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Review

The opposing and complimentary roles of IL-4 and TGF-β in directing programs of T cell differentiation

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ABSTRACT

T cells are well adapted to sense and respond to cues from their environment. Cytokine cues are particularly important when T cells are first activated. During their initial activation, the cytokine milieu directs the differentiation of T cells towards a particular T helper program while suppressing other fates. Production of T helper-specific cytokines by naive T cell must be prevented to force their dependence on outside cues. If these cues are not provided, or are inappropriately interpreted, the immune response will fail to develop appropriately. This could result in excessive stimulation, and lead to allergy or autoimmunity. In contrast, inadequate responses could lead to immunodeficiency. In this review, we illustrate this dichotomy using TGF-β and IL-4, two cytokines that, when delivered in the presence of IL-2, can drive cells towards the inducible regulatory T (iT_{reg}) cell or the T_H2 cell program. Interestingly, TGF-β and IL-4 antagonize one another and actively suppress the differentiation program induced by the other. Furthermore, the combination of the two signals drives T cells to adopt a different helper program that is characterized by production of the cytokine IL-9, thus defining them as T_H9 cells. Recent data has revealed key mechanisms by which IL-4 and TGF- β promote and/or suppress T_H2 and iT_{reg} cell differentiation programs. Additionally, the molecular pathways that result from the cooperation of TGF-β and IL-4, resulting in T_H9 generation, have been recently defined. We will integrate these new findings and discuss how defects in pathways that help T cells interpret these external cues lead to inappropriate immune responses and can have deleterious consequences.

KEYWORDS: IL-4, TGF-β, T_H2, T_H9, T_{reg}, T cell differentiation, Foxp3, GATA-3, SOX-4, PU.1, IRF-4, STAT6, Ndfip1, Itch, Gfi-1, IL-4, IL-9

INTRODUCTION

The differentiation of naive T cells into the various T helper cell programs requires cytokine cues provided by the local microenvironment. These processes need to be tightly regulated to ensure that the appropriate response occurs. This ensures that immune activation avoids causing disease as it promotes the elimination of deleterious pathogens. For years it has been appreciated that signaling by either IFN-γ or IL-4 drives cells down the T_H1 or T_H2 cell fates, respectively [1]. Advances in our understanding of the numerous cytokines and transcription factors involved in this process, and improved detection methods, have led to the recognition that T_H cell differentiation is a much more complex and plastic process than originally thought. There are numerous T_H cell fates that have been described that now include T_H1, T_H2, T_H9, T_H17, and iT_{reg} cells. Here we will focus on the T_H cell

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lineages regulated by IL-4 and TGF-β, namely T_H2, T_H9, and iT_{reg} cells. IL-4 signaling leads to the activation of STAT6 and up-regulation of GATA-3 while TGF-β signaling leads to the up-regulation of Foxp3. Interestingly, there appears to be a dynamic interplay amongst the two signaling pathways and the impact of this interplay is not completely understood. However, new findings shed light on the molecular players involved. We will discuss these new findings in the context of the T_H2, iT_{reg} cell and T_H9 cell differentiation programs as summarized in Figure 1.

Inhibition of T_H2 differentiation by TGF-β

TGF-β is a pleiotrophic cytokine with many functions. Before its known role in promoting iT_{reg} cell differentiation, TGF-β was shown to have immunosuppressive effects in various models [2]. In an antigen feeding model of tolerance, both T_H1 and T_H2 responses were suppressed upon feeding of the oral antigen Ovalbumin (OVA) [3]. The inhibition of T_H1 and T_H2 responses in this model correlated with high levels of TGF-β found in the peripheral lymph nodes following OVA feeding [3]. While TGF-β can negatively regulate T_H1 and T_H2 cells as well as T cell proliferation [4, 5], this review will focus on the effect of TGF-β on T_H2 cell differentiation.

