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The Current STATus of lymphocyte signaling: new roles for old players (STATs in lymphocyte signaling)

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Summary

Recently, our understanding of helper/effector T cell differentiation has changed significantly. New subsets of T cells continue to be recognized, including Th17, Treg, and Th9 cells. In addition, the signaling pathways that contribute to their generation continue to be refined. It has become clear that STAT family proteins play a major role in these "new" T cell fates, along with their critical role in more classical fates. Importantly, genetic studies implicate STATs in autoimmune and primary immunodefiency diseases in humans. Focusing on how STATs work in concert with other transcription factors will hopefully provide a better mechanistic understanding of the pathogenesis of various autoimmune diseases.

Introduction

The selective production of cytokines by subsets of CD4+ T-cells is a major mode of immunoregulation and an important mechanism by which T cells orchestrate immune responses. In addition to Thelper 1 (Th1) and Th2 cells, which produce interferon (IFN)-γ and interleukin (IL)-4 respectively, new lineages of T cells continue to be recognized. These include regulatory T cells (Tregs), Th17 cells and more recently T cells that selectively produce IL-9 and IL-21 [1,2]. It is also well established that cytokines themselves are major factors involved in differentiation, and many of these cytokines bind Type I/II cytokine receptors. This class of receptor signals via JAKs (Janus Kinases) and STAT (Signal Transducer and Activator of Transcription) family DNA-binding proteins [3,4]. STATs play critical roles in cell growth, survival, and differentiation of many types of cells, but are particularly important in controlling helper/effector T-cell differentiation (Figure 1). In this review we will explore the latest information on STAT transcription factors and how they regulate the "new" T cell fates. We will also discuss how these proteins co-ordinate their actions with other signaling molecules and how mutations and polymorphisms in these proteins are associated with an increasing number of human diseases.

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Genetic data in humans link cytokine signaling variants with susceptibility to autoimmune disease

Numerous studies have implicated cytokines and cytokine signaling in animal models of autoimmune disease. While these models are useful in defining potential immunopathogenic mechanisms, an essential question is what contributes to the propensity of humans to develop autoimmune disease? Recent genomewide surveys have provided exciting clues that alterations in cytokine signaling are related to the development of autoimmune disease in humans. For instance, a polymorphisms in the gene encoding the IL-23 receptor influences susceptibility to inflammatory bowel disease (IBD) [5] [6]. IL-23 signals through JAK2 and STAT3, and interestingly, polymorphisms in *JAK2* and *STAT3* are associated with susceptibility to Crohn's disease [7] [8]. Also, a variant allele of STAT4 is associated with increased risk of developing systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and Sjogen's syndrome [9]. Polymorphisms in the gene encoding the Janus family kinase, TYK2, have also been reported to be associated with SLE [10], whereas polymorphisms of *IL2R* and *IL7R* have also emerged as risk factors for multiple sclerosis (MS) [11]. Taken together, these new genetic data clearly argue that variation in genes encoding cytokines and their downstream signaling molecules are contributors to the diathesis for autoimmunity.

Additional evidence for the criticality of cytokines in human autoimmune disease is the efficacy of cytokine antagonists in treating these disorders. Newer, promising cytokine antagonists, include the blocker of IL-12 and IL-23 called, ustekinumab, and the anti-IL-6R monoclonal antibody, tocilizumab [12,13]. In addition, JAK inhibitors are now being tested in RA, IBD, psoriasis, and in transplant rejection [14]. For all of these reasons, it is clearly relevant to continue to refine our understanding of cytokine signaling and Type I/II cytokine receptors. As it will become clear, STATs continue to remain central to these processes.

STAT3 and Th17 differentiation – mouse and man

STAT3 is activated by a variety of cytokines and has a variety of critical functions. Recent evidence has pointed to a new function of STAT3, namely the regulation of Th17 cell differentiation. IL-17 is now known to be critical for host defense against extracellular bacteria and fungi, but is also implicated in the pathogenesis of a number of autoimmune-mediated diseases. Helper T cells that selectively produce IL-17 are induced by T cell receptor signaling in conjunction with TGFβ-1, IL-6 and IL-21 [15] [16]. These cytokines induce expression of the transcription factor RORγt, which promotes IL-17 and IL-21 production. Originally thought to be critical for the induction of Th17 cells, IL-23 is now recognized to be important for sustaining and expanding Th17 cells and affecting their pathogenicity [17,18]. In addition, IL-23 is critical for production of another cytokine, produced albeit not exclusively by Th17 cells, IL-22. IL-22 is especially important for mucosal immunity against extracellular bacteria in the lung and gut [19,20]. It is important in preserving the epithelial barrier and inducing the expression of antimicrobial proteins. In addition, IL-22 also has critical anti-inflammatory actions in the liver and gut [21,22].

