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JAKs and STATs in Immunoregulation and Immune-Mediated Disease

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Summary

A landmark in cell biology, the discovery of the JAK-STAT pathway provided a simple mechanism for gene regulation that dramatically advanced our understanding of the action of hormones, interferons, colony stimulating factors, and interleukins. As we learn more about the complexities of immune responses, new insights into the functions of this pathway continue to be revealed, aided by technology that permits genomewide views. As we celebrate the 20th anniversary of the discovery of this paradigm in cell signaling, it is particularly edifying to see how this knowledge has rapidly been translated to human immune disease. Not only have genomewide association studies demonstrated that this pathway is highly relevant to human autoimmunity but targeting JAKs is now a reality in immune-mediated disease.

The importance of interferons (IFNs) and hormones such as erythropoietin, growth hormone and prolactin has been recognized for more than half a century. With the advent of molecular biology era came the discovery of a plethora of other cytokines, which we now know regulate all aspects of cell development and differentiation. Cytokines, though, represent a collection of structurally distinct ligands that bind to different classes of receptors. A major subgroup of cytokines, comprising roughly 60 factors, bind to receptors termed Type I/II cytokine receptors. Cytokines that bind these receptors include Type I IFNs, IFN-γ, many interleukins and colony stimulating factors. From an immunology perspective, these cytokines are important for initiating innate immunity, orchestrating adaptive immune mechanisms and constraining immune and inflammatory responses.

As discussed by Darnell and Stark in this issue, the discovery of JAKs and Stats stemmed from attempts to understand how IFNs exerted their effect. However, we now know that all Type I/II cytokine receptors selectively associate with JAKs (JAK1, JAK2, JAK3 or TYK2). For these receptors, activation of the receptor-bound JAKs is critical for initiating phosphorylation of the cytokine receptor and subsequent recruitment of one or more STATs. Over the past two decades, multiple lines of evidence have clearly established the roles of different JAKs and STATs in mediating the effect of cytokines that use Type I/II cytokine receptors in immunoregulation, host-defense and immunopathology (Darnell et al., 1994; Leonard and O'Shea, 1998; O'Shea and Murray, 2008).

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JO'S and National Institutes of Health (NIH) hold patents related to targeting JAKs as targets for immunomodulatory agents and have a Collaborative Research Agreement and Development Award with Pfizer.

As our understanding of these processes have become more sophisticated, additional roles for this pathway have been recognized. For instance, with the identification of "newer" helper subsets comes the appreciation of important roles of STATs in these subsets as well as new roles for STATs in recognized subsets. As our understanding of the mechanisms involved in innate immunity expands, new roles of STATs in these processes become evident. In addition, new technologies also allow comprehensive views of STAT action whereas insights from genomewide association studies clearly implicate JAKs and STATs in human autoimmunity. Finally, the possibility of targeting the JAK-STAT pathway in autoimmune disease has now become a reality. In this review, we will try to briefly discuss these exciting advances. We recognize that this is a challenging task given the immense amount of exciting work in this field. In the interest of brevity, we have been forced to limit our discussion and we apologize in advance in advance for any omissions.

New insights into the immunoregulatory roles of JAKs and STATs

When the STATs were first discovered, the palette of helper T cells was simple - Th1 and Th2 cells. TYK2, JAK2 and STAT4 were found to be critical for IL-12 signals and Th1 differentiation whereas JAK1, JAK3 and STAT6 were key for IL-4 signaling (Darnell et al., 1994; Leonard and O'Shea, 1998; O'Shea and Murray, 2008). In various models of infectious disease and immune-mediated disease, deficiency of STAT4 and STAT6 had the expected outcomes [Goenka, 2011 #3629; Wurster, 2000 #3633; Murphy, 2000 #3636; [Oestreich, 2012 #3692; Paternoster, 2011 #3436].

