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Review / Derleme

The Structure and Signaling Mechanisms of Type 1 Cytokine Receptors: A Brief Overview

Tip 1 Sitokin Reseptörlerinin Yapısı ve Sinyal Mekanizmaları: Kısa Bir Genel Bakış

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ABSTRACT

Cytokines, the secreted messenger molecules, act on their target cells by binding specific membrane receptors. Many cell functions are regulated by members of cytokine receptors mediated intracellular signaling mechanisms. The classification of cytokine receptors is based on structural homologies of extracellular cytokine-binding domains and shared intracellular signaling mechanisms. A simple classification of cytokine receptors contains type 1 cytokine receptors, type 2 cytokine receptors, tumor necrosis factor receptor family, interleukin 1 receptor family, and seven transmembrane G-protein-coupled receptors. This article focuses on the structure and associated signaling pathways of type 1 cytokine receptors.

Keywords: Cytokines; receptors; type 1 cytokine receptors.

ÖZ

Salgılanan haberci moleküller olan sitokinler hedeflerindeki hücreleri belirli membran reseptörlerini bağlayarak etkiler. Pek çok hücre işlevi sitokin reseptörü aracılı hücre içi sinyal mekanizmalarının üyeleri tarafından düzenlenir. Sitokin reseptörlerinin sınıflandırması hücre dışı sitokin bağlayıcı alanlar ve ortak hücre içi sinyal mekanizmalarının yapısal homolojilerine dayanır. Sitokin reseptörlerinin temel bir sınıflandırması tip 1 sitokin reseptörlerini, tip 2 sitokin reseptörlerini, tümör nekroz faktör reseptörü ailesini, interlökin 1 reseptörü ailesini ve yedi transmembran G protein-kenetli reseptörleri içerir. Bu yazıda tip 1 sitokin reseptörlerinin yapısına ve ilişkili sinyal yollarına odaklanıldı.

Anahtar sözcükler: Sitokinler; reseptörler; tip 1 sitokin reseptörleri.

Cytokines, the secreted messenger molecules, act on their target cells by binding specific membrane receptors. Many cell functions are regulated by members of cytokine receptors mediated intracellular signaling mechanisms. The classification of cytokine receptors is based on structural homologies of extracellular cytokine-binding domains and shared intracellular signaling mechanisms. A simple classification of cytokine receptors contains type 1 cytokine receptors, type 2 cytokine receptors, tumor necrosis factor receptor family, interleukin 1 (IL-1) receptor family, and seven transmembrane G-protein-coupled receptors.[1] Type 1 and type 2 cytokine receptors lack intrinsic tyrosine kinase activity and instead rely on cytoplasmic kinases to initiate intracellular signaling.[2] Signaling through these receptors occurs by Janus kinase-Signal Transducer and Activator of Transcription (JAK-STAT) signaling, which is described in detail later. Type 1 cytokine receptors family includes receptors for IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-11, IL-12, IL-13, IL-15, granulocyte colony-stimulating and granulocyte-macrophage colony-stimulating factors, erythropoietin, thrombopoietin, and also the receptors for leptin, prolactin, and growth hormone. Type 1 cytokine receptors are also known under the name hematopoietin receptors since most of the receptors of soluble factors functioning in the hematopoietic system belong to this cytokine receptor superfamily. For instance; granulocyte colony-stimulating and granulocyte-macrophage colony-stimulating factors, erythropoietin, and thrombopoietin

promote the growth, differentiation and proliferation of the granulocyte-monocyte progenitor cells and megakaryocyte-erythroid progenitor cells via their cell surface receptors. However, this important receptor family also regulates key processes such as growth, lactation, and immune function and contributes to oncogenesis. Also, these receptors are expressed on multiple cell types, i.e. IL receptors in this receptor family are expressed on hematopoietic cells (especially on lymphoid lineage cells), osteoclasts, and keratinocytes, etc. The major effects of the growth hormone occur by increased production of insulin-like growth factor 1 by hepatocytes via growth hormone receptors. However, the liver is the major target organ of the growth hormone and the growth hormone receptors are expressed in a wide variety of tissues such as bone, cartilage, muscle, skin, placenta, and lung. Prolactin receptors and leptin receptors are expressed mainly in mammary gland and brain, respectively, but both of these receptors are also expressed in several other tissues.

