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New Insights into the Roles of Stat5a/b and Stat3 in T Cell Development and Differentiation

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Abstract

T cell development and differentiation is carefully orchestrated by a series of cytokines. The importance of STAT family proteins in mediating signals by these cytokines is well-known, but new information on the role of STATs in novel aspects of T cell function and new T cell subsets continues to accumulate. Recent studies have placed Stat5a/b and Stat3 center stage in T cell development and differentiation. Stat5a/b are indispensable in T regulatory (Treg) cell development and maintenance, and negatively regulate T helper 17 (Th17) cell differentiation. Conversely, Stat3 is essential for Th17 differentiation and inhibits Treg cells. The balance of Treg and Th17 cells is thought to be critical in maintaining immune tolerance, while preserving effective host defense. Therefore, Stat5a/b and Stat3 are emerging to be key players in T cell differentiation and homeostasis.

Keywords

Stat5a/b; Stat3; cytokines; immunoregulation; T cell development and differentiation; Th17; Treg

1. Background

Effective immune responses depend on an array of soluble mediators, collectively called cytokines, which mediate communication between stromal cells, cells of the innate and cells of the adaptive immune system [1]. Binding of cytokines to their receptors results in activation of receptor-associated Janus family tyrosine kinases (JAKs). Activated JAKs in turn phosphorylate latent cytoplasmic transcription factors called Signal Transducers and Activators of Transcription (STATs), inducing their dimerization, nuclear accumulation and DNA binding. STATs regulate genes that control cell proliferation, differentiation, development and survival [2]. In addition to cytokines, hormones and growth factors also activate STATs in various types of cells and tissues. In this respect the concept of a JAK/STAT pathway may be overly simplistic.

Since the first members of this transcription factor family, Stat1 and Stat2, were identified more than 10 years ago as mediators of the cellular response to interferons, the mammalian STAT protein family has been expanded to include seven members: Stat1, Stat2, Stat3, Stat4, Stat5a, Stat5b, and Stat6. While the roles of STATs in the differentiation of T lymphoid cells has been a major focus of many reviews [3-5], the present review will highlight recent advances in the understanding of the function of Stat5a/b and Stat3 in T cell development and differentiation.

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Stat5a/b were first recognized as mammary gland factor, activated by prolactin (PRL) through Jak2, which regulates milk protein beta-casein expression [6]. Subsequently it has been shown that large number of additional cytokines and growth factors also signal through Stat5a/b. Those include cytokines using common gamma chain (γc, CD132)(IL-2, IL-7, IL-9, IL-15 and IL-21), the common beta chain (IL-3, IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF)), granulocyte-CSF, M-CSF, epidermal growth factor, platelet-derived growth factor, PRL, erythropoietin (EPO), thrombopoietin (TPO), growth hormone (GH), IFN-α/β, IFN-γ, IL-22, oncostatin M, FMS-like tyrosine kinase 3 ligand (Flt3l), and thymic stromal lymphoprotein (TSLP) [7-22]. Activation of Stat5a/b results in regulation of a number of genes that play key roles in cell apoptosis, survival, as well as proliferation in a cell-type- and stimuli-specific manner [23].

The mammalian *Stat5a* and *Stat5b* genes share 96% homology and are linked on chromosome 17 in the human and chromosome 11 in the mouse, adjacent to the *Stat3* locus in both species. STAT5A and STAT5B proteins differ by 12 C-terminal amino acids, which results in molecular weights of 94 and 92 kDa, respectively. For many cells, Stat5a and Stat5b display partially redundant functions, but ablation of the individual genes has revealed unique physiological functions. Stat5a-deficient mice develop normally and are indistinguishable from wild-type littermates in size, weight, and fertility. However, mammary lobuloalveolar outgrowth during pregnancy is curtailed, and females fail to lactate after parturition because of a failure of terminal differentiation. Thus Stat5a appears to be the principal and obligate mediator of mammopoietic and lactogenic signaling, presumably through prolactin [24]. On the other hand, deficiency of Stat5b leads to a major loss of multiple, sexually differentiated responses associated with the sexually dimorphic pattern of pituitary GH secretion, suggesting a role for Stat5b in maintaining sexual dimorphism of body growth rates and liver gene expression by mediating GH signaling [25].