New roles for STATs in "old" helper T cell subsets

It is now appreciated, however, that Th2 responses can occur in the absence of STAT6(van Panhuys et al., 2008). In fact, early Th2 differentiation can by driven by IL-2, which upregulates GATA3 and enhances IL-4 receptor expression(Paul, 2010). Activated by IL-2, STAT5A/B can directly bind the *Il4r* gene and promote its expression (Liao et al., 2008); however, STAT5A/B can also enhance Th1 responses by regulating *Tbx21* and *Il12rb2* (Liao et al., 2011b). Interestingly, STAT3 is also a contributor to Th2 differentiation and binds Th2-associated gene loci (Liao et al., 2008; Stritesky et al., 2011). Thus, in contrast to the previous views equating STAT6 with Th2 differentiation, it appears that this process involves more subtle and complex interactions of STAT3, STAT5 and STAT6 with the relevant genetic loci.

Role of STATs in Treg cell function

Along with TGFβ, IL-2 is a key regulator of differentiation of Treg cells in the thymus and the periphery. As mediators of IL-2 signaling, STAT5A/B are critical for the differentiation of Treg cells. Their effect is very direct in that STAT5/A directly bind the *Foxp3* gene and drive expression of this key gene (Burchill et al., 2007; Yao et al., 2006; Yao et al., 2007; Zorn et al., 2006). In addition, STAT5A/B regulate *IL2ra*, expression of which is also a critical for Treg cells. Surprisingly, STAT3 also has an important role in Treg cell function (Chaudhry et al., 2009). Deletion of STAT3 in Treg cells results in lethal gastrointestinal disease, but the effect is selective and does not globally impair Treg cell function. Treg cells retain the ability to limit T cell proliferation but have impaired ability to block Th17-mediated pathology. Of interest, STAT3 physically associates with Foxp3.

Roles of STATs in "new" helper cell subsets

With the recognition of a multiplicity of fates for T cells, it has become clear that STATs are also key elements for these "new" subsets. We now know that STAT3 is critical for Th17 differentiation both in mouse and humans, mediating signals by IL-23 and IL-6(Chen et al., 2006; Mathur et al., 2007; Milner et al., 2008; Yang et al., 2007). STAT3 regulates Th17

differentiation by directly binding *Il17a/f*, *Rorc* and *Il23r*, as well as other genes involved in Th17 differentiation (Durant et al., 2010).

Interestingly, IL-2, acting via STAT5A/B, is an important negative regulator of Th17 differentiation (Laurence et al., 2007). In this case, the action of STAT5A/B action is very direct – they compete with STAT3 binding to the *Il17a/f* locus (Yang et al., 2011). Intriguingly, by sequestering IL-2, regulatory T cells promote Th17 differentiation (Chen et al., 2011b; Pandiyan et al., 2011).

One of the newest "lineages" of CD4 T cells is the follicular helper T cell, which provides help to B cells in germinal centers. Cytokines like IL-6 and IL-21 act on STAT3 and promote expression of Bcl6 and other molecules that contribute to the phenotype and function of this subset (Batten et al., 2010; Eddahri et al., 2009; Nurieva et al., 2008). However, IL-12 and STAT4 also turn out to be drivers of Tfh cells (Nakayamada et al., 2011; Schmitt et al., 2009). STAT4 directly binds many genes involved in Tfh differentiation, including *Bcl6* and *Il21*. Conversely, IL-2 inhibits Tfh differentiation and once again, the action of STAT5 appears to be very direct. It competes with STAT3 binding to the *Bcl6* locus and also promotes expression of *Prdm1*, which encodes Blimp1 (Johnston et al., 2012; Nurieva et al., 2012; Weinmann, 2012).

Perhaps less surprising given its role in transmitting IL-4 signals, STAT6 is an important regulator of Th9 cells (Goswami et al., 2011).