Type 1 cytokine receptors are dimers or trimers that typically consist of unique ligand-binding chains and one or more signal-transducing chains, which are often shared by receptors or different cytokines. These chains contain one or two domains with a conserved pair of cysteine residues and a membrane proximal peptide stretch containing a tryptophan-serine-X-tryptophan-serine motif, where X is any amino acid.[3] The tryptophan-serine-X-tryptophan-serine motif consensus sequence is thought to serve as a recognition site for functional protein-protein interaction of cytokine receptors and is located proximal to the transmembrane domain (Figure 1). The conserved sequences of the receptors from structures which bind cytokines that have four-alpha-helical bundles are referred to as type 1 cytokines, but the specificity for individual cytokines is determined by amino acid residues that vary from one receptor to another. Each receptor complex consists of at least one signal transducing receptor chain containing membrane-proximal Box 1 and Box 2 motifs associated with JAK docking.[4]

Cytokine receptors of type 1 and type 2 receptor families engage signal transduction pathways that involve non-receptor tyrosine kinases called JAKs and transcription factors called STATs. There are four known JAKs (JAK1-3 and tyrosine kinase 2) in mammals.[5] The name was taken from the two-faced Roman god of beginnings and endings, Janus, because the JAKs possess two near-identical phosphate-transferring domains. One domain exhibits the kinase activity, while the other negatively regulates the kinase activity of the first. Seven STATs associated JAK-STAT pathways have been identified in mammals: STAT1-4, STAT5a, STAT5b, and STAT6.[6]

The sequence of events in the JAK-STAT signaling pathway is well defined. Inactive JAK enzymes are noncovalently attached to the cytoplasmic domains of type 1 cytokine receptors. These receptors exist largely as inactive dimer in absence of ligand.[7-9] When two receptor molecules are brought together by binding of a ligand, the receptor-associated JAKs are activated and phosphorylate tyrosine residues in the cytoplasmic portions of the clustered receptors. Recently, Brooks et al.[10] provided a mechanistic description for this process, focusing on the growth hormone receptor and its associated JAK-2. The researchers found that

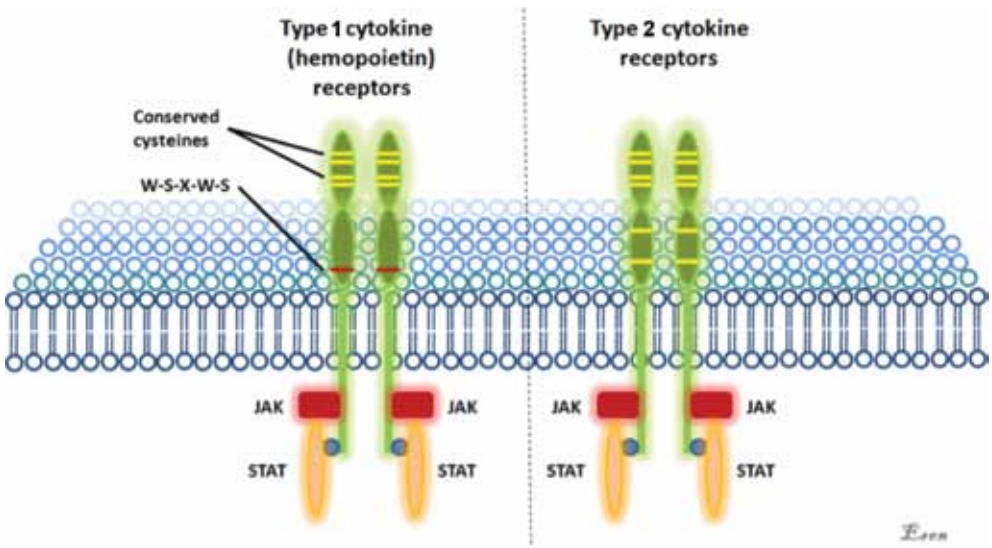

Figure 1. Structure of type 1 and type 2 cytokine receptors. W-S-X-W-S: Tryptophan-serine-X-tryptophan-serine; JAK: Janus kinase; STAT: Signal transducer and activation of transcription.

