JAK-STAT 2:1, e24198; January/February/March 2013; © 2013 Landes Bioscience

STAT signaling in inflammation

Mark H. Kaplan

Department of Pediatrics, and Microbiology and Immunology; Indiana University School of Medicine; Indianapolis, IN USA

Since their discovery, STAT proteins have been intimately tied to controlling the development of hematopoietic cells that regulate inflammation, and mediating the responses of target cells to inflammatory cytokines. Although our understanding of STAT protein-dependent gene expression during inflammation has grown considerably over the past 15 years, the identification of new cell types that require STAT proteins for development, and new gene targets of STAT-dependent regulation, has added to the already complex network of cells and cytokines in immune-mediated diseases. The review articles in this special focus provide perspective on a number of areas of recent research and highlight some of the next important questions in understanding how STAT proteins contribute to inflammatory disease.

Inflammation can be broadly defined as the recruitment of lymphoid and myeloid cells to a site of injury or infection. Cytokines are integral to the development of inflammation and as a result, STAT proteins are critical mediators of immunity to pathogens, and in the development of inflammatory disease.[1] Indeed, inflammation was one of the earliest biological functions associated with STAT proteins, from the anti-viral functions of STAT1, to the polarized T helper cell responses that required STAT4 and STAT6. In this special focus on STAT Signaling in Inflammation, six review articles by leading researchers describe the importance of STATs in immune responses, cellular development, and as targets for therapy of immune-mediated diseases. Although there is considerable work on how STAT proteins impact adaptive immunity, particularly in T helper cell development, less work has focused on innate responses and the development and function of innate immune cells. The reviews in this special focus highlight some of the important milestones in understanding how STAT proteins regulate inflammation, and suggest some of the unanswered questions remaining in the field.

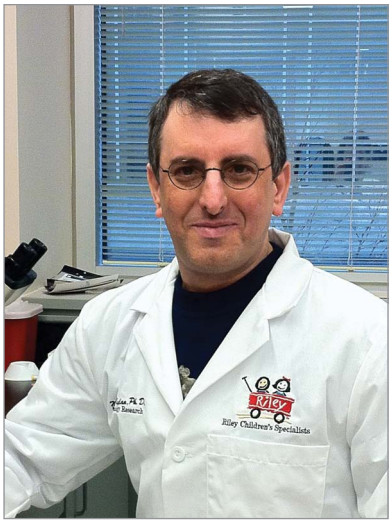
STAT1 is activated by type I and type II interferons and promotes an anti-viral state within stimulated cells. Mice deficient in STAT1 exhibit enhanced susceptibility to viral infections, succumbing to lethal viremia at typically non-lethal doses of infection. However, the IFN/STAT1 pathway is important for immune responses more broadly than viral immunity. Rauch, Müller and Decker[2] review the many ways that the IFN/STAT1 pathway promotes inflammation, including inducing expression of chemokines, regulating the differentiation and death of hematopoietic cells and promoting production of reactive oxygen species and nitric oxide. They further explore how IFN signaling cooperates with pattern recognition receptor signaling in generating innate immune response to bacteria, and bacterial products during systemic and localized inflammation. This is particularly important in the intestine where the reciprocal interactions between the gut microbiota and host cells broadly impact health and disease.

Chowdhury and Farrar[3] focus on STAT2, activated only by type I and type III IFN receptors. STAT2 is also unique in its obligate "partner" status in heterodimerizing with STAT1. Yet, STAT2 provides a central role in anti-viral responses, conferring the ability of type I and III IFNs to activate a set of genes distinct from those genes activated by IFNγ and STAT1 homodimers. The authors describe how STAT2 contributes to inflammation, and how STAT2 is now recognized as an important target of viral immune evasion during infection. STAT2 is the most evolutionarily divergent among all STAT proteins, a feature that likely contributes to the host range and susceptibility to viral infection. Although STAT2 has not been studied as extensively as some of the other STATs, it remains a fascinating nexus for host-pathogen interactions.