IL-6, IL-21 and IL-23 all preferentially activate STAT3 and deletion of STAT3 within T cells impairs expression of IL-17 and IL-21 [23–25]. Conversely, deletion of the STAT3 inhibitor, Socs3, results in elevated numbers of Th17 cells [26]. Hyper-IgE or Job's syndrome, is a human primary immunodeficiency disorder characterized by recurrent staphylococcal abscesses, pneumonia, eczema, and high levels of IgE in the serum. Recently, it was demonstrated that dominant-negative mutations of STAT3 underlie this disorder [27,28]. This is associated with impaired Th17 development, establishing the importance of STAT3 in humans, as well as mice [29–32]

These observations beg the question of how STAT3 works. Chromatin immunoprecipitation assays document that the *Il17* and *Il21* genes are direct targets of STAT3. Additionally, STAT3 is important for IL-23R expression [25]. Furthermore, Th17 cells express several transcription factors that are critical for their function including RORγt, the arylhydrocarbon receptor (AHR), and IRF-4 [33–37] The extent to which STAT3 regulates or interacts with these other transcription factors remains unclear. RORγt expression is dependent upon STAT3; however, it has not been established whether STAT3 directly binds the *Rorc* gene. Runx1 also upregulates RORγt expression. RORγt and Runx1 bind the *Il17* gene. How STAT3 might coordinate with these other factors is not known [37].

STAT5 regulates Th17/Treg balance

STAT5, like STAT3, has multiple roles in many tissues; consequently, its complete deletion in mice typically leads to death in the neonatal period. The master regulator of Tregs is a transcription factor, Foxp3, whose expression is induced by T cell activation in the presence of TGF-beta, IL-2, and other cytokines that signal through the common gamma chain. These cytokines activate STAT5 and the absence of STAT5 abrogates Treg differentiation [38,39]. The action of STAT5 also appears to be very direct, as STAT5 binds the *Foxp3* gene.

IL-6, which as indicated above activates STAT3, is also an important negative regulator of Foxp3 [15,39]. Similarly, the Th2-asscociated cytokine IL-4, which activates STAT6, also inhibits Foxp3 expression. Whether the effects of these STATs are direct, indirect, or both have not been fully ascertained. However, STAT6 has been reported to bind to the *Foxp3* promoter leading to reduced TGFβ1-mediated Foxp3 activation and chromatin modification [40].

In addition to its role in positively regulating Tregs, STAT5 also inhibits Th17 differentiation; both STAT5 and IL-2 deficient mice have elevated serum levels of IL-17 [23]. STAT5 also binds the *Il17* gene, but precisely how it inhibits IL-17 production is unknown. Several possibilities exist: first, as indicated, STAT5 activation induces Foxp3, which can bind RORγt and inhibit its function [41,42]. The overproduction of IL-17 in STAT5-deficient mice could be due to cell-intrinsic effects, loss of Tregs or both. Second, STAT5 activation can also upregulate Socs3, which impairs IL-6 signaling and Th17 differentiation [26]. Third, STAT5 could compete with STAT3 and inhibit transactivation.

Additionally, AHR interacts with STAT1 and STAT5, but not with STAT3 or STAT6 [43]. Curiously, along with its role in positively regulating Th17 differentiation, AHR has been reported to positively regulate Foxp3 expression when activated by a different ligand, namely dioxin [35]. Exactly how AHR might positively regulate both Tregs and Th17 cells is perplexing; regardless, it will be of interest to better define how AHR and STATs regulate the balance of Th17 and Treg cells.

Also of note, STAT5 can promote Th2 differentiation. One mechanism by which this occurs is that STAT5 mediates IL-2- dependent IL-4Ralpha expression thereby increasing T-cell responsivness to IL-4. Using chromatin immunoprecipitation assays, it was demonstrated that STAT5 binds to the *Il4ra* locus [44]. Much like with STAT3, many questions involving STAT5's role in Th cell differentiation remain to be answered.

