The JAK/STAT Pathway

Douglas A. Harrison

Department of Biology, University of Kentucky, Lexington, Kentucky 40506

Correspondence: DougH@uky.edu

Cellular responses to dozens of cytokines and growth factors are mediated by the evolutionarily conserved Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway (Fig. 1). These responses include proliferation, differentiation, migration, apoptosis, and cell survival, depending on the signal, tissue, and cellular context. JAK/STAT signaling is essential for numerous developmental and homeostatic processes, including hematopoiesis, immune cell development, stem cell maintenance, organismal growth, and mammary gland development (Ghoreschi et al. 2009).

Janus kinases (JAKs) were identified through sequence comparisons as a unique class of tyrosine kinases that contain both a catalytic domain and a second kinase-like

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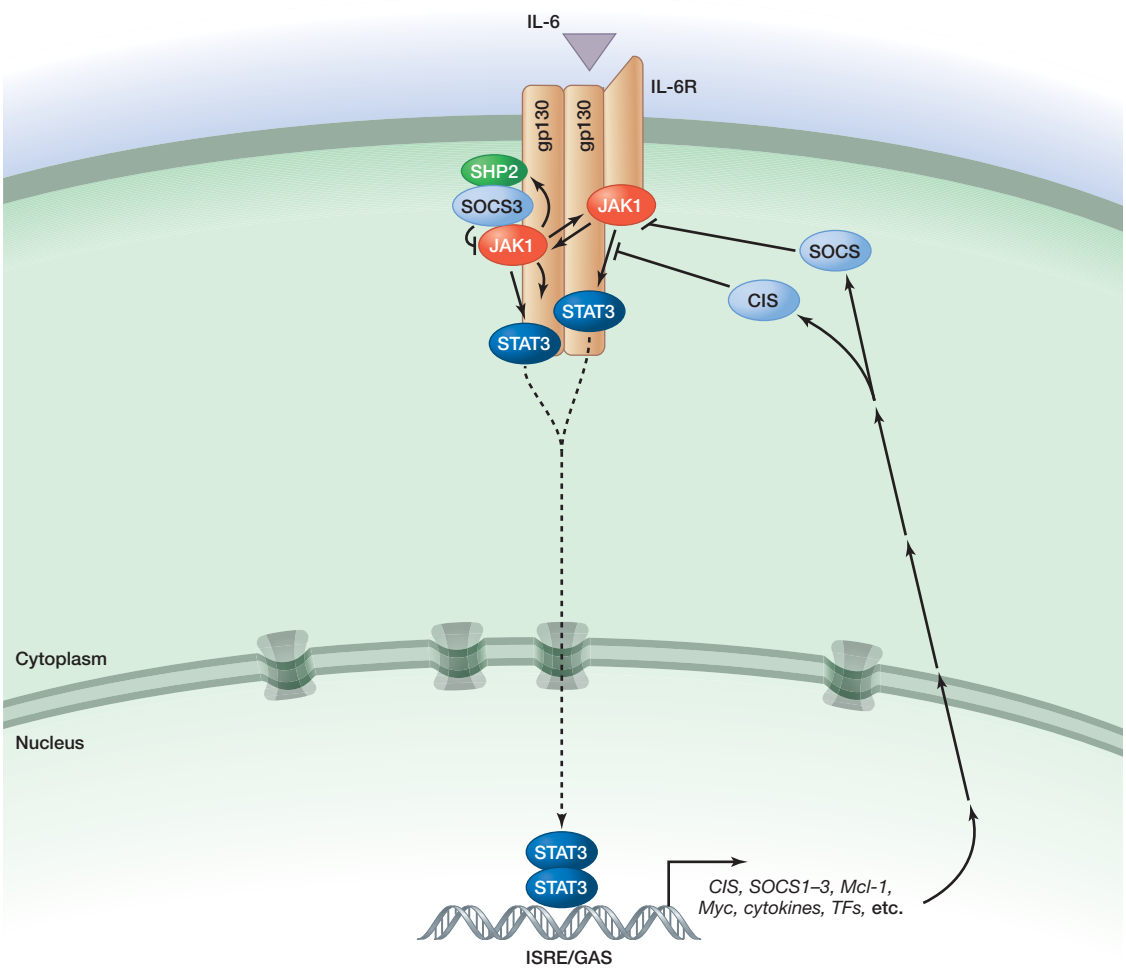

Figure 1. The JAK/STAT pathway (simplified view).

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domain that serves an autoregulatory function, hence the homage to the two-faced Roman god. They were functionally linked to STATs and interferon signaling in powerful somatic cell genetic screens (Darnell et al. 1994; Schindler and Plumlee 2008). The JAK/STAT cascade is among the simplest of the conserved metazoan signaling pathways. The binding of extracellular ligand leads to pathway activation via changes to the receptors that permit the intracellular JAKs associated with them to phosphorylate one another. Trans-phosphorylated JAKs then phosphorylate downstream substrates, including both the receptor and the STATs. Activated STATs enter the nucleus and bind as dimers or as more complex oligomers to specific enhancer sequences in target genes, thus regulating their transcription (Fig. 2).

