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Cytokine Signaling: Birth of a Pathway

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Cytokine biology is now recognized as a fundamental component of immunology and the actions of cytokines are understood to be essential mechanisms underlying host defense, immunoregulation, and autoimmunity. Moreover, cytokines themselves and cytokine antagonists have become some of the most successful new drugs. On a more basic level, the biochemistry of cytokine action has become a paradigm for understanding rapid, evolutionarily conserved membrane-to-nucleus signal transduction, offering remarkable opportunities for understanding how extracellular cues are sensed and translated into the control of gene expression. As we approach the 20th anniversary of the discovery of the Jak-STAT pathway, it is useful to reconsider the pivotal insights that led to these discoveries, to briefly comment on the present status of this field, and consider future challenges.

Members of the Type I/II cytokine receptor superfamily like erythropoietin, growth hormone, prolactin, and IFN were first purified more than 50 years ago. Colony stimulating factors began to be studied in the 1960s and '70s, and the discovery of the first lymphokines and interleukins followed quickly thereafter. Thus, knowledge of the criticality of cytokines is by no means new. Less obvious was any notion that these factors were all structurally related and used common elements in mediating their biological actions. With molecular cloning and structural analysis, it began to become clear that the 4-α helical family of cytokines comprises a rather large group of secreted factors with diverse functions (1). Nonetheless, the question remained (and remains): how do these diverse factors exert their unique effects on cell behavior?

During the late 1980s, the Darnell and Stark labs began to tackle this question by identifying rapidly inducible IFN-stimulated genes (ISGs)(2–4). With the isolation of genomic clones of these inducible genes, it was appreciated that they shared promoter elements that were responsible for IFN-mediated induction. Two types of elements were identified: IFN-stimulated response elements (ISRE) and IFN-γ-activated sites (GAS elements). Jim Darnell, David Levy, Thomas Decker, and colleagues began to identify nuclear complexes induced by IFNs that bound to ISREs and soon recognized that the ISRE-bound complex ISGF3 comprised multiple subunits(5–7). The cloning of these constituents led to the identification of the first two signal transducer and activator of transcription (STAT) proteins, STAT1(8) and STAT2(9). The third component of the complex was a member of the IFN response factor (IRF) family, IRF-9(10). Complexes bound to GAS (GAFs) also turned out to be STATs. Independent work from other labs, interested in prolactin(11) and IL-6 signaling(12), identified similar complexes, the cloning of which also demonstrated the existence of new family members, STAT5 and STAT3, respectively(13 – 15) (13).

Many of the aforementioned discoveries represent groundbreaking work. However, the exciting finding we chose to highlight was the discovery that these new factors not only

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bound DNA, but they were also tyrosine phosphorylated, making it clear that this new transcription factor family might be directly linked to a signaling pathway. Schindler et al. (14) analyzed the covalent modifications and trafficking of the constituents of the ISGF3 complex. Using metabolic labeling, they showed IFN-dependent tyrosine phosphorylation and translocation from the cytoplasm to the nucleus where, presumably, active transcription was induced. The figure in the paper depicting the findings described many of the features we now associate with STATs. The nature of the kinase responsible for such effects was still unknown but was presumed to be cytoplasmic in nature.

Another equally striking feature of the STATs was the presence of an SH2 domain, a recognition motif for phosphotyrosine, which was further evidence of linkage to the action of tyrosine kinases. A key subsequent finding was that STATs bound cytokine receptors (15). This put STATs in the position of being receptor-to-nucleus shuttles, directly connecting events from the extracellular milieu to de novo transcription(16).

The importance of tyrosine phosphorylation as a mechanism of signal transduction became widely appreciated with the discovery of various oncogenes that were themselves tyrosine kinases (PTK) and the cloning of receptor tyrosine kinases like the insulin receptor and the epidermal growth factor receptor. The race was on to identify other tyrosine kinases, and investigators used PCR-based approaches or low stringency screening to identify new members of this family. Out of such screens came tyrosine kinase 2 (Tyk2)(17, 18), Janus kinase (Jak)1 and Jak2 (19), which were recognized to represent a new class of PTK but at this stage lacked a clearly assigned physiological function.

In the meantime, George Stark and Sandra Pellegrini were engineering mutant cells that were defective in IFN-α/β and IFN-γ signaling. This somatic cell mutagenesis approach yielded several classes of mutant lines(20), which were then used to identify a component that restores signaling. The approach led to an explosion of papers that established the criticality of various Jaks and STATs in signaling via different cytokines(16). The study by Velazquez et al. (21) was the first report showing that defective IFN-α signaling was complemented by a clone encoding a Jak, in this case Tyk2. The report linked the Jaks with a function for the first time – and it was an important one. Not only were Jaks involved in cytokine signaling, they were absolutely essential elements.

The approach of Pellegrini and colleagues involved the use of drug-sensitive cell lines mutagenized to select for insensitivity to IFN-α. Revertants were then isolated and genomic clones that conferred the IFN-sensitive phenotype were identified by construction of a cosmid library and transfection back into IFN-resistant cells. The cosmid responsible for phenotype conversion contained the gene coding for the tyrosine kinase Tyk2 which, at that point, had unknown function but exhibited homology to Jak1. This study provided unambiguous genetic evidence of the essential function of a Jak in IFN signaling. The schematic model provided in the paper inserts Tyk2 as the receptor-associated proximal factor responsible for phosphorylation of ISGF3.