New STAT4 targets

STAT4 has been well characterized as important in promoting Th1 development. It is activated by IL-12, but is also activated by IL-23 and type I IFNs. Considerable effort has been directed toward identifying STAT4 targets to help explain its ability to transmit cytokine signals. Known STAT4 targets include *Ifng*, *Il18R*, and *Hlx1* genes [45]. Recent work has identified two new STAT4 targets that have rather different function, Map3K8 and Furin [46,47]. Map3K8 is an

upsteam activator of ERK, which is inducible by IL-12 and T cell receptor-dependent signals. Chromatin immunoprecipitation assays revealed that STAT4 directly binds the *Map3k8* gene. Interestingly, deficiency of Map3k8 in T cells interferes with IFN-γ production. In vivo, this results in impaired host defense against *Toxoplasma gondii* and exacerbates allergic disease. In a positive feedback loop, Map3k8 promotes the expression of T-bet, the master regulator of Th1 cells, as well as STAT4 itself. *Furin*, another gene induced by IL-12, is also bound by STAT4. However, deletion of this gene in T cells results in widespread autoimmune disease. Furin is essential for processing TGFβ-1 to its biologically active form and is thus critical for preserving peripheral tolerance, having important functions in both Treg and effector T cells. The complex network involving STAT4 signaling remains to be fully elucidated.

Towards a comprehensive understanding of STAT target genes

While compelling evidence from mouse and man point to critical roles of STATs in helper cell differentiation, our understanding of STAT target genes is remarkably limited. Fortunately, new technology provides the opportunity to define targets in a more comprehensive manner. One such technology involves chromatin immunoprecipitation followed by massive parallel sequencing (ChIP-seq) [48]. Chip-seq mapping of STAT1 binding revealed more than 11,000 sites in unstimulated cells and 40,000 sites following IFN-γ stimulation [49]. Clearly there are no paucity of STAT-target genes. However, this surfeit of STAT1 targets begs the question – is STAT1 really a major player in terms of regulation of all these genes? Gene regulation is not only controlled by transcription factor binding but is also influenced by epigenetic modifications. Such modifications include acetylation and phosphorylation of histone tails, variant histones and DNA methylation. ChIP-seq technology can also be used to assess genome-wide epigenetic modifications [50]. A recent report argues that for most genes, ligand-dependent STAT1 binding is preceeded by histone modification [49]. Assessment of STAT-binding sites along with epigenetic modifications can be determined by Chip-seq surveying wild-type and STAT-deficient cells to better define genes for which STATs are critical regulators.

Conclusion

CD4+ T helper (Th) cells are central players in immunity, critically coordinating innate and adaptive responses. Clearly, much is left to learn about how effector T helper cells differentiate from naïve CD4+ T cells; however, information is rapidly accumulating regarding transcriptional and epigenetic regulation of helper/effector differentiation. Moreover, new tools are being developed, which will facilitate our understanding of the process. The bane and the boon of these new technologies is the massive amount of information that is generated from simple experiments. It will require coordinated and multidisciplinary teams to fully elucidate this process. Given their established critical function, understanding how STATs contribute to T cell fate determination, especially on a genome-wide scale, should provide a clearer picture of mechanisms underlying these processes.

Bibliography Text:

1. (Ref 5–9) These studies argue that alterations in cytokine signaling truly contribute to the pathogenesis of human autoimmune disease.
2. (Ref 27–30) These are the first data demonstrating that STAT3 is essential in humans for Th17 differentiation
3. (Ref 48–50) These studies use a new technology, ChipSeq, to assess epigenetic modification and transcription factor binding on a genome-wide scale.

