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T cell regulation of hematopoiesis

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1. ABSTRACT

It has long been known that thymus-derived lymphocytes (T cells) can produce cytokines that have powerful effects on hematopoiesis. All major classes of T cells-- CD4 T helper cells, CD4 regulatory T cells, CD8 T cells, γδ T cells and NKT cells-- produce a number of cytokines and chemokines that can modulate hematopoiesis. More recent research has shown that specific T helper cell types, such as Th1, Th2 and Th17 cells, with the development of each subset depending on distinct STAT proteins, have the potential to modulate the hematopoietic response in different ways. In a teleological sense, the overall orchestration of the immune response by T helper cells fits with the concept that T helper cells would modulate the production of cells of the innate immune system by regulating hematopoiesis. Here we will review the literature on how T cell subsets regulate hematopoietic cell differentiation, and discuss how this regulation may complement the specific function of the T cell type.

2. INTRODUCTION

T cells secrete several well-known cytokines, such as IL-3, IL-5, IL-6, GM-CSF and M-CSF that strongly influence and promote hematopoietic cell development. These cytokines act on hematopoiesis through mechanisms that are both direct and indirect (1-3). Each of these cytokines can potentially regulate hematopoiesis at several stages, including the regulation of hematopoietic stem cells (HSC), hematopoietic progenitor cells (HPC) and mature cells in the periphery. However, the exact role of T cells in modulating hematopoiesis has been difficult to decipher since most hematopoietic regulatory cytokines are also produced by cells other than T cells. Experiments performed in the 1980's using an *in vitro* culture system suggested that T cells might regulate hematopoietic progenitor cell activity (4-8). However, as discussed in this review, only in the last few years has more direct evidence been found that T cells, and specific T helper cell subsets, regulate hematopoiesis *in vivo*. Apart from the well-known

hematopoietic cytokines listed above, differentiated CD4 and CD8 effector T cell subsets produce IL-4, IL-9, IL-10, IL-13, IL-17, IFNγ, TNFα, TGFβ and a large number of different chemokines that also each have powerful effects on hematopoiesis. One complicating factor for understanding the role of these factors in T cell-mediated regulation of hematopoiesis is that many T cell-derived cytokines and chemokines can be produced by other cell types besides T cells. This fact precludes a simple assignment of the hematopoietic effects of a particular cytokine to a specific T cell subset, or even strictly to T cells. Along these lines, there is evidence that T cells can be redundant for hematopoietic regulation (9). Another problem for understanding the role of T cells in controlling hematopoiesis is that several of the cytokines and chemokines made by a given T cell type have opposing effects on hematopoiesis when tested in isolation, making readout of overall T cell effects on hematopoiesis highly complicated. For these reasons, the role of specific types of T cells on hematopoiesis is very poorly understood. In this review, we will focus on work demonstrating a direct link between T cell-derived cytokines and effects on hematopoiesis.

3. T CELLS ARE REQUIRED FOR MYELOID CELL MATURATION

Mice that completely lack the development of T cells, including *nu/nu* mice and SCID mice, have decreased numbers of mature monocytes and PMNs in their peripheral blood (10). Moreover, there is an accumulation of HPC in the bone marrow, suggesting that T cell promote the development of mature cells from the uncommitted progenitor cells. This alteration in myeloid cell development can be corrected by thymus grafting and by the transfer of isolated CD4 T cells but not by the transfer of isolated CD8 T cells. Mice defective in CD8, class I MHC-restricted T cell development do not have altered myeloid cell development, suggesting that CD8 T cells are not responsible for this phenotype. Moreover, the CD4 T cell-derived factors that mediate myeloid cell maturation require T cell activation for expression. CD4 TCR transgenic T cells do not rescue myeloid cell development unless they are stimulated with antigen, indicating that production of hematopoietic regulatory factors is dependent upon T cell stimulation. As the relevant hematopoietic regulatory factors were not identified in the Montiero *et al* study, it is not known if STAT proteins are required for this process (10). Nonetheless, the Montiero *et al* data clearly indicate an important role for CD4 T cells in promoting myeloid cell development and differentiation (10).

