responsiveness or anergy. Furthermore, the process of T cell activation can be inhibited by the additional engagement of co-inhibitory receptors, such as programmed cell death 1 (PD-1; CD279) with a PD-1 ligand 1 (PD-L1; CD274, also known as B7 homolog 1 (B7-H1)) on the surface of APC.

The signaling pathways downstream of the costimulatory molecules usually engage the phosphatidylinositol-3-kinase (PI3K) pathway generating phosphatidylinositol 3,4,5-trisphosphate (PIP$_3$) at the plasma membrane and recruiting PH domain-containing signaling molecules such as, phosphatidyl-inositol-dependent kinase 1 (PDK1). These are essential for the activation of protein kinase C (PKC) theta (PKCθ) [9], which cooperates with the protein Ser/Thr phosphatase, calcineurin [6] in transduction of signals leading, among other things, to the activation of enzymes and transcription factors, including c-Jun N-terminal kinase (JNK) and Nuclear factor of activated T-cells

(NFAT), and the synthesis and secretion of the interleukin-2 (IL-2) growth factor [10].

This Special Issue on Signal Transduction Mechanisms in T lymphocytes compile twelve manuscripts that review the current knowledge on some of the most important effector molecules and cellular mechanisms that govern and regulate T cell behavior.

In a manuscript by Makoto Yamagishi and Toshiki Watanabe, the authors discuss many of the signaling pathways that are involved in the regulation of T cell activation and differentiation and the implications of deregulated events on T cell disorders and T cell transformation leading to leukemia [11]. The authors describe crosstalk between signaling pathways that dictate developmental cues governing T cell differentiation and function under both normal physiological and pathological conditions.

Balachandra K. Gorentla and Xiao-Ping Zhong review the current information relevant to both proximal and distal TCR-linked signaling pathways and describe the role of adaptor proteins and other effector molecules in assembling the proximal signalosome required for signal transduction from the activated TCR [12]. They also discuss the role of the ζ-associated protein of 70kDa (Zap70) [5,13,14] and key adaptor proteins which serve as substrates for Zap70, including the linker for the activation of T cells (LAT), and the SH2- containing leukocyte phosphoprotein of 76 kDa (SLP-76) during the early activation phase of T cells [15,16]. T cell activation also promote the interaction of tyrosine-phosphorylated Zap70 with adaptor proteins that are not direct substrates for Zap70, such as members of the Crk adaptor protein family [17-19], which play a role in cytoskeletal reorganization and the assembly of the immunological synapse of the activated T cell [20].

A critical enzyme that operates downstream of the activated TCR is the PKCθ isoform, a member of the PKC family of Ser/Thr kinases that is expressed in all T cell subsets [9,21,22]. Productive engagement of T cells by APCs results in recruitment of PKCθ to the T cell-APC contact area where PKCθ interacts with and phosphorylates effector molecules that activate a chain of events, leading to signal transduction into the cell's nucleus [23,24].

The role of PKCθ in the regulation of TCR proximal signaling and its potential usage as a drug target for T cell-mediated diseases is discussed by Noah Isakov [25]. PKCθ was discovered two decades ago [26] and found to be essential for mature T cell responses [27]. TCR/

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CD28 engagement induces the translocation of PKCθ to the center of the immunological synapse where it undergoes posttranslational modifications and becomes fully active [28,29]. It then couples the activated TCR and the CD28 costimulatory receptor to downstream signaling pathways [30] leading to the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), AP-1 and NF-AT transcription factors, which regulate T cell survival, activation and differentiation [31-35]. PKCθ participates in cellular mechanisms leading to excessive inflammatory responses, autoimmunity, and graft vs. host (GvH) disease, but is dispensable for beneficial immune responses against viruses and during graft vs. leukemia responses [36-38]. Based on the above observation it has been suggested that PKCθ may serve as a drug target for catalytic and allosteric inhibitors in selected T cell-mediated diseases.

CD28 is the most important co-stimulatory molecule in T cells [39], and together with ICOS, the two represent a group of co-stimulatory surface receptors that are expressed in constitutive or transient manner [40]. A second group of receptors with an opposing effect on T cells can downregulate or terminate responses of activated T cells. They are members of a group of co-inhibitory receptors that includes molecules such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4; CD152) [41] and PD-1 [42,43].

Recent developments in the field of co-inhibitory receptors are summarized by David Escors and colleagues who emphasize the effects of PD1 interaction with its ligand, PD-L1 and the impact of activation of PD1 on the regulation of T cell activation and differentiation [44]. In addition, they discuss future directions of manipulation of co-inhibitory receptors in tumor immunotherapy [45,46].

A complementary review on co-inhibitory receptors, by Bin Wei and colleagues, focuses on the PD-1 and CTLA-4 mediated inhibitory signals that potentially lead to T cell exhaustion during chronic viral infections [47].

Recent studies indicate that chronic infections are associated with increased expression of the PD-1 and CTLA-4 co-inhibitory molecules, which play similar but non-redundant roles in T cell exhaustion [48-51]. Engagement of these receptors by their ligands inhibit T cell proliferation and cytokine secretion and attenuate immune responses, while blockade of PD-1 and CTLA-4 restores effector functions of exhausted T cells. The authors discuss the role of effector molecules that are being recruited to the activated receptors and contribute to signal transduction leading to inhibition of protein kinase B (PKB; Akt). They further discuss PD-1 and CTLA-4 as potential drug targets during chronic viral infections that may enhance antiviral T cell activity.