Stat3 was originally discovered as a factor activated by IL-6 family cytokines through gp130 receptor [26,27]. However, like Stat5a/b, Stat3 is also activated by an array of cytokines, interferons and growth factors. Deletion of Stat3 results in embryonic lethality due to placental insufficiency related to failure of leukemia inhibitor factor (LIF) signaling [28]. Consequently, a variety of mice in which Stat3 is deleted in a tissue- and cell-specific manner have been generated [29-38]. These mice have documented critical roles of Stat3 for liver acute-phase responses [30], myocyte apoptosis [34], survival of motor neurons [35], keratinocyte migration and wound repair in the skin [36], mammary gland involution [37], as well as body weight and body fat percentage [38]. From an immunological perspective, Stat3 is essential for the actions of IL-6 [26], IL-10 [39], IL-11 [40], IL-21 [21], IL-23 [41], and LIF [42]. Those cytokines play critical roles in lymphoid development and differentiation.

2. Stat5a/b, Stat3, and lymphoid development

With respect to lymphocyte development, deficiency of Stat5a or Stat5b individually has relatively minor consequences, suggesting functional redundancy [43-46]. In fact, germline deletion of both *Stat5a* and *Stat5b* initially led to the conclusion that Stat5a/b are not essential for T or B cell development [47,48]. Specifically, peripheral B cells and bone marrow precursors were found to be reduced but not eliminated. In younger mice, both splenic and thymic cellularity was preserved. The numbers of $CD4^+$ T cells were increased at the expense of $CD8^+$ T cells and cells of both lineages expressed markers associated with activation [49-53]. More recently, a 5- to 10-fold reduction in fetal thymocytes was demonstrated in these mice, but after birth the number of thymocytes returned to normal. Furthermore, with age, these animals develop a lymphoproliferative disease associated with splenomegaly and colitis. This is in marked contrast with the *in vitro* findings that Stat5a/b deficient T cells were incapable of proliferating in response to polyclonal activation in the presence of IL-2 [48,54,55].

A complication of the initial Stat5a/b knockout mice is that the gene targeting strategy resulted in mice in which amino-terminal truncated and partially functional STAT5A/B proteins were generated (subsequently designated *Stat5*$^{\Delta N}$) [56,57]. As a result, the phenotype of the mice can be viewed in retrospect as a consequence of Stat5 hypomorphic alleles rather than a complete knockout. Subsequent analysis of mice in which the entire *Stat5a/b* locus was deleted led to some different conclusions [58]. In many respects though, the initial mice pointed to functions of Stat5; however, the phenotype was just not as severe as that seen with more effective deletion [57,59].

First, deletion of *Stat5a/b* locus results in >99% perinatal lethality. The few mice that survive are extremely runted and anemic. By analysis of the few survivors and fetal lymphoid development, it became clear that Stat5a/b are essential for the normal development and differentiation of all lymphoid lineages. B cell development is profoundly affected by complete Stat5a/b deficiency. Development is blocked at the prepro B cell stage, and thymocyte numbers are profoundly reduced in the double negative state, congruent with the phenotype of mice with deficient of IL-7, the cytokine that is critical for B cell development [60]. Natural killer cells are also absent in Stat5a/b null mice, consistent with the requirement of IL-15 for the development of these cells.