4. Th1 CELLS REGULATE HEMATOPOIETIC PROGENITOR CELL HOMEOSTASIS

The homeostasis of hematopoietic progenitor cells is regulated by Th1 cell activity. Mice that are deficient in Stat4, and have reduced Th1 cell development, have decreased numbers of hematopoietic progenitor cells (HPC) in the bone marrow and have a lower percentage of HPC in cell cycle (11). Conversely, mice deficient in Stat6, which have increased Th1 activity, have increased HPC numbers in the spleen and bone marrow and that a higher percentage of these cells are actively dividing (11, 12). The T cell-specific nature of these alterations in HPC homeostasis was demonstrated using two techniques. First, expression of Stat4 or Stat6, in a transgenic system where expression is restricted to T cells only using a CD2 locus control region on the background of the respective gene-deficient mice, corrected the defect in HPC activity. Secondly, *in vivo* depletion of CD4 cells but not CD8 cells decreased HPC activity in Stat6-deficient and wild type mice that have *in vivo* Th1 cells. However, *in vivo* depletion of CD4 cells did not decrease HPC activity in Stat4-deficient mice that lack *in vivo* Th1 cell generation.

Th1 cells control HPC homeostasis by the production of Oncostatin M (OSM). While Stat4-/- Th1 cultures had normal expression of IL-3, IL-6, GM-CSF and MCSF mRNA, the production of OSM in Th1 cultures was decreased (11). Moreover, the production of OSM in Stat6-/- Th2 cultures was increased. OSM had previously been identified as a Stat5 target gene and a potential IL-12-induced gene. Moreover, OSM has important roles in controlling hematopoiesis and myeloid transformation (13-16) . While OSM had minimal effects on HPC activity when injected into wild type mice, OSM injection into Stat4-/- mice returned HPC numbers and cycling to wild type levels (11). In contrast, IL-6, another potent hematopoeitic regulatory cytokine that shares cytokine receptor chains with OSM, had no effect on the HPC numbers or cycling in Stat4-/- mice (11). Thus, Th1 cells regulate steady state HPC levels through an OSM-dependent mechanism.

Importantly, the effects of Th1 cells appear restricted to regulating myeloid and erythroid at the HPC stage and do not affect the number or development of more primitive precursor cells. There are no decreases in mature granulocytic cells, neutrophils, monocytes, platelets or red blood cells (11, 12). While homeostatic numbers of mature cells are not altered, it is possible that during an inflammatory response the ability of T helper cells to promote the development of new myeloid cells would be compromised. Given the important role of Stat4 in the development of inflammation (17), it will be interesting to further examine the role of myeloid cell production in an inflammatory disease model system. Despite the increase in colony-forming unit and burst-forming unit cell numbers in Stat6-/- mice, there was no difference in the numbers of "cobblestone area"-forming cells (CAFC) or the numbers of lineage-negative cells that were either c-kit+ Sca-1- or c-kit+ Sca-1+ (12). Moreover, Stat6-/- bone marrow cells were largely indistinguishable from wild type cells in their ability to confer radioprotection and to competitively repopulate hematopoiesis in irradiated mice.

HPCs developed in the absence of Stat4 and Stat6 also have alterations in their responsiveness to other growth factors. Bone marrow cells from Stat6-deficient mice have increased sensitivity to GM-CSF and SLF, compared to wild type cells (18). Increased responsiveness is dependent upon T cells as bone marrow from CD4-depleted mice, but not CD8-depleted mice, lose the hyper-responsive

phenotype. In contrast, bone marrow cells from Stat4-deficient mice have normal responsiveness to growth factor but are resistant to the myelo-suppressive effects of chemokines (18). These effects are likely indirect as chemokine receptor expression was normal on bone marrow cells from Stat4-deficient mice, and we did not observe expression of Stat4 in progenitor cells. Thus, Stat4 and Stat6 have multiple roles in regulating the numbers, proliferation and growth-factor responsiveness of HPC *in vivo*.