STATs and CD8 memory

IL-7 and IL-15 are important for CD8 memory and accordingly STAT5A/B are also important (Hand et al., 2010; Tripathi et al., 2010). STAT5A/B are essential for the survival of viral-specific CD8 T cells and expression of Bcl-2. In contrast though, in the setting of viral infection, the numbers of CD4 effector T cells are unaffected by the absence of STAT5A/B. However, STAT5A/B are not the only family members important for CD8 cell function; STAT3 is also important, mediating signals by IL-10 and IL-21 (Cui et al., 2011). Expression of such key molecules as Eomes, Bcl-6, Blimp-1, and Socs-3 are all reduced in STAT3-deficient CD8 T cells. A similar defect in CD8 T cell memory was seen in patients with hyperimmunoglobulin E syndrome and dominant-negative *STAT3* mutations(Siegel et al., 2011).

STAT5 in B cells

IL-7, acting via STAT5A/B, is important in B lymphopoiesis, controlling survival and development (Malin et al., 2010). Conversely, the B cell adapter, BLNK, antagonizes IL-7 signaling via inhibition of JAK3, and absence of BLNK leads to constitutive JAK-Stat activation and leukomogenesis(Nakayama et al., 2009).

STATs and innate immunity

STATs also have numerous functions in innate immunity – too many to review in detail in a short review(Murray, 2007; O'Shea and Murray, 2008). The importance of STAT1 in mediating IFN effects has long been recognized as has the role of STAT3 in IL-6 signaling and the acute phase response. CSFs and cytokines like GM-CSF, G-CSF and IL-5, which regulate myeloid development, also signal via STATs. Consequently, STATs have key functions for neutrophils and macrophages (Croker et al., 2004; Lee et al., 2002; Nguyen-Jackson et al., 2010; Panopoulos et al., 2006; Zhang et al., 2010a). GM-CSF inhibits Flt3L-mediated plasmacytoid DC production and conventional DC growth and STAT5 is important in this process(Esashi et al., 2008). In contrast, STAT3 is important for the expansion of DC progenitors.

The importance of IL-22, acting via STAT3, in regulating the barrier function of epithelial cells and wound repair is a topic of considerable interest (Sonnenberg et al., 2011). Like IL-10, IL-22 is produced by and acts on innate immune cells, and has critical anti-inflammatory properties (Sonnenberg et al., 2011; Zenewicz and Flavell, 2011). Precisely how STAT3 promotes inflammation in some circumstances and inhibits in others is an important, but challenging question (El Kasmi et al., 2006). STAT3 can negatively regulate IFN responses and has been proposed to inhibit TLR signaling either by inducing anti-inflammatory molecules or by a direct suppression of NF-κB (Wang et al., 2011). Nonetheless, a clear understanding of the pro- and anti-inflammatory actions of STAT3 remains elusive.

Recently, the role of innate immune cells in promoting Th2 responses has become increasingly apparent (Oliphant et al., 2011; Saenz et al., 2010). Thymic stromal lymphopoetin (TSLP) in particular is an important Type I cytokine that promotes allergic responses. It acts on multiple cells, but a critical effect is on basophils, which are major producers of IL-4 (Siracusa et al., 2011; van Panhuys et al., 2011)The identity of the JAKs responsible for signaling had been enigmatic, but we now know that TSLP signals via JAK1 and JAK2 to activate STAT5 (Rochman et al., 2010).

In addition to the classical mode of activating macrophages via IFN-γ, the appreciation of the importance of Th2 cytokines to generate alternatively activated macrophages (AAM) is now recognized (Gordon and Martinez, 2010). AAM appear to be important in a range of processes including host defense, fibrosis, metabolic regulation, obesity and cancer. As IL-4 and IL-13 are major drivers of the AAM, STAT6 is a key player for these cells. STAT6 is important in regulating insulin action, lipid metabolism and expression of proliferation-activated receptor isoforms (Ricardo-Gonzalez et al., 2010; Szanto et al., 2010). Very recently, AAM and STAT6 have been implicated in the mammalian stress response, the response to cold (Nguyen et al., 2011). Intriguingly, AAM secrete catacholamines in a STAT6-dependent manner and induce thermogenic gene expression in brown adipose tissue and lipolysis in white adipose tissue. Beyond their role as transcription factors, a direct role of STATs in mitochondrial function makes the argument for key roles in metabolism even more compelling (Gough et al., 2009; Potla et al., 2006; Wegrzyn et al., 2009).