Absence of Stat5a/b also reduces thymocyte number by >98% and abrogates T cell receptor gamma rearrangement. Stat5a/b deficiency also impairs $CD8^+$ T cell development in thymus although other STATs may compensate to some extent. Peripheral $CD8^+$ T cells are also lacking in Stat5a/b knockout mice, whereas $CD4^+$ T cells accumulate in these mice [57]. Thus, Stat5a/b deficient mice exhibit a severe combined immunodeficiency picture that is similar in many respects to deficiency of IL-7R, γc, and Jak3 [61-63]. The importance of Stat5a/b for T cell function was also examined by deleting these transcription factors at the double positive stage of T cell development using *CD4-Cre*, *Stat5a/b*$^{fl/fl}$ mice. Transgenic overexpression of Stat5a or Stat5b markedly increases $CD8^+$ memory T cell numbers and induces development of $CD8^+$ T cell lymphoblastic lymphomas [46,64]. Taken together, it should be evident that Stat5a/b play important role in lymphoid development (Fig 1).

Selective deletion of Stat3 demonstrated its diverse roles in myeloid cells [29,65-67]. However, in contrast to Stat5a/b, deletion of Stat3 has not been reported to have any significant effect on development of T and B cells [68]. Deletion of Stat3 in T cell compartment has no significant effects on total T cell numbers or CD4/CD8 ratios in thymus, spleen, and lymph nodes [31]. Similarly, establishment of the peripheral B-cell compartment, and baseline serum antibody levels were all unperturbed by the absence of STAT3 [68].

3. The role of Stat5a/b and Stat3 in $CD4^+$ helper T cell differentiation

$CD4^+$ or helper T (Th) cells orchestrate host defense against diverse pathogens by differentiating into discrete subsets that secrete distinctive cytokines. These patterns are important in the successful elimination of a particular pathogen, and limiting damage to host tissues [69]. Classically, differentiating $CD4^+$ T cells were thought to have two fates - T helper1 (Th1) and Th2 cells - depending upon the pathogenic challenge and STAT family transcription factors are known to have critical roles in these processes [70]. Specifically, intracellular pathogens were noted to promote the production of IL-12 by dendritic cells (DC). In concert with antigen stimulation, IL-12 acting via the transcription factor Stat4, induces the development of Th1 cells that produce the signature cytokine IFN-γ. Among its actions in Th1 cells, Stat4 directly binds the *Ifng* gene promoter but how it influences transcription is unknown. In an autocrine or paracrine manner, IFN-γ activates Stat1 and promotes the expression of the transcription factor T-bet, further enforcing Th1 differentiation [3]. In contrast, helminthic pathogens promote the generation Th2 cells that produce the key cytokine

IL-4. IL-4 in turn activates Stat6, which promotes expression of a key transcription factor, Gata3 that is essential for Th2 cell differentiation and maintenance [71,72]. Inappropriate immune responses mediated by Th1 and Th2 cells have also been found to result in some self-inflicted injury including Th1-mediated systemic pathology and Th2-mediated allergy and asthma [73]. Stat4 and Stat6 knockout mice have impaired Th1 and Th2 responses respectively and have the expected consequences with respect to host defense [4].

Interestingly, a recent genome-wide association study has revealed that polymorphisms in *STAT4* confer risk of developing autoimmune diseases including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [74]. While RA has typically been view as having elements consistent with Th1-mediated pathology, SLE would not be considered a prototypic Th1 disease. Although the pathogenesis of SLE is very poorly understood, recent advances have documented that these autoimmune disorders are characterized by an “interferon signature” determined by microarray analysis [75]. In this regard, it is important to note that Type I IFNs also activate Stat4 [76]. Depending upon the circumstance, Type I IFN signaling may or may not enhance Th1 responses [77]. Exactly how Stat4 and IFNs contribute to the pathogenesis of SLE is unknown, but this will be an important area to follow.

This simplistic Th1 and Th2 dichotomotous view of T cell differentiation has recently been challenged by the recognition of surprising heterogeneity of differentiated T cells. New fates for $CD4^+$ T cells includes new T cell lineages such as regulatory T (Treg) cells, follicular helper T cells and Th17 cells [78,79]. In addition, different subsets of T cells are major producers of IL-10, a key immunosuppressive cytokine [80].