Kallal and Biron[4] focus on an additional, and seldom considered, aspect of STAT biology in anti-viral responses. Following changes in the environment during an infection, expression patterns of STAT proteins within the cell are altered, and as a consequence, the STAT proteins activated by a cytokine, and thus the genes activated by that cytokine, can differ. This finding demonstrates how the same cytokine may invoke different responses not only from two distinct cell types, but also from one cell type in two distinct states, such as resting and activated where the expression of STAT proteins has changed. The most dramatic example is in NK cells where altered expression of STAT1 changes the activation of STAT4, and the outcome of type I IFN stimulation. This paradigm provides not only a framework for understanding temporal changes in cytokine responses, but also a mechanism for cellular memory following exposure to an inflammatory environment. In systems where STAT protein expression is considered to be a constant, it will be important to extend these observations and determine how dynamic changes in STAT expression contribute to multiple aspects of inflammation.

As part of their function in mediating cytokine signals, STAT proteins are also required for cellular differentiation of immune effectors. STAT6 was the first STAT shown to be required for differentiation of a T helper subset. STAT6-dependent Th2 development contributes to a variety of inflammatory diseases, positively impacting allergic inflammation and negatively affecting autoimmunity.[5,6] Subsequently, STAT4-dependent Th1 differentiation was shown to be required for autoimmunity and inflammatory disease.[7] This model has expanded to fit the growing list of T helper subsets, and has adjusted to the realization

Correspondence to: Mark H. Kaplan; Email: mkaplan2@iupui.edu
Submitted: 03/04/13; Accepted: 03/04/13
Citation: Kaplan MH. STAT signaling in inflammation. JAK-STAT 2013; 2:e24198; http://dx.doi.org/10.4161/jkst.24198



About Dr Mark H. Kaplan. Dr Kaplan received a BSc from the University of Windsor and a PhD in Immunology and Microbiology from Wayne State University. After postdoctoral training at the University of Texas Southwestern Medical Center and at the Harvard University School of Public Health, he joined the faculty at the Indiana University School of Medicine. He became the Director of Pediatric Pulmonary Basic Research in the Department of Pediatrics, leading a research program in asthma, allergic disease and pulmonary inflammation. His research focuses on transcription factors in the differentiation of T helper subsets and their contribution to the development of immunity and disease.

that multiple STAT proteins can contribute to a single T helper subset phenotype, and one STAT protein can be required for the development of several T helper subsets.[8,9]

The requirement for STAT proteins in the development of effector phenotypes is also observed in T regulatory cells. Mahmud, Manlove and Farrar[10] review the importance of the IL-2/STAT5 signaling pathway in the development and function of T regulatory cells. Although IL-2 was initially identified as a T cell growth factor, it is now established as important for the T regulatory arm of the immune response. Mice deficient in IL-2, or that have T cells deficient in expression of IL-2R components or STAT5 have impaired development of thymic-derived natural T regulatory cells (nTreg). The IL-2/STAT5 pathway promotes stability and effector function in inducible Tregs (iTreg). STAT5 confers at least some of its function by binding to regulatory elements of the Foxp3 gene. The activation of other STATs in iTreg can impair their development or function, re-iterating the paradigm that cells integrate multiple cytokine/STAT signals.

T helper cells are not the only hematopoietic lineages that are developmentally impacted by cytokines and STAT proteins. Huang, Li and Qi[11] provide a review of cytokine and STAT protein effects in the development of innate myeloid and lymphoid effector cells. The authors first review the requirement for cytokines and STAT proteins in the development of myeloid effector cells including basophils, mast cells and eosinophils. STAT5 is of particular importance, not only for development of myeloid cell types, but also in the regulation of cytokine production from these cells, through mechanisms that can be distinct from regulation of cytokines in T cells. The authors then discuss our developing understanding of innate lymphoid cell (ILC) subsets. Although the requirement for STAT proteins in these cells is not well documented, recent reports have begun to define transcription factors that are involved in ILC subset development and cytokine expression. If STAT proteins are required for ILCs, it may change the interpretation of results from inflammatory disease models using mice that are globally or conditionally deficient in STAT proteins.