Other complementation studies quickly filled in the gaps, placing different Jaks and STATs with different cytokines(22–27). Related studies showed that Jaks physically associated with cytokine receptors. The next phase in Jak/STAT biology was to assess whether data generated in a single mutant cell line had in vivo relevance. The answer was an unequivocal yes. Strikingly, in vivo evidence of the importance of the Jak/STAT pathway came from a human primary immunodeficiency, Jak3-SCID(28, 29). Within two months, the same phenotype was revealed in Jak3-knockout mice (30, 31), and a few months later the phenotype of STAT1-knockout mice was reported(32, 33). STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6 knockouts were soon generated and the message was clear:

the Jak/STAT pathway was fundamentally important for the development and differentiation of diverse cell types (34). Knocking out Jaks and STATs had profound effects on immune cells, host defense, and immunoregulation. Thus, it became clear very quickly that George Stark's mutant cell lines really did predict the essential functions of the Jaks in signaling by Type I/II cytokines. However, the impact of Jak-STAT signaling was far more extensive than just IFN signaling.

The attempt to elucidate IFN-inducible genes was accelerated by microarray technology, which showed that hundreds of genes were induced by these cytokines; however, this technology did not allow one to discriminate direct vs. indirect actions of STATs. Which of the genes were true STAT target genes? Newer technologies for mapping genome-wide transcription factor binding include ChIP-on-chip and ChIP-seq technology, and these technologies have quickly expanded our understanding of STAT action(35). Coupling ChIP-seq data with expression data (either microarray or more recently RNA-seq data), now readily discriminates direct and indirect effects of STATs. Currently, genome-wide binding of all STATs have been profiled by ChIP–seq, and the original datasets are publicly available through the Gene Expression Omnibus (GEO) repository. Moreover, this technology permits one to examine the impact of STATs, not only on transcription but also on epigenetic changes in differentiating cells (36).

During the last decade, more and more evidence for direct relevance of the Jak-STAT pathway in humans is emerging. We now know that gain-of-function *JAK2* mutations result in the myelofibrosis spectrum of disorders(37), and many malignancies are associated with constitutive activation of the Jak-STAT pathway. Loss-of-function *STAT1* mutations are associated with impaired cellular responses to IFN-γ and susceptibility to viral and mycobacterial infections(38, 39), but conversely, gain-of-function *STAT1* mutations underlie a disorder termed chronic mucocutaneous candidiasis(40). These *STAT1* mutations result in enhanced IFN signaling and suppression of IL-17 production. Dominant-negative mutations of *STAT3* in humans also have profound effects on Th17 cell generation. Such *STAT3* mutations result in a disorder known as hyper-IgE syndrome (HIES; also known as Job's syndrome), a classic primary immunodeficiency(41, 42). Homozygous missense mutations of *STAT5b* are linked to a growth hormone insensitivity phenotype associated with autoimmunity and impaired Treg cell function(43).

The advent of large-scale genome-wide association studies has also implicated cytokines, Jaks, and STATs in more common complex autoimmune diseases. For example, polymorphisms of *IL-23R*, *JAK2* and *STAT3* are linked to susceptibility to inflammatory bowel disease and ankylosing spondylitis(44). Similarly, a variant allele of *STAT4* has been found to be associated with rheumatoid arthritis, systemic lupus erythematosus (SLE) (43, 45), Sjögren's syndrome(46), and inflammatory bowel disease(47). SLE is associated with an "interferon-signature" and STAT4, like STAT1, is activated by type I IFNs (48). Consistent with this idea, polymorphisms of *TYK2* may also be associated with SLE (49).

Finally, the clear genetic evidence of the essential functions of Jaks had equally clear implications for the development of a new class of immunosuppressive drugs(50). The discovery that *JAK2* mutations underlie myeloproliferative disorders provided a logical rationale for targeting this kinase in the clinical setting. Remarkable progress has been made in the generation of Jak inhibitors. Tofacitinib was the first clinically useful, highly selective and potent, oral Jak inhibitor and is now showing efficacy in rheumatoid arthritis, psoriasis, Sicca syndrome, and the prevention of renal transplant rejection. Ruxolitinib, a Jak1 and Jak2 inhibitor, has shown efficacy in myeloproliferative disease (51). Many other Jak inhibitors are at different levels of development at this time.

In conclusion, we have endeavored to put the studies by Schindler et al. and Velazquez et al. in historical and biological context. What arose from efforts to understand the rapid action of IFN on gene expression was the discovery of a new, linear biochemical pathway of membrane-to-nucleus signal transduction, which had implications for dozens of factors critical for human health and disease. Still, there is much to learn. Recent evidence points to roles of STATs in mitochondrial function (52, 53) and Jaks as histone modifiers(54). The ChIP-seq approach has vastly expanded our understanding of STAT action, but the challenge remains to decipher how STATs regulate transcription and control the epigenome on a biochemical and mechanistic level. In one sense, the pathway is remarkably simple and elegant, but do we really know all the elements? Hints from *Drosophila* suggest that there is more complexity(55). In addition, STATs work in concert with other transcription factors, including NF-κB. This will all need to be sorted out. The challenge, of course, is to really understand specificity in signaling; hopefully, genomic approaches will help elucidate this aspect of cytokine action as well.

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