Regulatory T cells are a critical subset of cells that play an essential role in the controlling of inflammatory responses [81]. Treg cells comprise a population of cells enriched in $CD4^+CD25^+$ T cells that suppresses T-cell proliferation and function and attenuates immune responses against self- or nonself-antigens. They are derived from thymic precursors as natural Treg (nTreg) or be converted from naïve $CD4^+$ T cells in the periphery (inducible Treg, iTreg) and are very abundant in the gut [82]. The importance of Treg cells has been documented in a variety of models of autoimmune disease [83].

Treg cells express the transcription factor Foxp3. Although it has been debated whether Foxp3 is necessary or sufficient and is a true “master” regulator of Tregs [84], it is clear that it is an essential factor. Mutation of Foxp3 in mice (scurfy) results in early autoimmune disease [85], whereas mutations of human Foxp3 are associated with a disorder known as immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) [86].

The mechanisms underlying Treg development and maintenance are still not fully understood [87,88]; however, we know that γc cytokines are essential for nTregs development/maintenance and can promote Treg conversion [89]. Deficiency of IL-2 and its receptor subunits, IL-2Rα (CD25) and IL-2Rβ (CD122), is associated with autoimmune disease, which is now interpreted to be due to impairment in Treg cells [50,90-97]. IL-2 was shown to be required for Treg suppressive function *in vitro* [98,99], whereas neutralization of circulating IL-2 by anti-IL-2 monoclonal antibody selectively reduces the number of Foxp3-expressing $CD4^+CD25^+$ and can elicit autoimmune diseases. All these data argue for an important role for IL-2 in the maintenance of nTregs and peripheral T cell tolerance [100].

IL-2 signals through γc, which is associated with Jak3 [101]. Jak3 and γc are essential for Treg development and maintenance, and Jak3 or γc deficient mice lack CD25 and Foxp3 expression in the thymus and spleen [102,103]. While IL-2 is important for Tregs, deficiency of IL-2 does not abrogate Th17 development, contrasting with the consequences of γc and Jak3 deficiency. This argues that other γc cytokines, like IL-7 and IL-15, might also contribute to Treg development and homeostasis.

Since Stat5a/b are activated by γc cytokines, it was logical to predict these factor might be important for Treg cells. $CD25^+$ or $Foxp3^+$ Tregs are not detected when *Stat5a/b*-deficient stem cells were transplanted into $Rag2^{-/-}$ host [104]. Moreover, deletion of Stat5a/b in $CD4^+$ T cells results in marked reduction of $Foxp3^+$ and $CD4^+CD25^+$ cells in both thymus and periphery [91,104]. Moreover, humans with *STAT5A/B* mutations display immune dysregulation associated with decreased CD25 and Foxp3 expression, [105,106].

This raises the question as to how Stat5a/b might be functioning in Treg cells. In fact, its actions appear to be rather direct insofar as STAT5A/B can directly bind the murine and human *FOXP3* genes [91,104,107]. STAT5A/B binding motifs located in the first intron and 5' promoter regions of human and mouse *Foxp3* genes, and binding of this transcription factor was documented by chromatin immunoprecipitation assays. While these results argue for the direct role of Stat5a/b in regulating Treg lineage specific factor Foxp3 expression, Stat5a/b are also very important for regulating CD25 expression [44]. Taken together, Stat5a/b promotes Treg development and maintenance through direct regulation of both Foxp3 and CD25 expressions.

In contrast to IL-2, other cytokines like IL-6 negatively regulate Foxp3 expression [108]. This action of IL-6 is dependent upon Stat3, but exactly how Stat3 functions to negatively regulate Foxp3 has not been established [104].

4. Role of Stat5a/b and Stat3 in Th17 differentiation

Recently, the existence of a new effector cell lineage has become apparent. Though, the cytokine IL-17 was discovered more than 10 years ago, it has only recently become apparent that IL-17 is selectively made by a subset of T cells. IL-17 belongs to a family of cytokines (IL-17A-F). IL-17 acts through a ubiquitous receptor to induce the production of IL-6, G-CSF and various chemokines, which act to mobilize acute inflammation/neutrophilic responses. IL-17 can also induce the production of antibacterial peptides in mucosal epithelial cells [79]. Because of its proinflammatory nature, IL-17 has also been implicated in the pathogenesis of various autoimmune disease in mouse and man including arthritis, multiple sclerosis, psoriasis and inflammatory bowel disease [73]. Analogous to T-bet, Gata3, and Foxp3 in Th1, Th2 and Treg cells, Th17 cells preferentially express the retinoid receptors Rorγt and Rorα [33,109, 110].