While it has long been recognized that viruses can disrupt IFN signaling by disrupting STAT signaling (Ramachandran and Horvath, 2009), recent work shows that *T. gondii* alters host response by injecting a kinase, ROP16 that activates both STAT3 and STAT6 (Butcher et al., 2011; Saeij et al., 2007). In macrophages, the effect is down-regulation of proinflammatory cytokine signaling and deviation to an alternatively activated phenotype. Viruses can also activate STAT6 and can do so apparently in a JAK-independent manner (Chen et al., 2011a). In this case though, Stat6 activation is protective in terms of host response.

Towards a genomic view of STAT action: transcriptional and epigenetic roles

The advent of chromatin precipitation and massive parallel sequencing (ChIP-Seq) has permitted the understanding of STAT action on a global scale. Analysis of the genomewide targets of STATs via Chip-seq analysis for all the STATs has now been obtained, albeit in a limited number of tissues with relatively few stimuli and time points (reviewed in(Kanno et al., 2011; O'Shea et al., 2011). Gene expression is dramatically influenced by chromatin organization and until recently, the importance of STATs in regulating epigenetics has only been implicated by analysis of selected regions of certain genes. However, new technologies in in measuring cell-specific transcriptome and epigenome, coupled with the use of

knockout mice, allows assessments of the global impact of STAT-dependent signaling. What emerges is that STATs have thousands of genomic targets, and have major effects on transcription and epigenetic modifications on a substantial portion of these genes (Durant et al., 2010; Elo et al., 2010; Good et al., 2009; Kanno et al., 2011; Liao et al., 2011a; Wei et al., 2010) In the case of STAT6, about half of its target genes are affected in terms gene expression, epigenetic modifications or both when STAT6 is lacking in polarized Th2 cells (Wei et al., 2010). The impact of STAT4 in Th1 cells is less, but this is expected as both STAT4 and STAT1 contribute to Th1 differentiation (Schulz et al., 2009).

In addition to their roles in driving transcription, it is also clear from genomic studies that a major function of STATs is their role as functional repressors (Mandal et al., 2011a; Wei et al., 2010; Yang et al., 2011). In B cells, IL-7-mediated activation of STAT5 maintains proliferation and represses Igk germline transcription. Recently it has been shown that STAT5 binds the Igk intronic enhancer as a tetramer. This results in the recruitment of the histone methyltransferase Ezh2, which in turn induces histone H3 lysine 27 trimethylation, a repressive mark(Mandal et al., 2011a). Genome-wide analyses showed a STAT5 tetrameric binding motif is frequently associated with transcriptional repression. As indicated above, in T cells STAT5 displaces STAT3 and inhibits IL-17 expression (Yang et al., 2011). In Th1 and Th2 cells, STAT4 and STAT6 binding is frequently associated with repression. However, the mechanism of inhibition is not necessarily mediated by competition; in a large number of cases they bind distinct sites (Wei et al., 2010). Thus, it is clear STATs can both enhance and repress gene expression depending upon the complexes they recruit.

Equally intriguing is evidence that aside from phosphorylating STATs, JAK can have a direct role in regulating chromatin (Dawson et al., 2009). JAK2 has been found in the nuclei of haematopoietic cells, where it phosphorylates histone H3 tyrosine 41. Phosphorylation of this residue prevents heterochromatin protein 1alpha binding, and thereby counteracts gene silencing (Li, 2008; Shi et al., 2006).