The association of STATs with specific types of inflammation makes them attractive targets for therapy. The previous issue of *JAK-STAT* (volume 1, issue 4) had a series of reviews on the treatment of cancer with various approaches to inhibition of the STAT-signaling pathway. Although these approaches have been more extensively examined in cancer models, some are now being tested as approaches for inflammatory disease. Egwuagu and Larkin[12] explore approaches to inhibit STAT pathways that promote the development of CNS autoimmune diseases. The authors discuss the advantages and disadvantages of targeting specific STAT proteins in the development of autoimmune disease knowing that blocking one STAT pathway and T helper subset might lead to increased development of another subset of T helper cells. STAT3 is required for autoinflammatory disease and the authors discuss several approaches to inhibiting STAT3 directly, inhibiting STAT3-activating pathways, and inhibiting the function of the STAT3 target genes *Rora* and *Rorc*. Given the broad functions of STAT3 and its targets, the effectiveness of these approaches will need to be carefully tested in pre-clinical models and in patient studies.

As noted in many of these articles, STAT proteins function in multiple cell types, and that parallel activity contributes to the development of disease. For example, in the development of allergic inflammation (see cover images), STAT6 is required not only in T cells, but in airway epithelial cells, smooth muscle cells, B cells, macrophages and likely other cell types. Much of what we know about STAT6 function has been modeled on function in lymphocytes, and it is likely that STAT6 targets very different genes, and possibly even works through different kinetics with different co-factors in various cell types. As our efforts progress to understand how STAT proteins function in multiple cell types, and how best to therapeutically interfere with STAT-dependent gene regulation, the next frontier will be modifying those responses to inhibit inflammatory disease, but appropriately enhance immunity and immune memory to pathogens.

References

1. O'Shea JJ, Plenge R. JAK and STAT signaling molecules in immunoregulation and immune-mediated disease. Immunity 2012; 36:542-50; PMID:22520847; http://dx.doi.org/10.1016/j.immuni.2012.03.014
2. Rauch I, Müller M, Decker T. The regulation of inflammation by interferons and their STATs. JAK-STAT 2013; 2:e23820; http://dx.doi.org/10.4161/jkst.23820
3. Chowdhury FZ, Farrar JD. STAT2: A shape-shifting anti-viral super STAT. JAK-STAT 2013; 2:e23633; http://dx.doi.org/10.4161/jkst.23633
4. Kallal LE, Biron CA. Changing partners at the dance: Variations in STAT concentrations for shaping cytokine function and immune responses to viral infections. JAK-STAT 2013; 2:e23504; http://dx.doi.org/10.4161/jkst.23504
5. Glosson NL, Bruns HA, Kaplan MH. Wheezing and Itching: The Role of STAT proteins in allergic inflammation. JAK-STAT 2012; 1:3-12; http://dx.doi.org/10.4161/jkst.19086
6. Goenka S, Kaplan MH. Transcriptional regulation by STAT6. Immunol Res 2011; 50:87-96; PMID:21442426; http://dx.doi.org/10.1007/s12026-011-8205-2
7. Kaplan MH. STAT4: a critical regulator of inflammation in vivo. Immunol Res 2005; 31:231-42; PMID:15888914; http://dx.doi.org/10.1385/IR:31:3:231
8. O'Shea JJ, Lahesmaa R, Vahedi G, Laurence A, Kanno Y. Genomic views of STAT function in CD4+ T helper cell differentiation. Nat Rev Immunol 2011; 11:239-50; PMID:21436836; http://dx.doi.org/10.1038/nri2958
9. Stritesky GL, Kaplan MH. Changing the STATus quo in T helper cells. Transcription 2011; 2:179-82; PMID:21922060; http://dx.doi.org/10.4161/trns.2.4.16614
10. Mahmud SA, Manlove LS, Farrar MA. Interleukin-2 and STAT5 in regulatory T cell development and function. JAK-STAT 2013; 2:e23154; http://dx.doi.org/10.4161/jkst.23154
11. Huang H, Li Y, Qi X. Cytokine signaling in the differentiation of innate effector cells. JAK-STAT 2013; 2:e23531; http://dx.doi.org/10.4161/jkst.23531
12. Egwuagu CE, Larkin JI. Therapeutic targeting of STAT pathways in CNS autoimmune diseases. JAK-STAT 2013; 2:e24134; http://dx.doi.org/10.4161/jkst.24134