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SnapShot: JAK-STAT Signaling

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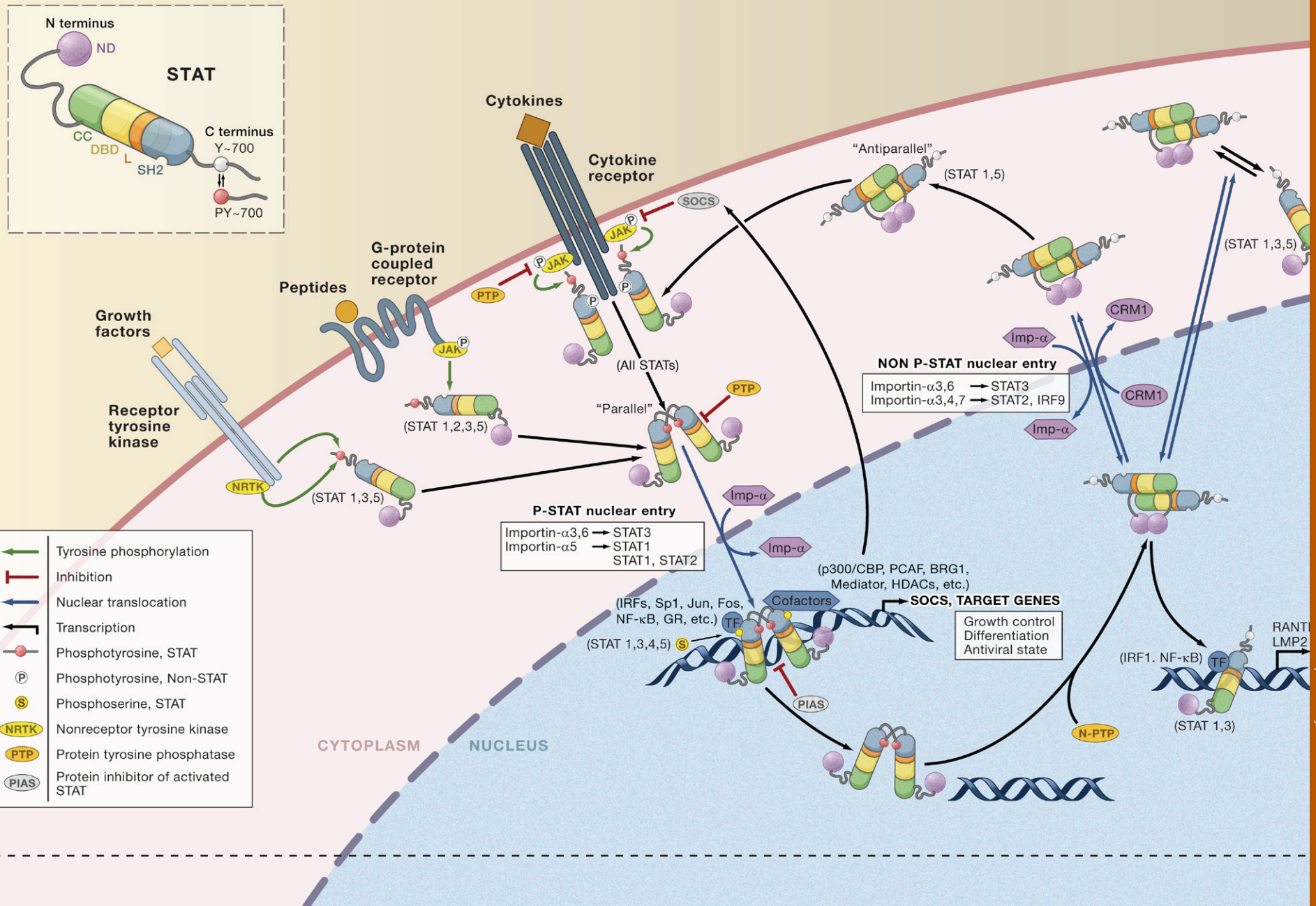