In mammals, there are four members of the JAK family and seven STATs. Different JAKs and STATs are recruited based on their tissue specificity and the receptors engaged in the signaling event (Schindler and Plumlee 2008). In invertebrates, the *Drosophila* JAK/STAT pathway has been extensively studied and comprises only one JAK and one STAT (Arbouzova and Zeidler 2006). Although the canonical JAK/STAT pathway is simple and direct, pathway components regulate or are regulated by members of other signaling pathways, including those involving the ERK MAP kinase, PI 3-kinase (PI3K), and others. Furthermore, non-canonical JAK and STAT activities influence the global transcriptional state through modification of chromatin structure (Li 2008; Dawson et al. 2009).

Human JAK mutations cause numerous diseases, including severe combined immune deficiency, hyperIgE syndrome, certain leukemias, polycythemia vera, and other myeloproliferative disorders (Jatiani et al. 2010). Because of the causative role in these diseases and their central significance in immune response, JAKs have become attractive targets for development of therapeutics for a variety of hematopoietic and immune system disorders (Pesu et al. 2008; Haan et al.

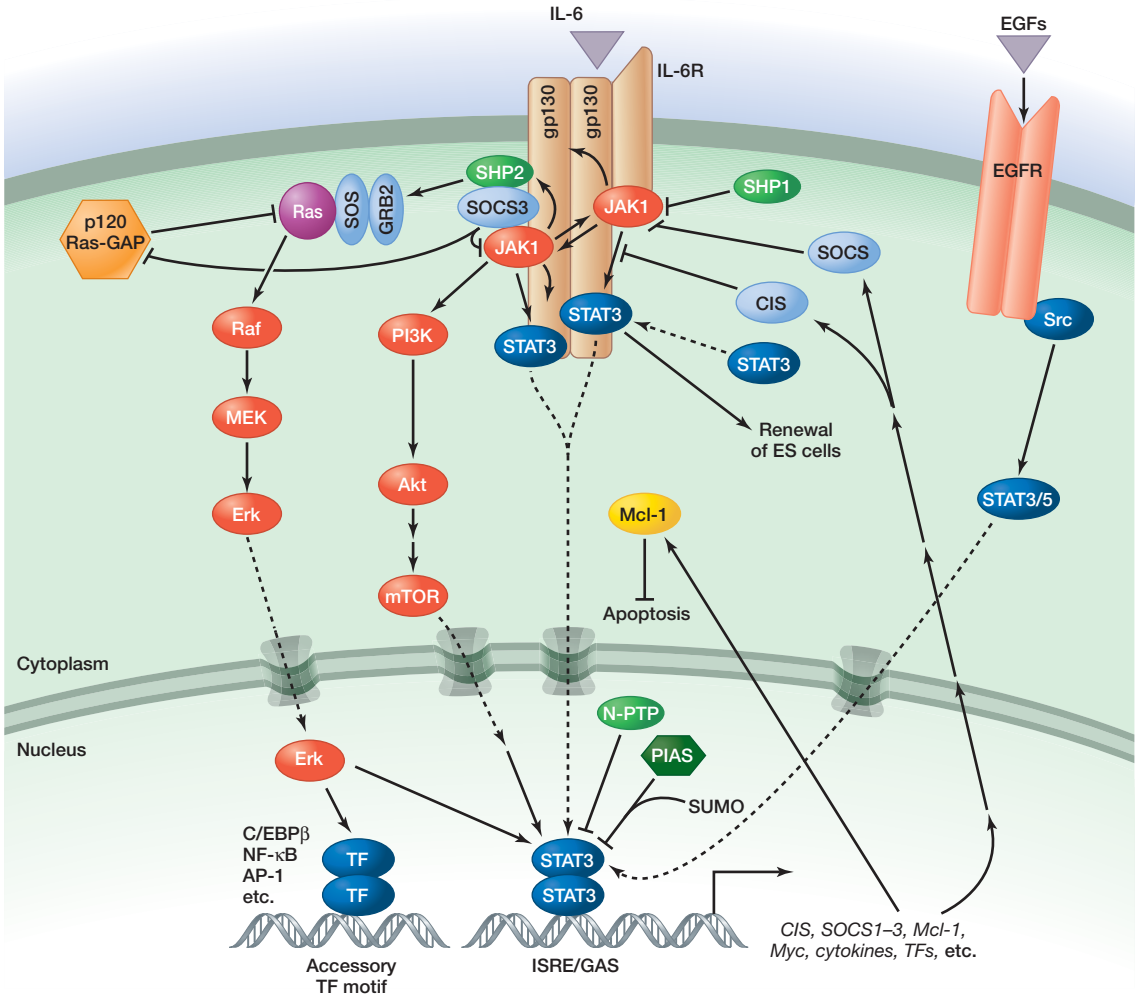

Figure 2. The JAK/STAT pathway.

2010). Owing to the pleiotropy of the JAK/STAT pathway, agents that selectively perturb specific family members are being sought.

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