In vitro culture of $CD4^+$ T cells with TGFβ-1 can promote the generation of $Foxp3^+$ Treg cells from naive $CD4^+$ T cells. In contrast, *in vitro* culture of $CD4^+$ T cells with TGFβ-1 and IL-6 promotes the differentiation of inflammatory Th17 cells and suppresses Treg cells. Thus, the differentiation of Treg and Th17 cells by TGFβ-1 appears to be reciprocally related [108, 111-113]. Th17 cells produce another cytokine, IL-21, which promotes Th17 differentiation in an autocrine manner [33,114-116]. A fourth cytokine, IL-23, expands and maintains Th17 cells *in vivo*, making them more pathogenic [117]. Other proinflammatory cytokines like IL-1 and TNF also promote the differentiation of Th17 cells [118].

Cytokines critical for Th17 differentiation and maintenance, including IL-6, IL-21, and IL-23, all signal primarily through Stat3. Accordingly, deficiency of Stat3 dramatically affects Th17 cells. That is, in the absence of Stat3, murine T cell IL-17 production is essentially abrogated [119]. A particularly dramatic example of the importance of Stat3 is the primary immunodeficiency disease Hyperimmunoglobulin E syndrome (HIES) or Job's syndrome, which is caused by mutations of *STAT3* in the DNA-binding or SH2 domains [120-122]. Patients with Job's syndrome have recurrent skin and bronchopulmonary infections with *S. aureus* and *Candida*. The increased susceptibility to infection can now be explained by the failure to generate Th17 cells [123].

With respect to Th17 differentiation, Stat3 appears to have several important direct actions. First, as demonstrated by chromatin immunoprecipitation assays, it binds the *Il17* and *Il21* genes. IL-6 and IL-23 both promote the expression of IL-23 receptor and Stat3 is also important for IL-23R expression; however, we do not know if the *Il23r* gene is a direct target. Stat3 also regulates the expression of Rorγt and Rorα [109], but again, it is unclear whether this is a direct or indirect effect of Stat3.

Because of their inflammatory nature, it should come as no surprise that there are many ways to negatively regulate Th17 cells. As IL-2, acting through Stat5a/b promotes Treg differentiation; however, it also negatively regulates Th17 differentiation and thereby serves to maintains balance between Tregs and Th17 cells [124]. Addition of exogenous IL-2 actively interferes with Th17 differentiation, possibly through down-regulation of Rorγt expression, whereas blocking of autocrine IL-2 by neutralizing antibodies promotes Th17 polarization *in vitro*. Accordingly, one aspect of the pathology seen in IL-2-deficient mice, is the overproduction of Th17 cells. Similarly, Stat5a/b deficient mice also develop more Th17 cells and naive Stat5a/b deficient $CD4^+$ SP thymocytes also have increased propensity to become IL-17 producers. These data argue that IL-2 may constrain Th17 differentiation through activation of Stat5a/b *in vivo*. Moreover, increased Th17 cells and decreased Tregs in both IL-2 and Stat5a/b deficient mice suggest that autoimmune phenotypes appeared in these mice may be partially due to unbalanced Th17-Treg ratio [125]. It should be noted, in memory cells, IL-2 may function to enhance rather than inhibit IL-17 production [126].

With respect to its mechanism of action, it appears that Stat5a/b can directly bind the *Il17a* gene, but whether it is truly acting as a transcriptional repressor in this setting is not known; it may also be working in a number of indirect ways [124]. A variety of other cytokines including IFN-g, IL-27 and IL-4 also inhibit IL-17 production and act through their cognate Stat proteins (Stat1 and Stat6); again, the mechanism of their inhibitory function has not been determined [127-129].