Evidence for genetic links between cytokines and cytokine signaling and human autoimmune disease

While data from numerous animal models have implicated Type I/II cytokine receptors and the JAK/STAT pathway in autoimmune disease, the limitations is that they are just models. However, human genetics provides the ability to directly link genes to human disease. The field has moved rapidly from candidate gene to genome-wide investigation of single nucleotide polymorphisms (SNPs); systematic interrogation of the entire genome through next-generation sequencing is also now feasible (Mardis, 2011). Genome-wide association studies (GWAS) have led to an explosion of loci associated with risk of immune-mediated diseases. Importantly, these data show that inherited variation in genes encoding cytokines, Type I/II cytokines, JAKs and STATs are associated with these disorders.

Among the strongest evidence is work showing that multiple genes in the IL-23 signaling pathway are involved in human autoimmunity. One of the first variants to be identified was a non-synonymous variant of the IL-23R (Arg381Gln)(Duerr et al., 2006), which is associated with reduced risk of of IBD, psoriasis (Cargill et al., 2007; Nair et al., 2009) and ankylosing spondylitis (Burton et al., 2007). More recently, additional coding variants have been found to influence disease susceptibility to Crohn's and Behcet's disease (Momozawa et al., 2011; Remmers et al., 2010b). Subsequently, polymorphisms of the genes encoding both subunits of IL-23 (p19/*IL23A* and p40/*IL12B*), *JAK2*, *TYK2*, and *STAT3* have all been linked to autoimmunity (Bowes et al., 2011; Chu et al., 2011; Franke et al., 2010; Jakkula et al., 2010).

STAT3 is also activated by IL-6 and its receptors, IL6R and gp130 (latter encoded by *IL6ST*), have also been implicated in immune-mediated disease (Alloza et al., 2011; Ferreira et al., 2011; Stahl et al., 2010). *IL6R* may also be associated with cardiovascular disease (Elliott et al., 2009) and a disease-associated missense allele correlates with CRP levels (Dehghan et al., 2011; Melzer et al., 2008).

Multiple genes in the IL-12 pathway have also been implicated by GWAS. *IL12A* and *IL12RB2*, which are unique to IL-12 and not shared by IL-23, and STAT4 are associated with multiple autoimmune diseases (Hirschfield et al., 2009; Mells et al., 2011; Radstake et al., 2010; Remmers et al., 2010a; Remmers et al., 2007; Trynka et al., 2011; Zhernakova et al., 2011). It needs to be borne in mind that STAT4 is not only activated by IL-12, but can be activated by IL-23 and Type I IFNs.

With respect to allergic disease, polymorphisms of STAT6, and IL13 are associated with IgE levels and atopic dermatitis (Granada et al., 2011; Paternoster et al., 2011).

Despite these exciting leads, there are challenges of interpreting the biological function of genetic association data. Most disease-associated SNPs fall outside of protein-coding regions, and several genes may be in the region of linkage disequilibrium (LD) surrounding the SNP. The best biological candidate gene in the region is assumed to be the causal gene, but this may not be the correct assumption. For instance, there is an association of RA and multiple sclerosis with a SNP near the *IL6ST* gene (Alloza et al., 2011; Stahl et al., 2010); there is no direct evidence that the disease-associated variant disrupts *IL6ST* function. Similarly, *IL12RB2* and *IL23R* are adjacent to each other, and it is not clear whether the associated Behcet's risk allele influences one gene or the other.

Another challenge is inferring function when genes can be involved in multiple pathways. STAT4 is one example, but Tyk2 is another – both are involved in signaling by IL-12, IL-23 and Type I IFNs. Exactly who is the bad actor? Bioinformatic methods have been developed to search for relationships across genetic risk loci in order to find patterns that might otherwise be difficult to decipher (Hu et al., 2011; Raychaudhuri et al., 2009; Rossin et al., 2011; Segre et al., 2010). Future studies aimed at functional integration of genetic risk loci are a major effort to follow-up GWAS findings. Regardless though, the data clearly implicate the JAK-STAT pathway and cognate cytokines in the human immune-mediated disease.