Activated Th1 cells produce IL-3, GM-CSF and M-CSF that can promote the differentiation of new macrophages by hematopoietic stem cells (11). However, activated Th1 cells also produce IFNγ and TNFα that both can suppress hematopoietic cell growth and differentiation (19-24). How hematopoietic stem and progenitor cells integrate these sometimes conflicting signals is unclear.

5. THE ROLE OF Th2 CELLS IN MODULATING HEMATOPOIESIS

The differentiation of Th2 cells is dependent upon Stat6, however a specific role for Th2 cells in steady state hematopoiesis is difficult to ascertain using the Stat4- and Stat6-deficient mice, since as described above, alterations in the Th1 compartment in these mice potently affect hematopoiesis via OSM and mask specific Th2 effects. Like Th1 cells, Th2 cells produce IL-3 and GM-CSF, and can generally promote hematopoietic differentiation. Th2 cells also produce several lineage-specific cytokines that can influence hematopoiesis, such as IL-4, IL-5, IL-9 and IL-13. While specific alterations of hematopoiesis during a Th1 cell immune response are not well-studied, there is a well-characterized modulation of hematopoiesis during a Th2 immune response. IL-5 has the important ability to promote the generation of eosinophils from primitive hematopoietic stem cells (25), and IL-5 produced by allergen sensitized CD4 T cells clearly has a role in the eosinophilopoiesis observed during allergic immune responses (25-29). While fully differentiated Th2 cells are dependent upon Stat6, the Stat6-dependence of IL-5 production during a Th2 response is not clear, in light of the fact that IL-5 can be produced independently of Stat6 in one parasite model (30). One explanation for this finding is that Th2 cytokines can also be produced at significant levels by innate immune cells such as mast cells (31, 32). CD8 T cells, which can be pushed to secrete Th2 cytokines (33-35), also regulate the production of IL-5 that promotes eosinophilopoiesis during an allergic response (26, 27). However, with the exception of IL-5, there have been few, if any, studies that link Th2 cytokine-mediated regulation of hematopoiesis specifically to Th2 cells. Since Th2 cytokines such as IL-4, IL-5 and IL-13 can be produced by other cells than Th2 cells, determining which cell types produce the Th2 cytokines is a critical issue.

6. IL-17-SECRETING "Th17" CELLS REGULATE PERIPHERAL NEUTROPHIL NUMBERS

Defining the role of IL-17-secreting T cells in regulating hematopoiesis is still in its infancy. In a model proposed by Ley and colleagues, IL-17 is at the heart of a regulatory circuit controlling neutrophil homeostasis (36, 37). In this model, neutrophils have homeostatic migration into tissues that, in the absence of inflammatory signals, results in apoptosis. Macrophages and dendritic cells, the major sources of the IL-17-inducing cytokine IL-23, phagocytose the apoptotic cells resulting in repression of IL-23 production. Decreased IL-23 leads to decreased IL-17 and lower levels of the IL-17 stimulated gene G-CSF. Decreased levels of G-CSF subsequently result in lower levels of neutrophil production.

Stark *et al* demonstrate that in mice deficient in genes that contribute to the migration and extravasation of neutrophils into tissues have increased numbers of neturophils in the peripheral blood (36). There is a corresponding increase in IL-17-producing T cells. These cells, which are collectively termed neutrophil-regulatory T cells or "Tn cells" are largely γδ T cells, but also contain NKT cells and a smaller percentage of CD4+ αβ TCR T cells. Data also showed that apoptotic neutrophils could alter IL-23 production and that injection of anti-IL-12/23p40 reduced IL-17 production and peripheral neutrophil numbers.