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The JAK (Janus kinase)-STAT (signal transducer and activator of transcription) signaling pathway is involved in transmitting information from extracellular polypeptide signals to target gene promoters in the nucleus. JAK-STAT signaling regulates many cellular processes including innate and adaptive immune function, development, cell proliferation, differentiation, and apoptosis. The principal players of the pathway are the STAT proteins, a family of latent cytoplasmic transcriptions factors. All seven mammalian STAT proteins (STAT 1, 2, 3, 4, 5A, 5B, 6) share six structural regions: an N-terminal domain (ND), a coiled-coil domain (CC), a DNA-binding domain (DBD), a linker domain (L), a Src homology 2 (SH2) domain, and a transcription activation domain at the carboxy (C) terminus. A single tyrosine residue (Y~700) within the C terminus is phosphorylated (red dot) when the molecule is activated. (Specific modifications for individual STATs are indicated where known.) Prior to activation, unphosphorylated STAT proteins form stable dimers in the cytoplasm, which are structurally distinct from the tyrosine-phosphorylated STAT dimers that form after activation. Unphosphorylated STAT1 and STAT5 dimerize through their N-terminal domains and through a CC:DBD domain interaction in an "antiparallel" conformation (the SH2 domains of the two molecules in the dimer point in opposite directions). STATs either may have to form dimers in order to be phosphorylated (STAT4) or may be activated as monomers.

The canonical JAK-STAT signaling pathway is initiated by binding of a cytokine ligand to a cell-surface cytokine receptor. The intracellular domains of many cytokine receptors are physically associated with tyrosine kinases of the JAK family. There are four mammalian JAKs (JAK1, 2, 3, Tyk2) that are associated with specific cytokine receptors. Binding of ligand triggers receptor dimerization/oligomerization and allows rapid transphosphorylation and activation of the receptor-associated JAKs. Activated JAKs then phosphorylate critical tyrosine residues on the receptor, which leads to recruitment of specific STATs through their SH2 domains followed by single tyrosine phosphorylation of the bound STAT. Tyrosine phosphorylation of STATs can also be stimulated by binding of growth factors to receptor tyrosine kinases (RTKs), such as epidermal growth factor receptor or platelet-derived growth factor receptor. This activation may be direct or indirect. The latter case involves the recruitment of nonreceptor tyrosine kinases (NRTKs) such as Src. Alternatively, the STATs can be tyrosine phosphorylated in a JAK-dependent manner after hormone- and chemokine-binding to G protein-coupled receptors (also known as seven-transmembrane receptors). Once phosphorylated, STAT proteins form "parallel" homo- or, in some cases, heterodimers (STAT1:STAT2, STAT1:STAT3) via reciprocal phosphotyrosine-SH2 interactions (the two SH2 domains point in the same direction). The parallel activated STAT dimer enters the nucleus via importin-α (Imp-α) dependent transport and binds to specific DNA targets. Nuclear import of different STAT proteins requires different transporters (e.g., STAT3 binds to importin-α3, STAT1 to importin-α5). In order to drive gene expression, STAT proteins cooperate with numerous other transcription factors (TFs; such as IRFs, Sp1, Jun, Fos, NF-κB, GR) and coactivators with functions in chromatin remodeling (such as p300/CBP, PCAF, GCN5, BRG1, HDACs) or in the formation of preinitiation complexes (such as the Mediator complex). Maximal transcriptional activation requires serine (S) phosphorylation of a conserved motif (L)P(M)SP in the STAT C terminus (yellow dot). Dissociation from DNA allows dephosphorylation of STATs by nuclear protein tyrosine phosphatases (N-PTPs), such as TC45 and SHP2, to complete the cycle of activation/inactivation. The STATs are stable throughout this cycle. The unphosphorylated dimer associates with the nuclear export factor, chromosome region maintenance 1 (CRM1), for transport back to the cytoplasm where it can be reactivated. Recent evidence shows that unphosphorylated STATs can enter the nucleus via importin-α-dependent (STAT2, STAT3) or carrier-independent transport (STAT 1, 3, 5). In unstimulated cells, unphosphorylated STATs (STAT 1, 2, 3, 5) constitutively shuttle between the nucleus and cytoplasm. Unphosphorylated STAT1 and STAT3 have been found to activate transcription by binding to other transcription factors (IRF1 and NF-κB, respectively).

Among the target genes of tyrosine phosphorylated STATs are the suppressor of cytokine signaling proteins (SOCS), which form a classical negative feedback loop that switches off the activity of JAKs. Other important negative regulators of JAK-STAT signaling are protein tyrosine phosphatases (PTPs) in the cytoplasm, which inactivate JAKs (SHP1, SHP2, CD45, PTP1B, TC45) and STATs (SHP2, PTP1B, and TC45). In the nucleus, STAT activity is restrained by PIAS (protein inhibitor of activated STAT) proteins, which block the DNA-binding activity of STAT dimers.

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