TGF-β can suppress T_H2 differentiation and block IL-4 production *in vitro* [1, 6-9]. One mechanism that underlies this block in T_H2 cell development is the regulation of GATA-3. TGF-β signaling leads to decreased levels of GATA-3 [8, 9]. However, TGF-β exposure does not interfere with proximal IL-4 signaling, since STAT6 activation is not significantly affected [8, 9]. Additionally, TGF-β limits expression of GATA-3 target genes. This is due to a direct interaction between GATA-3 and Smad3 [10]. While the Smad3/GATA-3 complex can induce IL-5 promoter activity in a luciferase reporter, IL-5 production was not

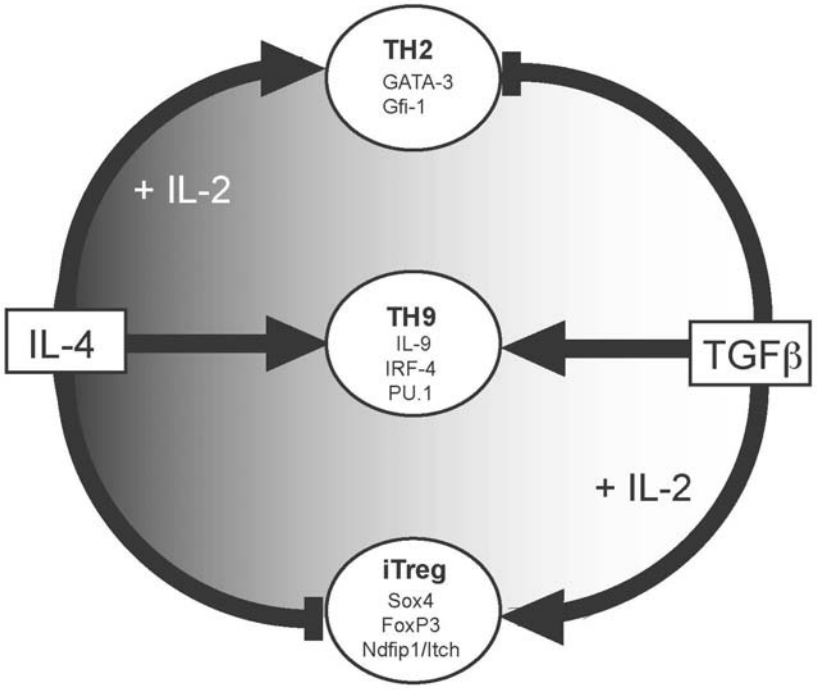

Figure 1. Model of how IL-4 and TGF-β regulate T cell differentiation. IL-4 receptor signaling during T cell activation can counteract the effects of TGF-β, thus inhibiting iT_{reg} cell differentiation while promoting the development of T_H2 cells. Signaling through the TGF-β receptor can induce the expression of factors that prevent IL-4 production and thus drive cells towards the iT_{reg} cell lineage. However, exposure to both IL-4 and TGF-β drive cells towards the T_H9 lineage. Some of the factors that promote these differentiation pathways are shown.

detected in cells exposed to TGF-β [10]. Together, this data suggested that the presence of Smad3 prevented GATA-3 transcriptional activity at the IL-5 locus. Interestingly, IL-10 production was enhanced by TGF-β [10], suggesting that Smad3/GATA-3 interactions can promote a unique group of target genes.

In addition to GATA-3, TGF-β can also inhibit the transcriptional repressor Gfi-1 [11], which promotes T_H2 differentiation. Gfi-1 is transiently expressed upon T cell activation [12, 13] and its expression is enhanced by IL-4 receptor signaling. Gfi-1 acts by promoting optimal T_H2 cell expansion while suppressing the differentiation of other lineages [11, 12]. Supporting this, Zhu *et al*. showed that Gfi-1 suppressed $CD103^+$ Foxp3 T_{reg} cell and T_H17 cell differentiation by acting as a transcriptional repressor. Thus, Gfi-1 promotes T_H2 cell expansion while restricting these other T cell fates. TGF-β actively down-regulates Gfi-1 expression to allow for T_H17 or $CD103^+$ T_{reg} cell differentiation [11]. In addition, it has been suggested that TGF-β inhibits the expression of other factors that promote IL-4 production and T_H2 differentiation. One likely factor is Thp5 since expression of Thp5 is inhibited under T_H17-inducing conditions (TGF-β plus IL-6) [14]. However, it remains to be determined whether IL-6 or TGF-β is responsible for the inhibition of Thp5 expression. TGF-β can also act more proximally to inhibit T_H2 cell differentiation. Chen *et al*. showed that TGF-β blocks the activation of the Tec kinase Itk, thus modulating calcium influx and NFATc translocation to the nucleus [15]. TGF-β-mediated alterations of T cell receptor signaling not only decreased T_H2 cell differentiation but also limited T_H1 cell differentiation [15].