STAT proteins impact this regulatory circuit at several points. G-CSF signaling may depend on Stat3 for some functions (38). The development of IL-17-secreting CD4+ T cells (Th17 cells), activated by IL-6 and IL-21, has recently been shown to be dependent on Stat3 (39-41) and IL-17 production may also be compromised in other T cell types lacking Stat3. IL-23 signaling depends on Stat3 and Stat4 (40). IL-17-secreting T cells may also secrete other factors that impact on hematopoiesis including IL-21 and IL-22 (42), although their functions in hematopoiesis have not been well studied. Further work will be required to determine if IL-17-secreting T cells have effects on hematopoiesis at other stages of development or on other developmental pathways.

7. NATURAL KILLER T CELL REGULATE HSC AND HPC ACTIVITY

Natural killer T (NKT) cells are a subset of T cells that recognize glycolipids in the context of CD1 and require Stat5 for development (43, 44). Recent evidence has also suggested that NKT cells can regulate hematopoiesis. Human HSC express CD1 and can present stimulatory antigen to NKT cells *in vitro* (45). Depletion of NKT cells from cord blood mononuclear cells decreases the CFU activity in the remaining population. Moreover, adding NKT to a short-term clonogenic assay increases CFU numbers through a GM-CSF-dependent mechanism (45). CD1-deficient mice that lack NKT cells also have significantly decreased platelet counts and granulocyte numbers in the bone marrow. Percentages and absolute numbers of lineage-negative, c-kit+ Sca-1+ cells are decreased in the absence of CD1 expression and there is corresponding decrease in BFU-E, CFU-GM and LTC-IC numbers, compared to wild type mice (45). NKT cells also seem to attenuate the myelosuppression following infection of mice with murine cytomegalovirus (46). Collectively,

these results suggest that NKT cells regulate homeostatic hematopoiesis, myeloid progenitor activity during infection and, like CD4 T cells, require activation by a requisite antigen to mediate control of the HSC and HPC activity.

8. CD8 CELLS CAN ALTER HEMATOPOIETIC PROGENITOR CELL ACTIVITY

Apart from the studies on eosinophilopoiesis noted above, very few studies have analyzed the effect of CD8 T cells on normal hematopoietic cell differentiation. Two studies from the 1990's, one in the mouse and one in the human, indicated that CD8 T cells could negatively regulate hematopoiesis (47, 48). IFNγ is a major cytokine made by CD8 T cells and is known to inhibit hematopoiesis (21-24), thus IFNγ may mediate the suppressive effects of CD8 T cells on hematopoiesis. TNFα is another cytokine made by CD8 T cells that can potentially inhibit hematopoiesis (19, 20). However a direct linkage between IFNγ, TNFα, CD8 T cells and hematopoiesis has yet to be established. At least one study showed that IFNγ made by CD4 T cells was more critical for regulating hematopoiesis than the IFNγ made by CD8 T cells (49).

