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Gene Section
Short Communication

STAT2 (Signal Transducer and Activator of Transcription 2)

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Abstract

Review on STAT2, with data on DNA, on the protein encoded, and where the gene is implicated.

Keywords
STAT2; JAK/STAT pathway

Identity

HGNC (Hugo): STAT2

Location: 12q13.3

DNA/RNA

Description

24 exons spanning 18657 bp

Transcription

There are two major transcripts. In transcript variant 1, mRNA is 4576 bp. Transcript variant 2 uses an alternate in-frame splice site in exon 3; as a result, it lacks an internal 12bp insertion compared to transcript variant 1. Another spliced form is generated by reading through the intron between exons 20 and 21, which correspond to the region encoding the SH2 domain. The spliced form contains a stop codon in the SH2 domain, giving rise to a short form of STAT2 when the mRNAs are translated. The putative translated proteins lack half of the SH2 domain, the tyrosine phosphorylation site required for dimerization and DNA binding, and the C-terminal activation domain.

Protein

Description

There are two major isoforms of STAT2.
The long form is known as isoform 1 and is a 851 amino acid protein (113KDa on gels).
Isoform 2 lacks an internal four amino acid segment compared to isoform 1.
The STAT2 gene product contains 6 domains: an N-terminal domain (NTD), a coiled-coil domain (CC), a DNA-binding domain (DBD), a linker domain (LD), a Src homology-2 domain (SH2), and a transactivation domain (TAD) (figure 1).
NTD is required for tyrosine phosphorylation of STAT2 in response to type I IFNs, binding of STAT2 to IFN receptors and cooperative binding of STAT1:STAT2 heterodimers or ISGF3 to promoters that contain tandem GAS or ISRE, respectively.
CC mediates protein interactions and is the domain IRF9 binds. DBD does not bind DNA as a part of ISGF3. DBD contains a bipartite nuclear localization signal (NLS) when ISGF3 forms. No function for LD is known. SH2 serves 2 main functions: binding to a phosphorylated IFN receptor, thereby making STAT2 available for Tyk2-mediated tyrosine phosphorylation; and binding to tyrosine phosphorylated STAT1 to form an active heterodimer.
The TAD is essential for recruitment of transcription regulators. TAD also contains the nuclear export signal (NES).

Figure 1. Schematic of the domain architecture of STAT2 and location of identified phosphorylation sites.NTD, N-terminal domain; CC, coiled-coil domain; DBD, DNA-binding domain; LD, linker domain; SH2, Src homology 2 domain; TAD, transactivation domain.

Nucleocytoplasmic shuttling of STAT2 is attributed to the constitutive binding of STAT2 to the NLS-containing IRF9 to transport STAT2 into the nucleus, while the STAT2 NES exports STAT2 back to the cytosol (Steen and Gamero, 2012).
Interferons (IFNs) activate the Janus kinase (JAK)/STAT pathway by binding to their corresponding receptor complex. Jak1 and TYK2 are pre-associated with type I and type III IFN receptors, and phosphorylate specific tyrosine residues within the receptor chain, which serve as docking sites for the recruitment of STATs. JAKs phosphorylate a conserved tyrosine residue situated in the C-terminal region of STAT2 (Y690) and STAT1 , thus allowing STAT1 and STAT2 to interact via reciprocal SH2-phosphotyrosyl interactions. Formation of the interferon-stimulated gene factor 3 (ISGF3) complex takes place when activated STAT1:STAT2 heterodimers are released from receptor chains to bind the DNA-binding adaptor protein, IRF9 (p48/ISGF3G). ISGF3 translocates to the nucleus and binds the DNA containing an IFN-stimulated response element (ISRE) by STAT1 and IRF9 to activate gene transcription of IFN-stimulated genes (ISGs). In addition, STAT2 can form heterodimers individually with either STAT1 or IRF9. Each of these complexes will bind IRSE or IFN-gamma activation sequences (GAS) to activate gene transcription of ISGs. Serine 287 phosphorylation can negatively regulate the biological activities of type I IFNs (Steen et al., 2013). IFNs are the only cytokines known to date that can activate STAT2.

Expression

STAT2 is ubiquitously expressed in most cell types.

Localisation

STAT2 predominantly resides in the cytoplasm. Nucleocytoplasmic shuttling occurs in the absence of IFN stimulation, but translocates to the nucleus upon tyrosine phosphorylation when stimulated by IFNs (Reich, 2013).

Function

Transcription factor. STAT2 mediates the transcription of numerous IFN-induced genes involved in linking adaptive and innate immunity and exerting antiviral, antiproliferative, apoptotic, and antitumor effects.

Homology

Shares homology with the other 6 mammalian STAT genes: STAT1, STAT3, STAT4, STAT5A, STAT5B, STAT6. Human STAT2 is relatively well conserved with macaque and chimpanzee. Human and murine STAT2 are highly homologous (76% identity over the first 712 amino acids).

Mutations

Note

Two mutations in intron 4 (Hambleton,et al., 2013) as well as the intron between exon 20 and 21 were found to prevent correct splicing of STAT2 (Sugiyama et al., 1996).

Implicated in

The antigrowth and immunomodulatory actions of interferons (IFNs) have enabled these cytokines to be used therapeutically for the treatment of a variety of hematologic and solid malignancies. The loss of IFN sensitivity may contribute to the development and progression of cancers. STAT2 is found to be decreased in many cancers including squamous cell carcinoma of the skin (Clifford et al., 2000; Clifford et al., 2002), fibrosarcoma (Krishnamurthy et al., 2006), astrocytomas (Ehrmann et al., 2008), melanoma (Mischiat et al., 2006), and prostate cancer (Ni et al., 2002). STAT2 has a tumor suppressor function (Clifford et al., 2002; Gamero et al., 2010; Yue et al., 2015) , though the mutations have not yet been identified in human cancer.
To evade the antiviral protective effects of IFNs, certain viruses have developed strategies to impair the IFN signaling pathway by specifically targeting STAT2. The strategies are to reduce STAT2 levels, to sequester STAT2 in the cytoplasm, or to prevent its tyrosine phosphorylation.

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