While TGF-β can inhibit the expression of transcription factors that promote T_H2 differentiation, such as Gfi-1 and GATA-3, TGF-β also induces the expression of two proteins that block T_H2 cytokine production, namely Ndfip1 (Nedd-4 family interacting protein-1) and Sox-4. Ndfip1 is an adaptor protein that binds to several members of the Nedd-4 family of E3 ubiquitin ligases *in vitro* [16]. *In vivo*, Ndfip1 promotes the catalytic activity of the E3 ubiquitin ligase Itch to promote JunB degradation, thus limiting IL-4 production in T_H2 cells [17]. We showed recently that TGF-β transiently induces expression of Ndfip1 during iT_{reg} cell differentiation [18]. This burst of Ndfip1 expression was needed to promote JunB degradation and thus block IL-4 production [18]. Together, these data show that TGF-β induces Ndfip1 expression to suppress IL-4 production thus allowing for iT_{reg} cell differentiation [18].

TGF-β also blocks T_H2 cytokine production by inducing the expression of the transcription factor Sox4 [19]. Sox4 belongs to the Sox family of transcription factors that regulate various developmental processes. Sox4 regulates T cell development in the thymus [20] as well as peripheral T cell differentiation. TGF-β promotes Sox4 expression, which then inhibits GATA-3 function by two separate mechanisms [19]. Sox4 binds directly to GATA-3 to prevent GATA-3 function, and Sox4 binds to the IL-5 promoter to prevent GATA-3 binding [19]. Thus, Sox4 is transcriptionally activated by TGF-β receptor signaling to limit T_H2 differentiation and T_H2-mediated airway inflammation [19]. Importantly, while Sox4 acts downstream of TGF-β signaling to block T_H2 differentiation, Sox4 was dispensable for iT_{reg} cell differentiation [19].

These data illustrate that TGF-β is a potent inhibitor of T_H2 differentiation and it employs several distinct molecular mechanisms to suppress the T_H2 cell program. While it is clear that Ndfip1 can act independently of Sox4 during iT_{reg} cell differentiation, whether these factors interact with one another to limit IL-4 production in T_H2 cells remains to be seen.

IL-4 blocks iT_{reg} cell differentiation

Although TGF-β suppresses T_H2 differentiation, IL-4 can potently block iT_{reg} cell differentiation in a dose dependent manner. We have shown that T cells increase their levels of IL-4R as they differentiate into iT_{reg} cells [18]. Increased expression of IL-4R is likely caused by IL-2 receptor signals that the cells receive during the activation process [21]. Thus, environmental cues received by the T cell as it is undergoing iT_{reg} cell commitment can alter its commitment to a particular differentiation program. The molecular cues that prevent iT_{reg} cell differentiation downstream of IL-4 receptor signaling are discussed below.

IL-4 receptor signaling leads to the up-regulation of factors that prevent Foxp3 expression. For example, IL-4 induces the expression of the transcription factors GATA-3, PU.1 and STAT6, all of which can bind to the Foxp3 promoter. Ectopic expression of GATA-3 blocks TGF-β-mediated Foxp3 expression [22-24] even in STAT6- [23] or IL-4- [22] deficient cells. To accomplish this, GATA-3 binds directly to the Foxp3 promoter [23, 24]. This suggests that, once GATA-3 is induced it does not require other IL-4R signaling factors to silence Foxp3 expression. However, while GATA-3 overexpression is sufficient to dampen Foxp3 expression, other factors may participate as negative regulators of Foxp3 expression and thus help to prevent iT_{reg} cell differentiation. Both PU.1 [23] and STAT6 [25] have been shown to bind to regions in the Foxp3 locus and repress TGF-β-mediated promoter activity. Moreover, IL-4 decreases acetylation of the Foxp3 promoter region near the STAT6 binding site at 48 hours after stimulation [25] suggesting that IL-4 may act through as yet undetermined mechanisms to block Foxp3 expression.

