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The Regulation and Defectiveness of T Cell Antigen-Receptor Signal Transduction with the Help of Kinase and Phosphatase for Regulation and Defectiveness when Lacking Thymic Isoform of p59 (fyn)

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T cell antigen-receptor signal transduction is helped by LAT (linker for activation of T cells), SLP-76 (SH-2 containing leukocyte protein 76), and Itk (inducible T cell kinase). With the help of CD3, CD4 or CD8, reorganization of the cytoskeleton as well as transcription activation can be carried out. This improves the TCR signaling as a whole. With the presence and balance of kinase and phosphate activities, signal transduction can be regulated but with thymic isoform lacking, signal transduction is defective. This micro review will discuss how T cell antigen receptor signal transduction works as well as why with a balance of kinase and phosphate it is regulated but with a lack of thymic isoform it is defective.

Introduction

T cell antigen-receptor is a subunit complex that consists of clonotypic alpha beta chains, which means unique to individual cells or members of a clone. The activation of T cells by antigen presenting cells is because of protein tyrosine kinases (PKT) activation. This is associated with CD 3, which is a T-cell co-receptor protein complex and is composed of four distinct chains, and T cell receptor (TCR) subunits CD4 and or CD8 which are a glycoprotein that are found primarily on the surface of helper T cells. With the presence of kinase and phosphate, it "enables the rapid coordinated assembly of effector and adaptor molecules, which catalyze the activation of a immune response". The phosphorylation state of these collected glycoproteins yields information regarding is kinase is an adaptor protein receptive to interacting partners or active. Knowing this information about kinase and phosphate has helped in the elucidation of the molecular constituents that interact to transmit signals from the cell surface to the interior of the cell as discussed in Schade.

Signal transduction is helped by LAT, SLP-76, and Itk for optimal T cell receptor induced activation. Without these adaptor proteins, signaling would have a negative effect. LAT, otherwise known as linker for activation of T cells, is a transmemebrane adapter protein expressed in T cells (natural killer cells). LAT couples the T cell regulation to phospholipase CA+. LAT is also important for signal transduction because LAT's is "palmitoylated on two juxtamembrane cysteine residues" which is required to bind LAT to glycolipid-enriched micro domains (GEMs). This is required for membrane T cell activation. SLP-76 is also another adapter protein required for successful signal transduction. SLP-76 is an adapter protein with an "amino acid terminal region that contains critical tyrosine phosphorylation sites", which ultimately, the carboxyl terminal SH2 binds tyrosine phosphorylation SLAP, which is a SLP -76 protein. With the binding of SLAP, SLP-76 has shown to be critical in the effectiveness of T cell signal transduction. Itk, Inducible T cell kinase, is recruited to the membrane by ways of an amino acid terminal and stimulated by CD28. Itk has been shown to be effective because like stated previously, the involvement and regulation of kinase is crucial for signal transduction. Deficient Itk show "mild defects in T cells development".

Recent Progress

Now that T cell antigen- receptor signal transduction is understood, finding out how the balancing of kinase and phosphate activities help regulate transduction is crucial for understanding more of signal transduction. A series of tyrosine phosphorylation is crucial for cellular activation, as well as inducible and reversible phosphorylation of

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proteins. Signal transduction of T cells has in the past focused only on kinase mediated pathways, mainly because kinase is responsible for transmitting information through the tyrosine phosphorylation. A way we can study the balance of kinase and phosphate is looking at their relationship of PI-3 K, an inhibitor, and PTEN, which is a signaling pathway. So when activation starts, PI-3 K phosphorylates the D-3 position changing the functional group of the molecule to PIP3, which in turns recruits other molecules like PDK1 that activates Akt. PTEN regulates this pathway and dephosphorylates PIP3. PIP3 counteracts anti- apoptotic (anti cell death) of Akt signaling pathway. The LAT adapter protein is used to study the relationship between kinase and phosphate by decreasing the tyrosine phosphorylation of it as discussed in Leeuwans article over T-cell antigen receptors. The de-phosphorylation of LAT mediated tyrosine phosphorylation, but since LAT is already at a high phosphorylation, it increased phosphate activity. This balance of kinase and phosphate studied for signal transduction was both a positive and negative regulation in the overall balance. Temperature plays a huge role in the balance of kinase and phosphate for if the temperature changes slightly, de-phosphorylation happens and T cell signal transduction can become inactive.

Now that the relationship of balancing kinase and phosphatase has been examined to understand more of how signal transduction is regulated, Thymic Isoform is looked at to better understand why if lacking, a T cell receptor signaling is defective. To find out if the nonreceptor protein tyrosine kinase p59 takes part of signal transduction of a T cell receptor, an experiment to produce mice that lacked Thymic Isoform p59 were performed in Appleby. Although all of the mice appeared normal through maturation, the mice had lymphoid defects as well as rejection to stimulation through T cell receptors with mitogen, which is a chemical substance that encourages a cell to commence cell division. It concluded that if lacking thymic isoform p59, that T cell receptor signaling would prove to be defective.

Discussion

Although there is still much progress to be learned from T cell receptor signaling transduction, knowing that the balance of kinase and phosphatase helps regulate signaling while the lack of thymic isoform makes it defective helps get some understanding about T cells and their signaling. Knowing this information, we can see that temperature and configuration play a huge role in balance and regulation while an increase in phosphorylation and proteins plays a huge role in defectiveness.

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