Recent studies have demonstrated that the vitamin A metabolite retinoic acid promotes TGFβ-1-induced Treg development and suppresses Th17 differentiation [130-132]. The mechanisms underlying these effects are unclear, but at less some data argue that this occurs independently of Stat5a/b or Stat3 [132].

5. Stats and regulation of IL-10

IL-10 is a critical immunosuppressive cytokine as evidenced by the fact that its deficiency is associated with fatal autoimmune disease [133,134]. Initially described as a product of Th2 cells that inhibited the production of IFN-γ by Th1 cells, it was soon recognized that other lymphocytes as well as myeloid cells also produced IL-10 [80,135]. Recent studies have shown, in addition to Th2 cells [136,137], Th1 [138], Th17 [139] and Treg [140] cells all produce IL-10 under certain conditions. Production of IL-10 in various T helper cell subsets serves as a self-control mechanism that limit pathological outcome of immune response [141]. In the case of Th17 differentiation, IL-10-producing Th17 cells appear to be relatively nonpathogenic, whereas Th17 cells that produce no IL-10 are able to efficiently mediate autoimmune disease in adoptive transfer models [117]. Induction of IL-10 can be induced by IL-27 or IL-6 in various T helper cell subsets. For IL-6, this is dependent upon Stat3, whereas IL-27-dependent IL-10 production is dependent upon Stat1 [117,128,141-143]. Therefore, Stat3 mediates not only signals that lead to lineage commitment for Th17 differentiation, but also feedback control that lead to production of immunosuppressive cytokine IL-10.

6. Future directions

In addition to the well-recognized ability of $CD4^+$ T cells to differentiate into selective lineages in response to different pathogens, it has also become clear that T cells have remarkable flexibility and heterogeneity. The extent to which cytokine producing T cells represent terminally differentiated "lineages" or is a reflection of their plasticity in response to a dynamic inflammatory milieu remains unclear. The data pointing to the relationship between Treg and Th17 lineage cells also presents an interesting question how flexible T cell phenotypes might be and the extent to which naïve T cells can be "converted" into Tregs or Tregs can switch to become Th17 cells remains unclear [144]. Regardless, it is clear that Stat family transcription factors are at the center of all these decisions. Clearly Stat5a/b and Stat3, in addition to Stat4 and Stat6 are critical players in T cell differentiation. And yet, we still do not know exactly what STATs are doing and how they do it. It will be exciting to determine whether STATS directly bind promoters of key regulators such as *Foxp3* and *Rorc*. If they are functioning as transcriptional activators, how are they accomplishing this? Conversely, if they work as repressors, understanding this mechanism will also be the key. Moreover, direct STAT target genes are beginning to be catalogued. This is in its infancy but new technology like ChIP-chip or Chip-Seq methodologies will quickly fill this void [145-147]. As more is learned about the epigenetic control, it will be important to understand how STATs affects the pattern of accessibility versus silencing of these genes relates to differentiation of Treg and Th17.

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Abbreviations

STAT, Signal transducer and activator of transcription; Treg, T regulatory cell; Th17, IL-17-producing T helper cell.

