The Continuing Fascination with Jaks and Stats: An Introduction

Thomas Decker and Mathias Müller

The origins of the discovery of Jak-Stat signal transduction date back to the late 1980s when research groups headed by Jim Darnell, Ian Kerr and George Stark were fascinated by the fact that gene transcription could be induced within minutes after treating cells with type I interferons (IFN-I). The speed with which a signal generated by the plasma membrane–associated IFN-I receptor travelled to nuclear target genes suggested few intermediate steps. The Darnell, Kerr and Stark labs identified bifunctional signal transducers and activators of transcription (Stats) as responsible for IFN-induced transcription by using complementary biochemical and genetic approaches (reviewed in Darnell et al. 1994). Shortly after this seminal discovery, the labs of Sandra Pellegrini, Jim Ihle and Christine Carter-Su independently identified non-receptor protein tyrosine kinases (pTK) in the signaling pathways stimulated by, respectively, the IFN, erythropoietin and growth hormone receptors (Argetsinger et al. 1993; Velazquez et al. 1992; Witthuhn et al. 1993). The same kinases had previously emerged from screens for novel pTKs, conducted in the labs of John Krolewski and Andrew Wilks and named Janus kinases by the latter (Firmbach-Kraft et al. 1990; Wilks et al. 1991). With recombinant Jaks and Stats at hand it was possible to reconstitute IFN signaling between receptor and nuclear targets with just two components: receptor associated Jaks that activate Stats by tyrosine phosphorylation. Tyrosine phosphorylated Stats localize to the cell nucleus and bind to promoter DNA of specific target genes (Fig. 1).

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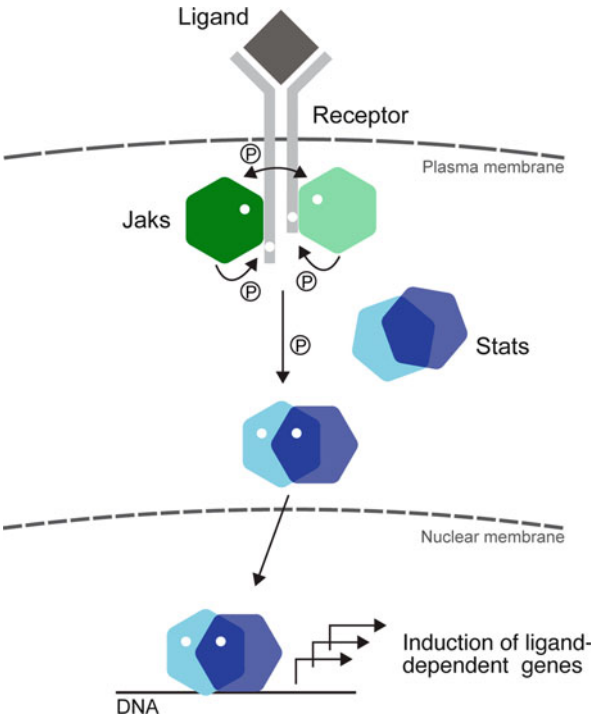

Fig. 1 The essential components of Jak-Stat signal transduction. Cytokine binding alters the conformation of the receptor complex, causing the Jak kinases to phosphorylate and activate each other. Phosphorylation of receptor tyrosines creates docking sites for the Stat SH2 domains. Stats are phosphorylated on a single tyrosine residue where upon they form dimers competent of nuclear translocation and able to associate with DNA binding sites. *White circles* symbolize phosphorylated tyrosines

Today Jak-Stat signal transduction is firmly established as the major route from all class 1 and class 2 cytokine receptors to the cell nucleus. In addition, it contributes to signaling by receptor tyrosine kinases and G-coupled receptors. Therefore it is not surprising that Jaks and Stats play important roles in organisms ranging from slime molds and insects to mammals. Virtually every complex biological process between embryonic development and aging is influenced by Jak-Stat signal transduction. Owing to its overwhelming importance this pathway has rapidly entered text books as a major signaling paradigm. So what is new and justifies yet another book reviewing Jak-Stat signal transduction?