The current understanding of the biological function and mechanism of action of co-inhibitory receptors during the early stage of T cell activation is further discussed by Jean G. Sathish and colleagues [52]. This comprehensive review relates to the role and the mechanism of action of many known co-inhibitory receptors, including CTLA-4, PD-1, B- and T-lymphocyte attenuator (BTLA), lymphocyte-activation gene 3 (LAG-3), leukocyte-associated immunoglobulin-like receptor (LAIR-1), T cell immunoglobulin mucin-3 (TIM-3), T cell Ig and ITIM domain (TIGIT) and sialylated glycoconjugates (siglecs) proteins in activated T cells [53,54]. The effects of the co-inhibitory receptors are mediated by extracellular mechanisms, such as ectodomain competition with counter receptors, or intracellular mechanisms mediated by protein phosphatases that counteract positive signals mediated by protein kinases. It is believed that co-inhibitory receptors can fine-tune the quality and strength of T cell-mediated immune response by acting as a checkpoint and threshold-setters, or modulators of activation and feedback mechanisms [55-57].

The activation process of T cells involves dramatic morphological changes leading to formation of the immunological synapse at the contact site with APC, secretion of specific cytokines and lytic granules in a polarized manner, and extravasation across vascular endothelium during inflammation. The morphological changes that occur in activated T cells are summarized by Mira Barda-Saad and colleagues [58] who review the current knowledge on the role of actin and actin regulatory proteins, including Wiskott-Aldrich syndrome protein (WASp) and WASp family verprolin-homologous protein (WAVE) during cellular remodeling that drive the effector functions [59]. The authors emphasize the role of actin regulating proteins in reorganization of the cell cytoskeleton. In particular, they focus on the structure and function of the WASp and WAVE [60,61] and address pathological aspects related to defects in these proteins and the relevant therapeutic approaches, including gene therapy and stem cell transplantation [62,63].

In an additional manuscript, Stefanie Kliche and colleagues [64] review recent findings relevant to adhesion and degranulation-promoting adapter protein (ADAP), Src kinase associated protein of 55 kDa (SKAP55), and SKAP-homologue (SKAP-HOM) cytosolic adapter proteins, which regulate inside-out/outside-in signaling of integrins [65,66]. Some of these proteins also play an essential role in the assembly of PKCθ/CBM/TRAF6/ADAP/TAK1 signalosomes that regulate JNK activity and JNK-dependent activation of NF-κB and Cdk2 [67]. The authors also examine and compare structure-function relationships of these proteins and discuss their role in T-cell adhesion, migration and proliferation.

Yashaswini Kannan and Mark S. Wilson further discuss the role of the tyrosine-protein kinase, Tec, and mitogen-activated protein kinase (MAPK) signaling pathways in T helper ($T_H$) cell development, $T_H$2 differentiation and allergic asthma [68]. They summarize the current knowledge on the role of Tec and MAPK in T cell development and differentiation with an emphasis on $T_H$2 cells [69-72]. In addition, they concentrate on the role of $T_H$2 cells in allergy development and provide a brief update on potential kinase inhibitors that were tested both *in vitro* and *in vivo* [73-75].

The review manuscript by Raffi Gugasyan and colleagues focuses on the role of NF-κB in T-lymphocyte development and function [76]. NF-κB is a ubiquitous transcription factor that regulates expression of a wide range of genes [77]. The review concentrates on the role of NF-κB in the process of T cell maturation in the thymus and on T-helper cell polarization to functionally distinct peripheral T cell subsets [78,79] and discusses crosstalk mechanisms between NF-κB and other signaling pathways in T cells [80,81].

Dietmar Zehn and colleagues [82] summarize the current understanding and the functional importance of low affinity T cells during infection, autoimmunity and cancer diseases, and discuss the mechanism by which T cell function is influenced by TCR affinity and TCR signal strength [83]. They also discuss the impact of inhibitory and activating receptors on the function of T cells possessing TCR with different affinity to antigens.

The last review in this Special Issue is devoted to signaling molecules and effector mechanisms that regulate metabolic processes in T lymphocytes undergoing cell activation [84], with emphasis on enzymes, such as phosphoinositide-3-kinase (PI3K), AKT, and adenosine-monophosphate- activated protein kinase (AMPK) [85-87].

Jonathan A. Lindquist and colleagues, discuss the metabolic profiles of activated T cells that characterize their differentiation into distinct T cell subsets and describe the mechanisms by which key molecules, such as AKT and AMPK, accomplish their tasks.

Collectively, the reviews included in this Special Issue demonstrate the complexity of signaling networks involved in the regulation of T cell behavior. They discuss the role of distinct surface receptors in signal delivery across the plasma membrane and the complexity of the crosstalk between various signaling pathways. Identification of all players in these 'arena' and characterization of their mechanism of action will facilitate the future design of new drugs and implementation of new therapeutic protocols for application in a range of diseases.

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## Conflict of Interest Statement

The author declares no conflict of interest.

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