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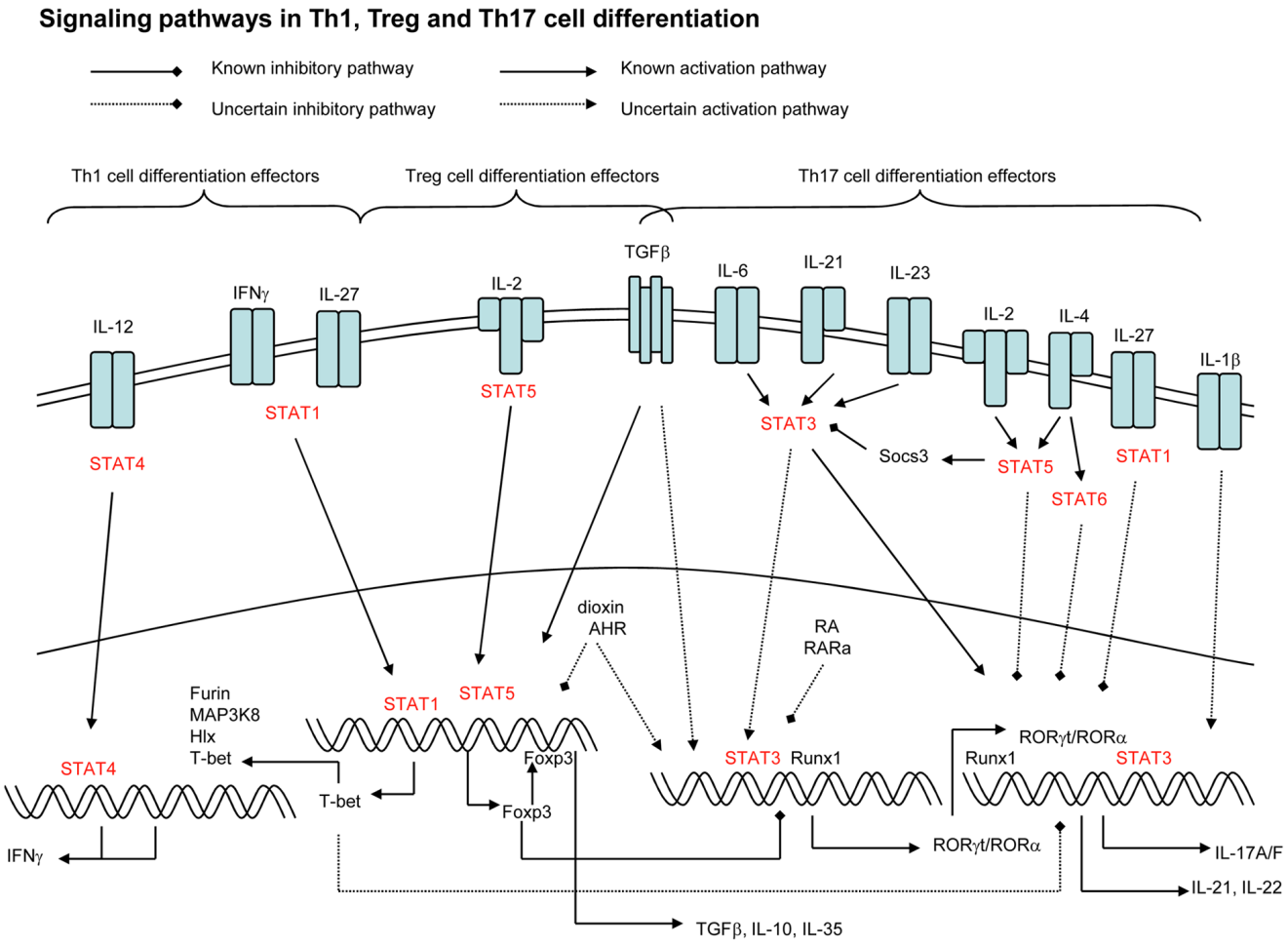

Figure 1.

CD4 T cell differentiation is critical in host defense. Following engagement of the T cell receptor, cytokines shape T cell commitment to various fates including Th1, Th2, Th9, Th17 and Treg cells. The important cytokines, their receptors, and specific STAT transcription factors that contribute to this intricate differentiation process are shown. In the case of Th1 cells, IL-12 drives naïve CD4+ cells to produce INF-γ. Other recently identified STAT4 target genes include Hlx, Map3k8 and Furin. Tregs develop from naïve T-cells in the presence of TGF-β and IL-2. Signaling through STAT5 results in the up-regulation of the transcription factor FOXP3, which also suppresses Th17 differentiation. Tregs play an important role in peripheral self-tolerance and immune suppression and secrete several cytokines including IL-10, IL-35, and TGF-β. Th17 cells develop from naïve CD4+ T cells through stimulation via IL-6 and TGF-β. The former activates STAT3, enhancing expression of the transcription factors RORγt and RORα, which in cooperation with the Arylhydrocarbon receptor promote expression of unique Th17 cytokine products: IL-17A, IL-17F, IL-21 and IL-22. Mutations of STAT3 underlie the human primary immunodeficiency syndrome hyperIgE or Job's syndrome. Th17 cells are involved in promoting inflammation and host defense against certain infectious agents. Activation of STAT1, STAT5, and STAT6 inhibit IL-17 production. Similarly, retinoic acid (RA) inhibits IL-17 but promotes Foxp3 expression.