the growth hormone exists predominantly as a dimer *in vivo*, held together by its transmembrane helices. These helices are parallel in the basal state, and binding hormone converts them into a left-hand crossover state that induces separation of helices at the lower transmembrane boundary. This separation results in removal of the pseudokinase inhibitory domain of one JAK-2, which is blocking the kinase domain of the other JAK-2, and vice versa. The proposed mechanism may extend to other members of type 1 cytokine receptors family. After activation of JAKs, some of phosphotyrosine moieties of the receptors itself and JAKs are then recognized and bind to Src homology 2 (SH2) domains of monomeric cytosolic STAT proteins. The STAT proteins are thus brought close to JAKs and are phosphorylated by the receptor-associated kinases. The SH2 domain of one STAT monomer is able to bind to a phosphotyrosine residue on an adjacent STAT protein. The STAT dimers that are generated translocate to the nucleus, where they bind to specific DNA sequences in the promoter regions of cytokine-responsive genes and regulate gene expression.[11]

The unique amino acid sequences in the different cytokine receptors provide the scaffolding for specifically binding, and thereby activating, different combinations of JAKs and STATs. The SH2 domains of different STAT proteins selectively bind to phosphotyrosines and flanking residues of different cytokine receptors. This is largely responsible for the activation of particular STATs by various cytokine receptors and therefore for the specificity of cytokine signaling. Several type 1 cytokine receptors are heterodimers of two different polypeptide chains, each of which binds a different JAK. Furthermore, two different STATs may heterodimerize on phosphorylation. Therefore, there is a significant amount of combinatorial diversity in the signaling that can be generated from a limited number of JAK and STAT proteins.[1,6]

In addition, type 1 receptors activate signaling pathways and transcription factors other than STATs. For instance, growth hormone receptor activates mitogen-activated protein kinase and also phosphatidylinositol 3-kinase pathways.[12] The list of transcription factors implicated in growth hormone regulation of gene transcription continues to grow and it will undoubtedly grow ever more rapidly as new technologies are applied to detection of growth hormone regulated genes.[13,14] Other type 1 cytokine receptors may similarly activate other signaling pathways in concert with the JAK-STAT pathways to elicit biologic responses to the cytokines.

Several mechanisms of negative regulation of JAK-STAT pathways have been identified. Proteins called suppressors of cytokine signaling (SOCS) can be identified by presence of an SH2 domain and a conserved 40-amino acid C-terminal region called a SOCS box. SOCS proteins serve as adaptors for multisubunit E3 ligase activity. They can bind to activated STATs and JAKs, and the tightly associated E3 ligases ubiquitinate the JAKs and STATs, thus targeting them for proteasomal degradation.[15,16] SOCS proteins can negatively regulate cytokine receptor signaling by two other mechanisms. Firstly, they can directly inhibit JAK kinases by binding to the receptor or to the JAK activation loop.[17] Secondly, they can compete with other signaling molecules containing SH2-domains for binding sites on the receptor.[18] In these ways, SOCS serve as negative feedback regulators of the cytokine-mediated activation of cells. Other inhibitors of JAK-STAT signaling include tyrosine phosphatases, such as SH2 domain-containing phosphatase-1 and 2, which can dephosphorylate and therefore deactivate JAK molecules. Another family of inhibitor proteins, called protein inhibitors of activated STAT, was originally defined as negative regulators of STATs. Protein inhibitors of activated STAT proteins bind phosphorylated STATs and prevent their interaction with DNA.[19]

Studies indicated that mutations in specific type 1 cytokine receptors was associated with hematological, immunological, endocrinological, and inflammatory diseases. The roles of type 1 cytokine receptors and cytokine receptor signaling through JAK-STAT pathway have attracted considerable interest as a potential source of therapeutic targets for the management of complex human diseases.[20,21]

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