Recent studies suggest that Gfi-1 prevents iT_{reg} cell differentiation. Gfi-1 is up-regulated by IL-4R signaling and enforced expression of Gfi-1 reduced the induction of Foxp3+ iT_{reg} cells [11]. However, Gfi-1 did not appear to have a direct effect on Foxp3 levels, rather it decreased iT_{reg} cell expansion.

Thus, to date GATA-3, STAT6 and PU.1 are the primary factors that block Foxp3 expression downstream of IL-4. Surprisingly, while ectopic expression of GATA-3 was sufficient to block Foxp3 expression, GATA-3 mRNA levels are undetectable 24 hours after stimulation with IL-4 and TGF-β, a time when Foxp3 was repressed by IL-4 [25]. This suggests that other factors, such as STAT6, may be required during early time points to suppress Foxp3 expression until GATA-3 levels are sufficiently high enough to enforce the suppressive program. Thus, the temporal regulation of these factors may help to define their precise role in suppressing Foxp3 levels under physiological settings.

While these data suggest that high levels of GATA-3 are deleterious to T_{reg} cell generation, recent data suggests that T_{reg} cells need GATA-3 expression to maintain Foxp3 expression. Supporting this, loss of GATA-3 in T_{reg} cells led to reduced Foxp3 levels and decreased T_{reg} cell function. Mice lacking GATA-3 in T_{reg} cells develop a late-onset autoimmune disease [26]. Whether this is due to a loss of GATA-3 in nT_{reg} cells, iT_{reg} cells, or both subsets, was not investigated. Thus, it remains possible that GATA-3 can function as either a repressor or enhancer of T_{reg} cell differentiation and function depending on the cellular context in which it is expressed. Consistent with this, TCR and IL-2 signaling can increase GATA-3 levels in cells that have committed to the T_{reg} cell lineage [27]. Furthermore, T_{reg} cells that express high levels of GATA-3 accumulate in mucosal tissues and limit inflammation at these sites [27]. Thus, while high levels of GATA-3 may limit the differentiation of T_{reg} cells, similarly high levels in committed regulatory cells may promote their suppressive function.

IL-4 and TGF-β induce T_H9 cell differentiation

In 2008, two groups showed that culturing naive T cells with IL-4 and TGF-β or T_H2 cells with TGF-β induced the differentiation of a new subset of T cells that were termed T_H9 cells [28, 29]. These papers supported previously published data showing that CD4+ T cells cultured in the presence of IL-4 and TGF-β developed into distinct cytokine producing effectors, capable of making IL-2 and IFN-γ [6]. However, Veldhoen *et al.* and Dardalhon *et al.* showed that the T_H9 effector population could promote tissue inflammation [28, 29]. Although a specific transcriptional regulator of T_H9 cell differentiation was not described by either group, Dardalhon *et al.* showed that GATA-3 deficient T cells were unable to become T_H9 cells. Thus, as with other T cell subsets, GATA-3 is essential for T_H9 cell differentiation [29]. More recently, two additional factors that drive T_H9 development have been described, namely IRF-4 and PU.1. These factors are discussed in more detail below.

IRF-4, a transcription factor that plays important roles in T_H2 and T_H17 differentiation, is also essential for IL-9 expression in T_H9 cells [30]. T cells lacking IRF-4 were unable to differentiate into T_H9 cells. This was because IRF-4 binds to

the IL-9 promoter and directly promotes IL-9 expression [30]. Interestingly, IL-9 production in human CD4+ T cells correlated with increased IRF-4 expression, suggesting that IRF-4 is relevant for human T_H9 cell differentiation and function as well [30].