Recently, mice deficient in the transcriptional repressor protein BAZF (BCL6b) were found to have an unusual hematopoietic phenotype involving regulation by CD8 T cells (50). BAZF is very closely related to the BCL6 oncogene that is deregulated in human non-Hodgkin's lymphoma. Both BAZF and BCL6 proteins are potent transcriptional repressors and bind a DNA consensus sequence highly similar (TTCYWNGAA) to the generic Stat factor DNA binding site (TTCNNNGAA) (51-53). Intriguingly, BCL6 has been shown to oppose the transcriptional activity of Stat factors (53-55). Whereas the function of BAZF is relatively unknown, BCL6 is known to be a critical regulator of B and T cell differentiation. BCL6-deficient mice have profound defects in antibody responses and develop severe, frequently fatal, Th2-type inflammation (53, 56). In contrast, BAZF-deficient mice have normal antibody responses and do not develop inflammatory disease (50). The reason for the different phenotypes of BAZF-deficient mice and BCL6-deficient mice is not known, though it likely relates to different expression patterns for the BCL6 and BAZF proteins, rather than divergent functions for the two transcriptional repressors. But, consistent with common functions for BAZF and BCL6, BAZF-deficient mice and BCL6-deficient mice both have defects in CD8 T cell responses as well as strikingly similar abnormalities in hematopoiesis (57-59). BAZF-deficient mice and BCL6-deficient mice both have a severe loss of HPC activity in the bone marrow, but greatly increased HPC activity in the spleen (50). HPC from these mice also display resistance to chemokine-mediated inhibition of growth, and HPC form these mice also have a loss of synergistic growth to SCF plus GM-CSF (50). Many of the hematopoietic abnormalities in BAZF-deficient mice were shown to be dependent upon CD8 T cells, suggesting that BAZF-deficient CD8 T cells produce a factor that strongly influences hematopoiesis (50). Given the shared defect in CD8 T cells and in hematopoiesis in BAZF-deficient mice and BCL6-deficient mice, a reasonable hypothesis is that hematopoiesis in BCL6-deficient mice is also regulated indirectly by abnormal CD8 T cell responses. The mechanism for how BAZF-deficient CD8 T cells affect hematopoiesis is completely unknown. This CD8 T cell pathway may be the result of the deregulation of more than one cytokine, as no single cytokine is known that can explain the complete hematopoietic phenotype of BAZF-deficient mice, or it may be due to the effect of a completely novel hematopoietic regulatory cytokine controlled by BAZF.

9. DO REGULATORY T CELLS INFLUENCE HEMATOPOIESIS?

Regulatory T cells (T-reg cells) expressing the transcription factor FoxP3 have recently been shown to be critical for the control of self-tolerance and for limiting the immune response (60-63). The expression of FoxP3 by T-reg cells is dependent upon IL-2 signals through Stat5 (64-66). T-reg cells mediate immune suppression through several known mechanisms, including secretion of the immune dampening cytokine TGFβ. TGFβ has been extensively studied as an inhibitor of hematopoiesis, and this function fits with the global immuno-suppressive effects of T-reg cells (67-72). However, there is currently no direct data that connects TGFβ secretion by T-reg cells to hematopoiesis. Whether T-reg cells alter hematopoiesis is an important question that will add to our knowledge of the overall physiological role of T-reg cells.

10. PERSPECTIVE

Understanding how different effector T cell subsets regulate both steady state hematopoiesis and "acute" activated hematopoiesis during an immune response is critically important for increasing our knowledge of both hematopoietic regulation and immune regulation. The role of STAT proteins in this process are clear as they are critical in the development of many lineages of T cells that can impact hematopoietic stem and progenitor cell development and function (Figure 1). However, as many different cell types besides T cells secrete cytokines that can modulate hematopoiesis, the precise role of T cells in modulating hematopoiesis has been difficult to study. A further difficulty for this area of research is the complex interplay of the many different factors produced by T cells. As a result, how cytokines and chemokines derived from specific effector T cell subsets influence hematopoiesis and how this hematopoietic regulation impacts on the immune responses is poorly understood. Even in one of the clearest examples of this type of regulation-- IL-5 produced by T cells in allergic responses promoting the production of eosinophils that participate in the allergic inflammatory process-- there are still unresolved questions such as the relative importance of CD4 versus CD8 T cells, whether T cells play a direct or indirect role in IL-5 production and whether committed Th2 cells are involved in this pathway. There is little doubt that