Targeting Cytokine Signaling

The role of cytokine and cytokine signaling in mediating immune-mediated disease, now supported by GWAS data, has made these attractive pharmacological targets (Plenge, 2010). In fact, monoclonal antibodies directed against cytokines and cytokine receptors (e.g. ustekinumab, tocilizumab, mepolizumab, lebrikinumab, and daclizumab) have already shown efficacy in a variety of clinical settings. Additionally, the prospect of targeting intracellular signaling by these cytokines is also now a reality.

Janus kinases Inhibitors (JAKinibs)

As discussed by Notarangelo/Holland/Casanova (cite review in this issue), the unequivocal in vivo importance of the JAK/STAT pathways was first established by the identification of patients with severe combined immunodeficiency with *JAK3* mutations. The profound, but selective phenotype associated with JAK3-deficiency led to the proposition that targeting JAKs would represent a new class of immunomodulatory drugs (Ghoreschi et al., 2009; O'Shea et al., 2004; Russell et al., 1995).

Tofacitinib, formerly designated CP-690,550, was the first JAK inhibitor to be studied in humans. It inhibits JAK3 and JAK1 and to a lesser extent JAK2. Consequently, tofacitinib potently inhibits common γ chain cytokines but also blocks IFN-γ, IL-6 and to a lesser extent IL-12 and IL-23 (Ghoreschi et al., 2011). Functionally, tofacitinib affects both innate and adaptive immune responses (Ghoreschi et al., 2011). Remarkably, tofacitinib has little activity on kinases other than JAKs (Karaman et al., 2008).

Tofacitinib was effective in preclinical models (Changelian et al., 2003)and has shown efficacy in a variety of Phase II and III trials in rheumatoid arthritis, as monotherapy and in combination with other drugs (Fleischmann et al., 2012; Kremer et al., 2009; Kremer et al., 2011; Tanaka et al., 2011). Importantly, Tofacitinib is effective in patients who have failed one or more biologic and also prevents structural damage. Tofacitinib is under investigation for psoriasis, inflammatory bowel disease, sicca syndrome and prevention of transplant rejection.

Other JAK inhibitors are also rapidly moving ahead in preclinical assessment and clinical trials (Table I) (Fridman et al., 2010; Lin et al., 2010; Lu et al., 2011; Stump et al., 2011). As discussed by Green and Staudt in this issue, the JAK1 and JAK2 inhibitor, Ruxolitinib, is efficacious in polycythemia/myelofibrosis, a disorder due to gain-of-function *JAK2* mutations. As might be expected, based on its ability to block cytokines that use JAK1 and JAK2, this drug is also efficacious in arthritis (Fridman et al., 2010). Conversely, drugs that have relative selectivity for individual JAKs (JAK1, JAK2 and JAK3), also appear to have utility in preclinical and early clinical trials (Table I)

The adverse effects associated with JAKinibs appear to be largely related to its mode of action. Infections are among the common adverse effects, but opportunistic infections are uncommon. Anemia and neutropenia, presumably related to JAK2 inhibition and interference with signaling by erythropoietin and other colony-stimulating factors, can also occur. Increases in serum LDL also occur, as has been seen with the IL-6 blocker, tocilizumab (Kawashiri et al., 2011). Little reduction in $CD4^+$ T cells has been noted in nonhuman primates treated with tofacitinib, but more significant reduction in NK cells and $CD8^+$ T cells can occur (Conklyn et al., 2004; Paniagua et al., 2005). Whether this is will be pertinent and clinically relevant in humans remains to be determined. A decline in functional Treg cells has not been noted in human subjects in a renal transplant study (Sewgobind et al., 2010).

