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Editorial Note: Special Edition

The ins and outs of T cell signaling

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ABSTRACT

This special edition summarizes major advances in our understanding of signaling by T lymphocytes. T cell interactions with antigen-presenting cells (APCs) and other immune cells are characterized by changes in T cell adhesion and major rearrangements of the actin cytoskeleton. This issue describes some of the mediators of these changes both within the T cells and on the T cell surface. The five articles focus on "inside-out integrin signaling" in T cells, components of the immunological synapse between lymphocyte and APCs, an unexpected role for T cell receptor (TCR) signaling from endosomes, transfer of membrane constituents from APCs to T cells via trogocytosis, immune deficiencies in these T cell signaling pathways, and the role of thymocyte-expressed molecule involved in selection (THEMIS) in thymocyte development and peripheral T cell function.

In the first article in this special issue on T cell signaling, Dr. Sari-Ak et al. [1] describe the process of "inside-out integrin signaling" in T cells, which is responsible for enhanced cellular adhesion during immune responses. The signaling pathway involving Rap1 and the downstream effector, Rap1-interacting adaptor molecule (RIAM), plays a role in cytoskeletal reorganization and activation in T cells and is critical for T cell adhesion. Phagocytosis, which also requires cytoskeletal remodeling, is dependent on RIAM. This review thus summarizes the properties of RIAM and provides updates on the function of the Rap1/RIAM pathway. As noted by the authors, it is becoming clear that RIAM might also mediate specific functional outcomes depending on the cell type and the microenvironment.

The second article [2], by Dr. Alcover and colleagues, introduces three evolutionarily conserved cell polarity regulators, which contain numerous protein–protein interaction domains. In turn, the domains become associated with multiple effector regulatory proteins. These complex interactomes control distinct types of cell polarity – namely, stable polarized states found in epithelium and neurons, or adaptable polarization for secretory or immune cells.

The review focuses on immune cell migration and immunological synapse formation by T and B lymphocytes, which

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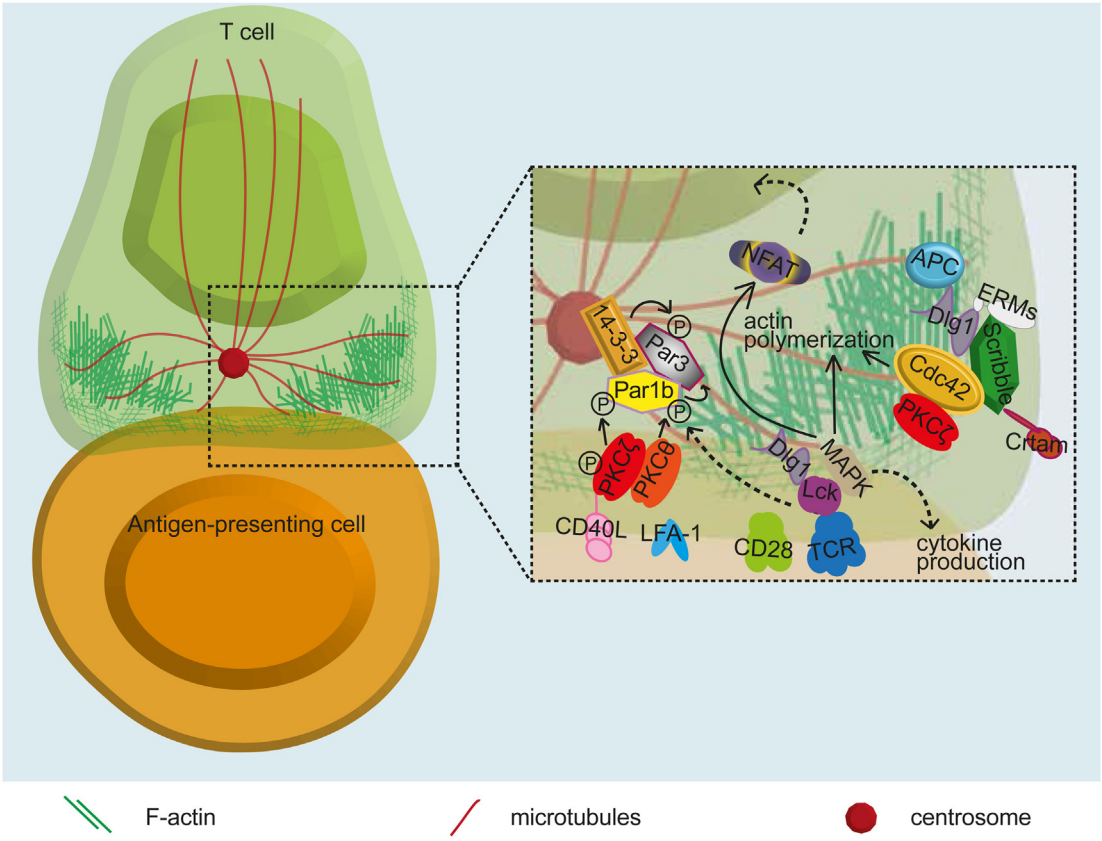

Fig. 1 Schematic depiction of an immunological synapse between a T cell (in green) and an antigen-presenting cell (in orange). TCR and CD28 signal transduction drives cytoskeleton reorganization, characterized by the close polarization of the centrosome to the cell contact. Source: Mastrogiovanni et al. [2].

involves reorganization of the actin cytoskeleton. This generates a lamellipodium at the leading edge, where polarity regulators interact with the small GTPases Rac1, Rap1 and Cdc42, which in turn, transduce signals to actin and microtubules. At the rear of migrating lymphocytes, the uropod contains adhesion molecules (ICAM1-3, CD44, CD43, P-Selectin ligand) and proteins of the ezrin, radixin, moesin (ERM) family. Large morphological changes occur when migrating T lymphocytes interact strongly with antigen-presenting cells (APC). T cell receptor (TCR) and CD28 signals initiate cytoskeletal reorganization, as described in Fig. 1.