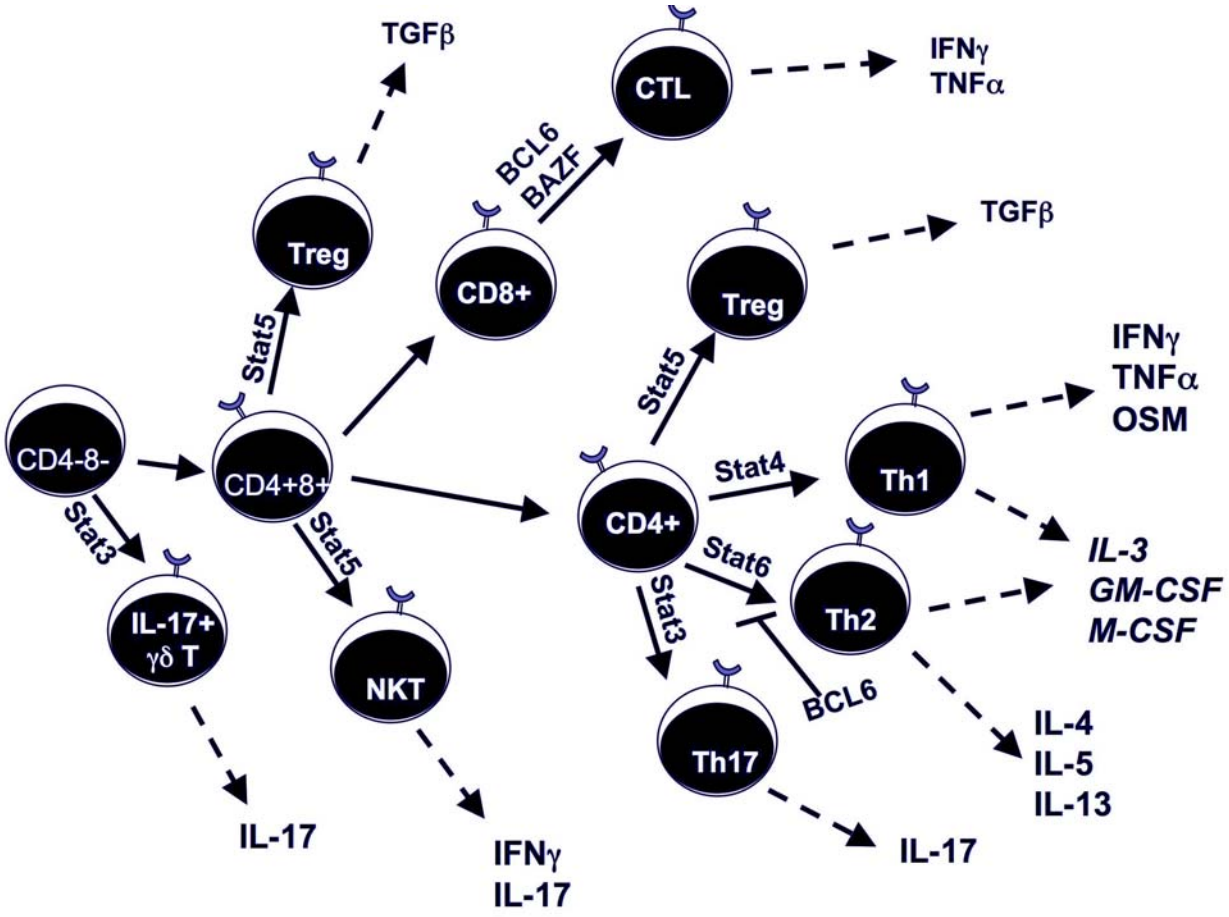

Figure 1. STAT proteins regulate T cell development and differentiation into cytokine-secreting effector cells. This cartoon illustrates the role of STAT proteins in the developmental pathways of various types of T cells that regulate hematopoiesis. The role of BCL6 as an inhibitor of Th2 development and of BCL6 and BAZF as regulators of CD8 T cell function are also indicated. Cytokines that have been linked to altered hematopoiesis are connected by dotted arrows to the T cell types that produce them.

dissecting the pathways by which specific T cell subsets uniquely regulate hematopoiesis is an important area for future immunologic and hematopoietic research.

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