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Immunological synapse: An emerging target for immune regulation

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Abstract

Immunological synapse is termed as a steady interface between immune cells (mainly T-lymphocyte) i.e., derived from thymus along with adhesion molecules and antigen presenting cell (APC). The synapse is often called as supramolecular activation cluster (SMAC) which has 3 prime compartments namely central, peripheral, and distal. After adequate contact between the two components of synapse, the signals move further in a coordinated, sequential manner after being decoded to promote T-cell activation. The synapse plays a major role in antigen recognition, orderly integration of immune signals and immune modulation.

Introduction

Immunological synapse is termed as the merger between an antigen presenting cell (APC) and lymphocytes: T-cell, B-cell, or Natural killer (NK) cell. In the early 1980s, Norcross gave this concept, although the term was given by Paul and Seder, 1994 in an article. And is an important event in the progression of adaptive immune response that results in the activation of T cell by stimulus driven segregation of molecules. The described mechanism is formed due to contact between T lymphocyte and APC where signals move in a coordinated, sequential manner after being decoded to promote T cell activation. Integrins, co-stimulatory receptors, and T Cell Receptors (TCR's) aggregate and the respective signals are integrated to elicit dynamic re-organization of microtubules and microfilaments for the initiation of cascade leading to gene expression [6].

Immunological synapse formation

The immunological synapse is also named as the supramolecular activation cluster (SMAC**)**. This synapse structure comprises of separated protein bands frequently stated as the bull's-eye model due to concentric rings. Firstly, c-SMAC (central-SMAC) composed of the protein kinase CD2, CD4, CD8, CD28, and Fyn. Then, p-SMAC (peripheral-SMAC) inside of

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which LFA-1 and cytoskeletal protein are clustered. In the outer part, d-SMAC (distal-SMAC) exists that is enriched with CD43 and CD45 molecules. Multispectral flow cytometry imaging was used for studies regarding receptor aggregation and maturation [3].

The foremost interaction occurs amongst LFA-1 existing in the p-SMAC, and non-specific adhesion molecules (such as ICAM-1 or ICAM-2) on cell to be targeted. After being in contact with a target cell, the T-cell can spread pseudopodia and check over the surface of target cell to search the specific peptide: MHC complex. The formation of synapse begins when TCR binds to peptide: MHC complex on APC and initiates activation of signaling via micro clusters/lipid rafts formation. There are certain specific signaling pathways that lead to polarization of T-cell by changing the orientation of its centrosome toward the site of synapse [8]. Promotion of cluster formation takes place having TCRs/CDR and integrins after actin is accumulated and re organized. The synapse formation process thereby upregulates via positive feedback itself. In case of CD8+ T cells, as the fundamental function is to eradicate the pathogen rapidly synapse formation is really quick. In CD4+ T cells, however, the whole process can take up to 6 hours. CD8+ T lymphocytes have lytic granules – specialized secretory lysosomes filled with various enzymes that aid in cell lysis like perforin, granzymes, lysosomal hydrolases and other cytolytic effector proteins. After these proteins are carried to the target cell, they begin its apoptosis. The effectiveness of killing lies on the TCR signal strength [4].

TCR interaction with MHC-peptide complex control not also the specificity of the immune response but also the source of antigens. TCR genes undergo rearrangement like that of antibody genes. These T cells are encoded with subunits of either α and β genes that make up the classical wide range of repertoire for immature cells. The composition of surface TCR comprises of two wholly expanded subunits for antigen detection that are basically exclusive for respective T cell, that maybe either in αβ or γδ form. This above-described complex is critical for signal transduction along with surface expression, but any such inherent catalytic action is lacking. Conventional T cells of αβ sub-type are denoted by different types of co-receptors that maybe either CD8 or CD4. CD8 binds to the site in between $\alpha 1$ and $\alpha 2$ in MHC I, and CD4 with that of α1 and β1 part of MHC II. During the T-cell development, thymocytes rearrange T Cell Receptor genes and test receptors for interaction with self-peptides on MHC. Next to it, a secondary recognition process is much importantly required for survival of thymocyte, and this is for the bias of the TCR action towards MHC recognition [2]. This self-recognition process is thought to set up the stage for foreign peptide recognition after providing the T cell with weak recognition of the peptide flanking, polymorphic α–helices of the MHC proteins, and provides major survival signals to mature T cells that is very much required. Till now the fact is very much under discussion if the germ-line-encoded TCR are biased based on evolutionarily point of view, or if the TCR repertoire has lack of biasness like an antibody.