In the third review article, Dr. Saveanu and her colleagues [3] discuss the ability of the TCR to signal from endosomes of activated T lymphocytes. The article schematically describes the structure of the TCR and the role of immunoreceptor tyrosine-based activation motifs (ITAMs) in the early steps of signal transduction upon TCR stimulation. Interestingly, several studies show that inactivation of some ITAMs of the TCR complex does not block TCR signals completely. However, a low ITAM number permits TCR activation, driving release of cytokines, but TCR-dependent proliferation requires a larger number of functional ITAMs. In addition, it was found that while CD3ζ chains (part of the CD3 complex) are important in TCR-mediated signal transduction, they also contribute to TCR stability at the plasma membrane. Indeed, mice lacking CD3ζ chain have a defect in T cell development.

In T lymphocytes, constitutive or activation-induced TCR internalizations take place through different mechanisms. The clathrin-dependent endocytosis of TCR is dependent on AP2-binding motifs: (a) tyrosine-based motifs (Yxxθ) and (b) di-leucine sequences, where θ represents hydrophobic residues. Furthermore, the transmembrane protein IRAP interacts with CD3ζ chains. In cells lacking insulin responsive aminopeptidase (IRAP), CD3ζ is found mainly at the plasma membrane, suggesting that IRAP is crucial for the internalization of CD3ζ chains or maintaining them in intracellular compartments.

Strongly activated TCRs are internalized by clathrin-independent endocytosis (CIE) pathways. Importantly, two Ras-related GTPases, TC21 and RhoG, are involved in CIE pathways of internalization of activated TCRs. One pathway affects the TCRs at the immunological synapse and the other involves internalization of TCRs bound to peptide-major histocompatibility complex (MHC) (pMHC) complexes "pulled" away from APCs. The latter mechanism is called trogocytosis and corresponds to the transfer of membrane constituents from APCs to T lymphocytes. This exchange of membrane components is not restricted to immune cells.

The review also presents evidence that TCRs can use endosomal platforms to propagate specific signals. This represents an important shift in the previous way of thinking because it demonstrates that, like many other immune or non-immune receptors, TCRs can signal via endosomal

platforms. The ability of endosomal TCRs to transduce signals from endosomes raises the question of the origin of endosomal TCR-activating ligands. Trogocytosis may explain how activating ligands reach endosomes. The pMHC complexes recognized by TCR are snatched from the APC and found in endosomes with phosphorylated CD3 and other mediators. Interestingly, several studies have shown that T lymphocytes undergoing trogocytosis are strongly activated when compared to T cells which are not trogocytic. Thus, $CD4^+$ T cells undergoing trogocytosis secrete more IL-2 and grow more efficiently, and trogocytic $CD8^+$ T cells display stronger cytotoxic activity and produce higher amounts of the cytokines TNFα and IFNγ.

The fourth article, by Dr. Latour [4], describes immune deficiencies and their effects on activation of T cells. Loss of function mutations in the T cell signaling pathways starting with the TCR complex with CD3, different protein kinases and phosphatases and their adaptor proteins, and the transcription factor, NF-κB, are associated with autoimmune disease and inflammation. However, mutations that affect signaling via co-stimulatory molecules (TNF, CD28, SLAM receptor families) have only a slight effect on T cell development, but they result in weaker T cell responses. One would have expected that the defects in co-signaling should have a generalized effect on immune responses, but curiously, they are associated with increased susceptibility to pathogens such as the Epstein–Barr virus or the Human Papilloma Virus, revealing a functional specialization of co-stimulator molecules not previously appreciated.

In the final review of this special issue, Dr Lesourne and colleagues [5] analyze the role of thymocyte-expressed molecule involved in selection (THEMIS) in thymocyte development and its functions in peripheral T lymphocytes. Experiments inactivating THEMIS showed that this molecule is required for positive selection of thymocytes. THEMIS-deficient mice have a major defect in maturation of double-positive (DP) thymocytes into $CD4^+$ and $CD8^+$ single-positive (SP) thymocytes, with a more severe decrease in $CD4^+$ SP thymocytes and peripheral T lymphocytes.

This review describes the molecular structure and function of THEMIS during T cell development, and the role of THEMIS-interacting partners – the tyrosine-phosphatases SHP-1 and SHP-2, the growth factor receptor–bound protein 2 (GRB2), and the RAC1 guanine exchange factor VAV1. The complex interactions of these molecules and the role of the phosphatases SHP-1 and SHP-2 on TCR signaling are thoroughly discussed. Significantly, the GRB2 and THEMIS interaction protects GRB2 from proteasome-mediated degradation.

The article also reviews recent data on THEMIS function in peripheral T lymphocytes. THEMIS is expressed in peripheral T cells at lower levels than in double-positive thymocytes. However, THEMIS expression varies in different T lymphocyte subsets. THEMIS is also needed to trigger the proliferation of $CD8^+$ T lymphocytes stimulated by IL-2 and IL-15, two cytokines endowed with important function in the homeostasis of $CD8^+$ T lymphocytes. Finally, the authors present interesting hypotheses suggesting that THEMIS may control T lymphocyte function via TCR-independent mechanisms.

All in all, this special issue makes clear that ample progress has been made in understanding how T cell signaling is initiated extracellularly and how the signals are propagated within the cell, but also reveals that major challenges remain to decipher the role of intracellular mediators in lymphocyte differentiation and effector functions.

Conflicts of interest

The authors are editors with Biomedical Journal.

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