Basics: Jak-Stat research continues to fill knowledge gaps and to produce unexpected findings. Starting with Jaks, whose structure is still not completely solved, the book reviews the state-of-the-art and the intramolecular regulation of Jak activity. Insect Stats were shown to display 'noncanonical' functions independently of tyrosine phosphorylation that regulate chromatin function. In mammalian cells and organisms noncanonical Stat signaling exerts transcriptional control. Moreover, Stat3 molecules lacking phosphotyrosine enter mitochondria and impinge on the respiratory activity of these organelles. This provides one of many links between Stats and cell metabolism that have recently emerged. Mitochondrial Stat3 may contribute to the Warburg effect, the predominant role of glycolysis in the provision of energy to transformed cells.

Early reports addressing mechanistic aspects of Stat activation and dimerization supported the notion that dimers capable of nuclear translocation formed from Stat monomers. The book provides a detailed review of the activation mechanism by dimer reorientation, rather than formation, which accommodates new findings and crystal structures from phosphorylated and unphosphorylated Stats. In addition this chapter presents new ideas of how the subcellular localization of Stats is regulated by postranslational modification.

Basic insight into mechanisms of transcriptional control by Stats has advanced in part because of the much improved general understanding of the molecular machinery regulating the initiation and elongation steps of transcription. Insight into the complex scenario established by the molecular machines mediating nucleosome remodeling, or the activities of histone and RNA polymerase modifying enzymes allows to investigate and understand how Stats interact with these molecules. Detailed analyses of promoter chromatin and associated proteins also provide a better understanding of how different cytokines and signals crosstalk to Stats in the form of gene co-regulation with other transcription factors. Furthermore, the opportunities provided by applying massive parallel sequencing in the context of ChIP-Seq and RNA-Seq technologies open up new prospects of Stat transcription factors embedded into genome-wide landscapes of histone modifications that define distinct functional states of chromatin.

Organismic homeostasis: Articles in this book take a close look at the role of Stats in the generation of hematopoietic cells and, in particular, natural killer (NK) cells, dendritic cells, T and B lymphocytes as regulators and effectors of immunity to infection and cancer. The fascination of Stat biology arises from the fact that the agonistic activity of different family members defines distinct lineages and subpopulations of both DC and T cells. At the same time their antagonistic activity may suppress the development of alternative developmental avenues. Among CD4 + T cells each of the major subsets can be defined by the activity of a different Stat. NK cells provide a striking example how different Stats regulate differentiation, and activation in one cell type.

Stats in disease: Many chapters in this book review new findings that link both physiological Jak-Stat activity to protection from disease and aberrant Jak-Stat signaling to cancer or infectious disease.

Jak2 and Stat5 stand out as regulators of hematopoiesis. Consistent with this both proteins are able to promote leukemic cell transformation if not properly controlled. Several contributions describe molecular mechanisms leading to the leukemic development and highlight the role of mutant Jak kinases as well as the prospect of treating such leukemias with recently identified Jak inhibitors.

Jak-Stat activity at the wrong place or time also favors the development of solid cancers. For example, Jak2, Stat3 and Stat5 promote the establishment or growth of breast cancers each in their own way. Particularly Stat3 is a driving force behind many solid cancers but studies reviewed in a contribution on inflammation-associated colon cancer suggest that cell and organ context determine the net activity of Stat3 as an oncogene or tumor suppressor as well as its antagonistic relationship to Stat1.

IFN signal through the prototypic Jak-Stat pathway to induce an antiviral state. Chapters dealing with the role of Jaks and Stats in infectious disease present the current understanding of the antiviral state as the combined activity of Stat target gene products. They also show how Stats are subject to viral evasion strategies. Since immunological activities of IFN are not limited to the struggle with viral pathogens, recent examples of their impact on bacterial infection are presented to show the pleiotropy of IFN action and the unpredictability of their impact on the course of infection.

This brief description of the book is much less intended to inform comprehensively about its content than it is to convince readers that Jak-Stat research is active, dynamic and timely and that many of the findings described by experts in their field could not have been presented in a similar book a few years ago. We thank our colleagues for their significant time investment in preparing each chapter.

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