

**Editorial Note** 

## **Editorial Note for STAT3 gene in JAK-STAT Pathway**

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STAT proteins were originally identified as inactive cytoplasmic transcription factors. The biological role of STAT proteins which regulate growth, survival, apoptosis, host defense, stress & differentiation in functions depending on the signaling pathway & the target tissue. STAT family consists of STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B &

STAT6genes. 90kDa to 115kDa is the size STAT proteins. The STAT proteins in JAK-signal transducer and activator of transcription (JAK-STAT) signaling pathway. STATs are nonfunctional in the cytoplasm. After, the Ligand-induced activation of inactive cytoplasmic JAK kinases leads to tyrosine phosphorylation of inactive monomeric or N-domain-mediated dimeric STAT proteins, promoting the formation of active SH2domain-mediated homodimers of STAT proteins. The tyrosinephosphorylated STAT dimers are actively transported to the nucleus by using metabolic energy and the importin  $\alpha/\beta$  and RanGDP complex. When the activated STAT dimers are present in the nucleus then they can bind to consensus DNArecognition motifs, called gamma-activated sites (GAS), in the promoters of cytokine-inducible genes, resulting in transcriptional activation. STATs can bind DNA as dimers or as N-domain-mediated tetramers. Except STAT2, all STAT family has been shown to form higher order tetramer complexes. The STAT proteins which are non- phosphorylated were continuously travels between the cytoplasm and nucleus, the phosphorylated STAT protein is remained in the nucleus and is only released from DNA when dephosphorylation occurs by nuclear phosphatases, following cytokine withdrawal, and the inactivated protein is then actively exported out of the nucleus to the cytoplasm by the exportin Crm-1/RanGTP complex.

Inactivation of STAT proteins is supported out by several mechanisms, including dephosphorylation of STAT proteins in the nucleus and degradation through the ubiquitin-proteasome pathway. The amino acids between residues 400 and 500 of STAT proteins regulate the DNA-binding site specificity. SOCS family proteins are inducible, with SH2 domain comprising inhibitors of cytokine signaling, and consist of eight members: CIS along with SOCS1 to SOCS7.

These inhibit STATs signaling in three ways, either by binding their SH2 domain to JAKs (in case of SOCS1), by binding to receptor cytoplasmic domain (in case of SOCS3), or by opposing with STAT-SH2 domains for the recruitment to the receptor complex (CIS, SOCS2). In addition, SOCS proteins also make proteasomal degradation pathway through SOCS box. **STAT: Structure and Functional domains** 

The molecular structures of all STAT proteins are common and are arranged into distinct functional domains. The STAT3 protein consists of four functional domains that support to its oligomerization, DNA binding, SH2 dimerization, and transactivation, individually. The NH2 terminus (N-domain) is involved in protein - protein interactions between adjacent STAT dimers on DNA, enabling the formation of STAT tetramers. It is also involved in the organization of dimers between non-phosphorylated STAT monomers, these are important for receptor-mediated activation and nuclear translocation of certain STAT proteins. Interactions with STAT cofactors, which positively or negatively regulate their transcriptional activity, occurs via the N-domain, the adjacent coiled-coil domain and the carboxy-terminal transactivation domain (TAD). The conserved serine residue (p-S), which is phosphorylated upon cytokine stimulation and is crucial for maximal transcriptional activation, located in the transactivation domain. In addition to the full-length form (STAT $\alpha$ ), STAT proteins can also be present as C-terminally truncated forms generated by alternative splicing (STAT $\beta$ ) or by proteolytic processing (STAT $\gamma$ ). The C-termini of STAT $\beta$  proteins differs from the STATa protein not only by being truncated but also by having additional amino acids inserted as a result of the splicing event.