Given the profound role of cytokines in disorders ranging from malignancy to autoimmunity, JAKinibs have enormous potential utility. The extent to which JAK inhibitors will be used as steroid-sparing agents or even supplant the use of steroids in diseases like the vasculitides or systemic lupus erythematosus remains to be seen. A surprise in the field is that targeting multiple kinases is not necessarily detrimental, especially in circumstances in which multiple cytokines drive pathogenesis. Conversely though, it is conceivable that more selective JAK inhibitors (e.g. selective JAK1 and JAK3 inhibitors) might have efficacy with reduced adverse effects related to JAK2 inhibition. It is likely that we will soon see if this is the case given the intense interest in JAKinibs.

The prospect of targeting STATs?

Given their importance and circumscribed functions, it would also seem logical to target STATs – especially if different STATs could be selectively targeted. A number of STAT inhibitors have been described (Nelson et al., 2011; Yue and Turkson, 2009); however, to date, there is no STAT inhibitor that is near clinical development. Conceptually, one might target STATs by: 1.) blocking STAT phosphorylation, 2.) disrupting STAT binding to phosphorylated receptors or dimerization (both of which are mediated by the STAT src

homology (SH)2 domain; or 3.) interfering with DNA binding. Phosphopepitidomimetics continue to be designed that interrupt phosphotyrosine-SH2 binding (Mandal et al., 2011b; Zhang et al., 2010b; Zhao et al., 2010); however, the challenge will be to generated compounds with in vivo efficacy and selectivity. Targeting of the N-terminal domain has also been proposed as a strategy (Timofeeva et al., 2007). Screening of libraries has also revealed that small molecules like pimozide, nifuroxaide and pyrimethamine may be useful STAT inhibitors (Nelson et al., 2011). Whether any of these strategies ultimately generate orally available drugs that have efficacy with acceptable safety remains to be determined. However, given the prominent role of STATs in cancer, it is like that work will continue in this area.

Conclusions

The elegance of the JAK-STAT pathway is that it provides a simple, membrane to nucleus mechanism for rapidly inducing gene expression. As complexities of immune cell function continue to be unraveled, JAKs and STATs remain central players in all of the key cells, ranging from the "newest" CD4 helper cell subset to alternatively activated macrophages. Curiously though, there is still a paucity of information on conditional JAK and STAT knockouts. While some were quickly generated and studies in other cases we are still relatively ignorant about tissue specific functions of others (e.g. JAK1, JAK2, JAK3, TYK2, STAT1, STAT4 and STAT6).

In addition, although the simplicity of the pathway is appealing, some subtleties have become apparent. For instance, in contrast to the simplistic linear view, most cytokines activate more than one STAT. Precisely what this means in terms of the molecular basis of cytokine action is still being unraveled. However, technologic advances have certainly facilitated a broader understanding of the function of STAT proteins. It is now clear that STATs activate and repress gene expression and serve to organize the epigenetic landscape of immune cells. Nonetheless, our understanding how this occurs is still in its infancy. Despite the gaps in our knowledge, it is clear that this pathway is directly relevant to human disease and the pathway can be successfully targeted. For all these reasons, the next twenty years are likely to be just as exciting as the first.

