A Pathway of the Immune System

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Introduction

Immunology is a science dedicated to investigating host defense mechanisms and immune cell functions under physiological and pathological conditions. This includes research on both the innate and adaptive immune response and processes such as pathogen recognition, immune cell activation and recruitment, cytokine secretion, inflammation, and antibody production. The illustrations found in this section highlight pathways that regulate these processes or mechanisms that may contribute to the development of inflammatory or autoimmune diseases.

Insulin, secreted by pancreatic beta cells, is the main regulator of blood glucose levels. It inhibits glucose production in the liver, stimulates glucose uptake in muscle and fat, promotes glycogen and lipid synthesis, and inhibits lipolysis. Insulin signaling promotes glucose uptake by activating intracellular signaling pathways that promote translocation of the GLUT4 glucose transporter to the plasma membrane. Additionally, insulin signaling inactivates GSK-3, which keeps Glycogen Synthase active, thereby promoting storage of glucose as glycogen. Insulin signaling can be enhanced or inhibited by adipocytokines secreted by the adipose tissue. The ability of these cytokines to influence insulin signaling suggests that changes in their levels may contribute to the development of insulin-related metabolic disorders such as Type II diabetes. In support of this hypothesis, one of the leading risk factors for Type II diabetes is obesity, a condition characterized by an increase in adipose tissue mass, altered adipocytokine secretion, and chronic inflammation. Obesity is associated with reduced Leptin sensitivity and decreased Adiponectin production, two adipocytokines that normally enhance insulin sensitivity.

These changes are coupled with an increase in the production of pro-inflammatory cytokines such as TNF-alpha and IL-6, which can negatively affect adipose tissue functions and promote insulin resistance. Characterizing the mechanisms by which adipocytokines enhance or interfere with insulin signaling pathways is critical to our understanding of how these factors may contribute to the pathogenesis of metabolic disorders. Caspases are a family of aspartate-specific, cysteine proteases that serve as the primary mediators of apoptosis. All caspases are synthesized as inactive zymogens containing a variable length pro-domain, followed by a large (20 kDa) and a small subunit (10 kDa). Caspase activation occurs following receipt of an extrinsic or intrinsic death signal. The extrinsic pathway of caspase activation is initiated by ligand binding to cell surface death receptors, such as TNF RI, Fas/CD95, DR3, TRAIL R1/DR4, or TRAIL R2/DR5.Ligand binding to these receptors leads to receptor oligomerization and recruitment of FADD and/or TRADD, two death domain-containing adaptor proteins. FADD subsequently recruits Pro-Caspase-8 and Pro-Caspase-10 through its death effector domain.

Clustering of pro-caspases in the cytosol near a death receptor leads to formation of the death-inducing signaling complex (DISC) and the subsequent cleavage of Pro-Caspase-8 and Pro-Caspase-10. The intrinsic pathway of caspase activation is initiated by events such as DNA damage, growth factor withdrawal, or loss of contact with the extracellular matrix. These events ultimately lead to changes in the integrity of the mitochondrial membrane, which is regulated by Bcl-2 family proteins. The balance between pro- and anti-apoptotic Bcl-2 family members determines whether or not a cell will undergo apoptosis. In healthy cells, phosphorylated Bad is sequestered in the cytoplasm by the 14-3-3 protein, and Bcl-2 and Bcl-xL bind to the pro-apoptotic Bax and BAK proteins to inhibit apoptosis. When cytoplasmic levels of free Bad increase, Bcl-2 and Bcl-xL bind to Bad and release Bax and BAK. Bax and BAK, or processed forms of these proteins, can then insert into the mitochondrial membrane, compromising its integrity. Loss of mitochondrial integrity results in the release of pro-apoptotic proteins including Cytochrome c, Smac/Diablo, HTRA2/Omi, Apoptosis-Inducing Factor (AIF), and Endonuclease G. In the cytoplasm, Cytochrome c interacts with APAF-1, which recruits Pro-Caspase-9 to form the apoptosome.

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