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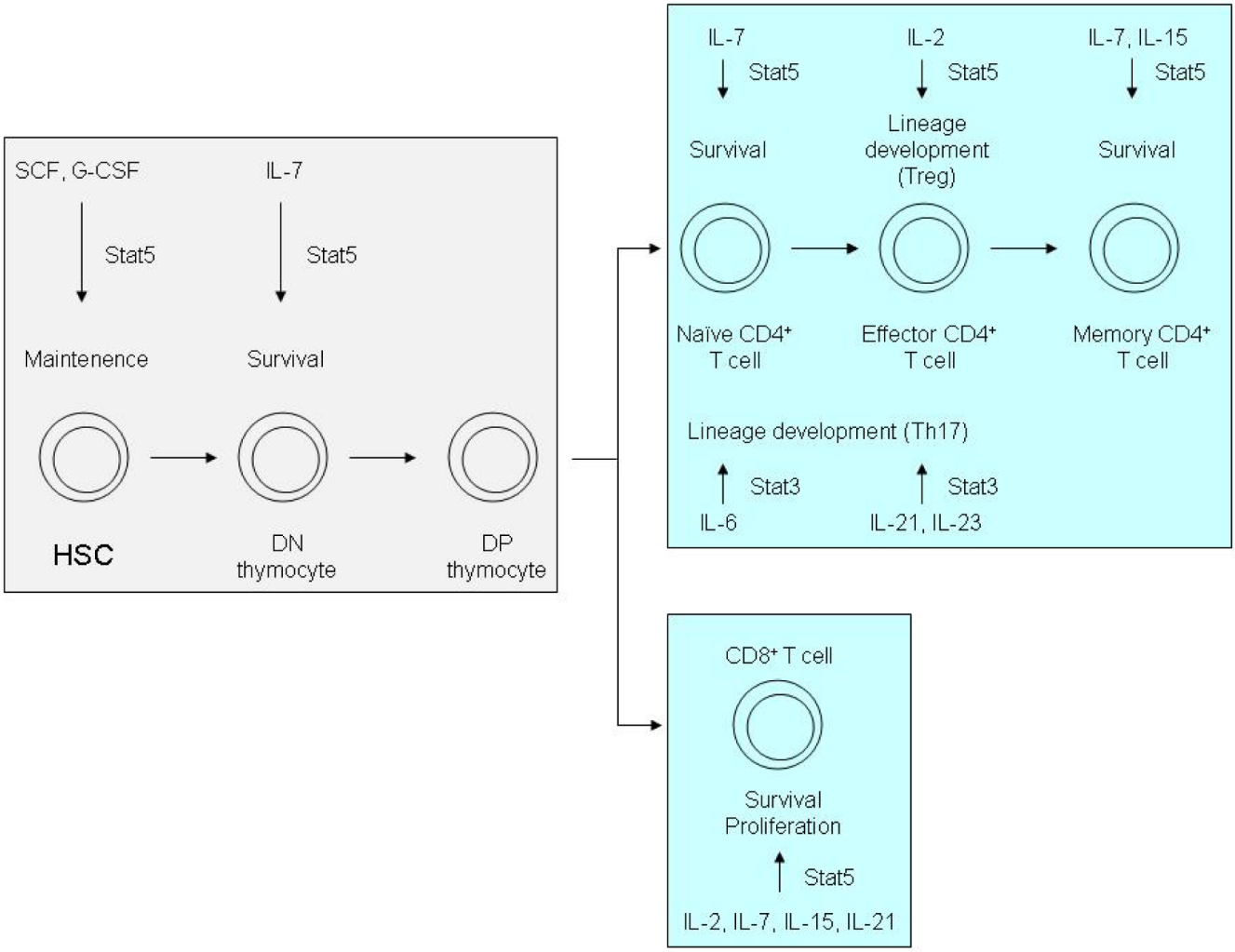

Figure 1. Stat5 and Stat3 in T cell development and differentiation

Stat5a/b (collectively called Stat5) is required for both bone marrow stem cell and early thmocyte development (grey box). Several cytokines, including Stem Cell Factor (SCF) and granulocyte colony stimulating factor (G-CSF) maintain the hematopoetic stem cell (HSC) pool acting though Stat5. IL-7 acting though Stat5 mediates double negative (DN) thymocyte survival. Peripheral T cells require both Stat3 and Stat5 signaling for maintenance and differentiation (green boxes). Stat5 mediates IL-7 and/or IL-15 signals that are critical for naïve and memory T cell survival. After activation by cognate antigen, Stat5 is critical for IL-2 dependent T regulatory (Treg) cell differentiation and maintenance, while Stat3 is required for IL-6, IL-21, and IL-23 dependent T helper 17 (Th17) cell differentiation.