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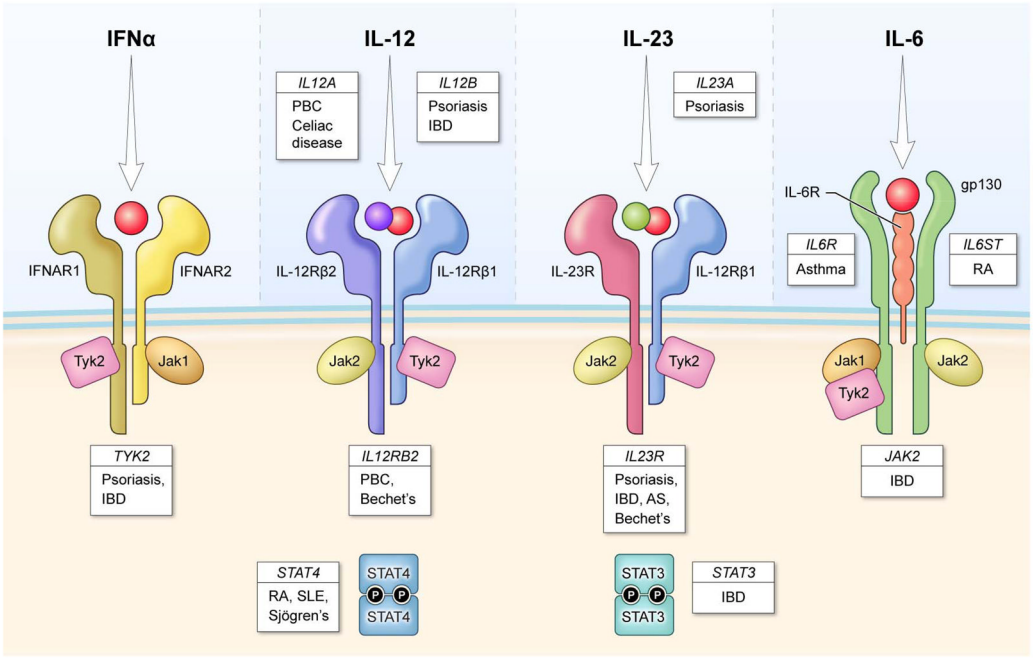

Figure 1.

Genetics links of cytokine signaling with human autoimmune disease. Although various animal models have implicated cytokines, their receptors, JAKs and STATs with autoimmune disease, genomewide association studies (GWAS) now show that these factors are truly relevant to human disease. This work shows that pathways that lead to STAT3 and STAT4 activation lie at the heart of many common autoimmune diseases Adapted from (Cho and Gregersen, 2011). AS – ankylosing spondylitis, IBD – inflammatory bowel disease; PBC –primary biliary cirrhosis, SLE – systemic lupus erythematosus.

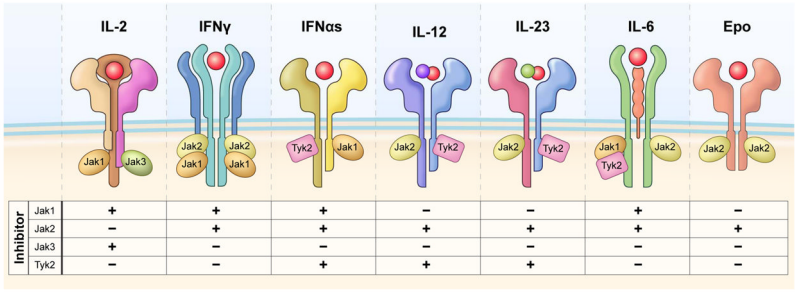

Figure 2.

Consequence of Jak inhibition on signaling by key immunoregulatory cytokines. A variety of JAKinibs have been developed with varying degrees of specificity for the different Jaks. The consequences of inhibiting each of the Jaks on these selected cytokines is depicted. Most inhibitors in clinical use inhibit more than one Jak; however, increasingly selective JAKinibs are in development. A selective Tyk2 inhibitor has yet to be reported.

Table 1

Selected JAKinibs

Agent	Targets	Indication/Phase
Tofacitinib	JAK3/JAK1/JAK2	RA/Phase III Psoriasis/Phase II IBD/Phase II
VX-509	JAK3	RA/Phase II
R-348	JAK3	RA/Phase I
Ruxolitinib	JAK1/JAK2	Approved – MF/PV
INCB-28050	JAK1/JAK2	RA/Phase II
GLPG-0634	JAK1	RA/Phase II
AC-430	JAK2	RA/Phase I Lymphoma/Phase I
Lestaurtinib	FLT3/TrkA/JAK2	AML/Phase III Psoriasis/Phase II Pancreatic cancer/Phase II
CEP-33779	JAK2	Preclinical