Co stimulatory action

These receptors have very limited signaling or adhesive activity of their own, but they can still

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enhance the adhesion and signaling action in the vicinity when added with any other stimuli, majorly through the TCR. Costimulatory receptors earlier were predicted to be as a corollary of the clonal selection model in which T cells were bound to be able for attenuating their responses towards harmless foreign proteins from the environment that is not present in the thymus and which could drive inappropriate immune responses in the system if not checked by some other mechanism for extrathymic tolerance [7]. The above-described stimulation method for mature T cells devoid of any extra co-stimulation aids to subsequent repetition of clonal deletion that defends the host against generation of unwanted immune responses towards harmless environmental antigens. Schwartz and Jenkins researched the basics of anergy in which the recognition of antigen with minimal co-stimulation could lead to a state of non-responsiveness.

TCR endocytosis and recycling

The TCR is a protein complex formed by an antigen-detection unit comprising of α and β chains, and a signal transmitting segment consisting of a ζ-chain homodimer and four CD3 chains present as γε and δε heterodimers. These intracellular domains of the ζ-chains and CD3 chains have specialized ITAMs that help in transduction after TCR engagement**.** The ability of a T cell to become activated is basically regulated by the number of TCRs expressed on the plasma membrane. In T cells that are still unstimulated, the TCR levels depend on the adequate equilibrium between numerous processes, viz. de novo synthesis and the subsequent transport of newly assembled receptors, TCR endocytosis, recycling, and degradation. Since, de novo synthesis and degradation rates are very little, endosomal recycling is the major criteria exploited by the T cells to control their TCR expression. Furthermore, the transfer of T Cell receptor- CD3 complex inside the cell has been anticipated as a major step in quality control of this receptor. Endocytosis of TCR takes place via clathrin-independent path and subsequently merged into endocytic network for signaling events that are crucial for T-cell activation [1].

Subsequent to the step of internalization, the plasma membrane receptors are transported into early endosomes, that majorly serve as a prime point of the endocytic pathway. They are also responsible for the sorting of internalized cargo to either recycling endosomes, or to late endosomes for lysosome-dependent degradation. The post-endocytic receptor traffic is majorly orchestrated by the ubiquitous Rab GTPases, their effectors and regulators that describe the basic function and identity of the endosomal subpopulations. On the contrary, these receptors in internal compartment endure regressive transit to the endocytic recycling compartment present in perinuclear site and are ultimately delivered to plasma membrane through microtubule-dependent route. Basically, this pathway has been studied extensively in lieu of immunological synapse assembly after the pivotal role of polarized TCR recycling in this process, it appears to also been exploited for constitutive recycling [10].

Conclusion and future perspectives

From the initial scenario of the TCR having constitutive recycling inside the quiescent cells to

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allow multiple opportunities for quality control during its long lifetime. Additionally, TCR has also been targeted for degradation after ligand-induced internalization. Furthermore, a rather complicated situation has emerged, where the fate is extended towards signaling and becoming incorporated into extracellular vesicles with the ability to affect the function of APCs. The study of endosomes composition may shed more light on whether the associated signaling complexes are like the ones assembled at activation sites or represent unique complexes that contribute towards signal diversification [5].

However, $CD4^+$ derived T cell exosomes can inhibit $CD4^+$ T cell proliferation and $CD8^+$ CTL responses, like that of Treg derived exosomes, and moreover some evidence suggests that these T cell exosomes may be implicated in tumor progression and invasion by targeting tumor cells as well as endothelial cells. Hence, an improved knowledge of the above-mentioned pathways for endocytosis that control immunological synapse assemblage and function is likely to shed more light upon new candidates in this newly chartered field for their modulation regarding immune dysregulation [9].

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