

JAK/STAT pathway



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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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This document contains 5 pathways and 1 reaction (see Table of Contents)

JAK/STAT pathway 7

Stable identifier: R-DME-209405



The JAK/STAT pathway is one of the main eukaryotic signalling pathways. In vertebrates, there are several ligands, receptors, JAK kinases and STAT molecules making detailed study of the system very complex. In Drosophila, the JAK/STAT pathway is much less redundant, offering one set of related ligands UPD (OS, UPD2, UPD3), a receptor Domeless (DOME), a Janus Associated Kinase Hopscotch (HOP), and a STAT transcription factor (STAT92E).

The DOME receptor, like many cytokine receptors, contains no tyrosine kinase domain. However, it is constitutively associated with the kinase HOP. The DOME receptor dimerises at the plasma membrane whereupon it binds a UPD ligand. This activates the receptor-associated HOP which are now able to phosphorylate each other and also the cytoplasmic tail of the DOME receptor. This creates a docking site for monomeric cytoplasmic STAT92E proteins which can bind via their SH2 domains. Once bound to the receptor complex, STAT92E is itself phosphorylated. It dissociates from the receptor complex and dimerises, the interaction stabilised by the SH2 domain of one molecule binding to the phospho-Tyr of the other. The dimer translocates to the nucleus where it binds to a palindromic DNA sequence in the pathway target gene promoters to activate transcription.

There are also negative regulators present in this pathway. Some are present in the nucleus and, in the case of SU(VAR)2-10 which is a Drosophila PIAS or Zimp protein, act by binding to STAT92E dimer. Others, such as the BCL6 orthologue, Ken and Barbie (KEN), bind to DNA sequences on target genes which overlap with STAT92E binding sites. There is a protein tyrosine phosphatase, PTP61F, that exists in two differently spliced forms. One is active in the cytosol and dephosphorylates HOP and STAT92E while the other dephosphorylates STAT92E in the nucleus.

A truncated version of STAT92E, deltaNSTAT92E, that lacks the N-terminal 133 amino acids has also been found. It is believed this truncated STAT forms homodimers and heterodimers with full-length STAT92E. Increasing the deltaNSTAT92E to STAT92E ratio in overexpression and RNAi experiments results in the repression of target gene transcription. This may be due to the truncated protein failing to attract coactivators or failing to form tetramers, necessary for activation of certain genes and assembled by the N-terminal domains, when two STAT binding sites for dimers are close together (Henrikson et al, 2002; Yan et al, 1996).

In mammalian systems, SOCS proteins negatively influence the JAK/STAT pathway. Activated STATs stimulate transcription of the SOCS genes and the resulting SOCS proteins bind phosphorylated JAK kinases and their receptors to turn off the pathway in a simple negative feedback loop. SOCS can affect their negative regulation in three ways. First, by binding phospho-Tyr on the receptors to physically block STAT recruitment. Second, by binding directly to JAKs or the receptors to specifically inhibit JAK kinase activity. Third, by interacting with elongin BC complex and Cullin 2, facilitating the ubiquitination of JAKs and, presumably, the receptors. Ubiquitination of these targets decreases their stability by targeting them for proteasomal degradation (Rawlings et al, 2004).

Three SOCS proteins have been identified in Drosophila: SOCS36E, SOCS44A, and SOCS16D. At the present time, there is no evidence to demonstrate a physical interaction between Drosophila SOCS proteins and another protein such as HOP or a receptor.

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Formation of the activated receptor complex 7

Location: JAK/STAT pathway

Stable identifier: R-DME-209209





Literature references

Arbouzova, NI., Zeidler, MP. (2006). JAK/STAT signalling in Drosophila: insights into conserved regulatory and cellular functions. *Development*, 133, 2605-16. 🛪

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Formation of the activated STAT92E dimer and transport to the nucleus **7**

Location: JAK/STAT pathway

Stable identifier: R-DME-209228





Literature references

Arbouzova, NI., Zeidler, MP. (2006). JAK/STAT signalling in Drosophila: insights into conserved regulatory and cellular functions. *Development*, 133, 2605-16. 🛪

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Phosphorylated STAT92E dimer activates transcription 7

Location: JAK/STAT pathway

Stable identifier: R-DME-209307

Type: transition

Compartments: nucleoplasm



Once in the nucleus, the phosphorylated STAT92E dimer binds to a palindromic DNA sequence in the promoters of the pathway target genes. This now enables transcription to be activated.

Literature references

- Small, S., Darnell JE, Jr., Desplan, C., Dearolf, CR., Yan, R. (1996). Identification of a Stat gene that functions in Drosophila development. *Cell*, *84*, 421-30. ¬
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Transcriptional repression by nuclear factors 7

Location: JAK/STAT pathway

Stable identifier: R-DME-210671





Literature references

Arbouzova, NI., Zeidler, MP. (2006). JAK/STAT signalling in Drosophila: insights into conserved regulatory and cellular functions. *Development*, 133, 2605-16. 🛪

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Dephosphorylation by PTP61F phosphatases 7

Location: JAK/STAT pathway

Stable identifier: R-DME-210688





Literature references

Arbouzova, NI., Zeidler, MP. (2006). JAK/STAT signalling in Drosophila: insights into conserved regulatory and cellular functions. *Development*, 133, 2605-16. 🛪

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