PU.1 is another important regulator of IL-9 production. In T_H9 cells, ectopic expression of PU.1 increases IL-9 production [31]. Supporting a central role for this transcription factor, PU.1 promotes T_H9-specific chromatin modifications at the IL-9 locus [31]. To do this, PU.1 interacts with histone acetyl transferases, such as Gcn5, to increase histone acetylation at the locus, thus promoting IL-9 expression [32]. PU.1 can bind directly to conserved non-coding sequences (CNS) in the IL-9 locus and thus directly regulate IL-9 expression. Thus PU.1 can drive T_H9 differentiation via distinct mechanisms.

While both PU.1 and IRF-4 are important regulators of T_H9 differentiation, it is not known whether these factors work together or separately at the IL-9 locus or whether they regulate unique subsets of T_H9-specific factors. Supporting the latter, it is clear that expression of these two transcription factors is driven by distinct signals. While, PU.1 is induced by TGF-β signaling, IL-4 signaling via STAT6 drives IRF-4 expression during T_H9 differentiation [33]. Furthermore, STAT6 signaling represses T-bet and Foxp3 expression downstream of IL-4 in T_H9 cells to direct cells away from other effector fates [33]. However, whether this requires IRF-4 is not known.

While TGF-β signaling alone can increase levels of PU.1, cooperation between TGF-β and Notch regulates the expression of other IL-9 inducing factors. Notch receptor signaling together with TGF-β receptor signaling promotes the formation of a complex that includes Notch1 intracellular domain (NICD1), Smad3 and RBP-Jκ [34]. This complex binds to and transactivates the IL-9 promoter [34]. Thus, while signals from TGF-β are sufficient to increase IL-9 expression, cooperation between TGF-β signaling and other signaling pathways are needed to drive optimal IL-9 production and T_H9 function [34].

Finally, while it has been shown that TGF-β and IL-4 can promote T_H9 differentiation of both mouse and human CD4+ T cells, there is evidence suggesting that the signals required for optimal T_H9 differentiation of human CD4+ T cells are unique. Supporting this, IL-33 can induce IL-9 production from human CD4+ T cells [35]. However, this remains controversial, as it was not observed in other studies. Nevertheless, pro-inflammatory signals such as IL-1β, IL-6, IL-10, IFN-α, IFN-β or IL-21, can enhance T_H9 differentiation of human CD4+ T cells [36]. Whether this is unique to human cells and how this regulates T_H9 function remains to be resolved.

Implications for human disease

How signals from TGF-β and IL-4 influence T cell fate, and ultimately modify their effector function, are only beginning to be defined. Furthermore, how these signals regulate human health and disease remains poorly understood. Supporting a role for these signaling pathways in immune function, single nucleotide polymorphisms (SNPs) in several factors discussed above have been identified. Importantly, many of these are more commonly found in patients with allergic inflammatory diseases, particularly those that occur at mucosal surfaces.

SNPs in the locus that encodes Ndfip1 were recently described [37]. As discussed above, TGF-β signaling in murine T cells induces an early spike in Ndfip1 expression. Ndfip1 promotes Itch ubiquitylation and consequent degradation of JunB, thus preventing IL-4 production during iT_{reg} cell differentiation. SNPs within the Ndifp1 locus were found more frequently in patients with ulcerative colitis [37], atopic dermatitis and asthma (unpublished observations). While further analysis is needed to determine whether these SNPs correlate with altered Ndfip1 expression or function, these data imply that Ndfip1 may regulate inflammation at mucosal surfaces. Supporting this, patients with a mutation in the gene encoding Itch have been described. This mutation, leading to a truncation in Itch that renders it inactive, was identified in a group of Amish children. These children presented with lung inflammation and, in some cases, multisystem autoimmune diseases in the liver and gastrointestinal tract [38]. These data suggest that defects in Ndfip1- and Itch-dependent ubiquitin

pathways can result in inflammatory and/or autoimmune diseases.

Two major factors driving biological changes downstream IL-4 receptor signaling are STAT6 and GATA-3. STAT6 lies within the chromosomal region 12q13-q24, a region that is genetically linked to asthma and related inflammatory phenotypes. Thirteen SNPs in the STAT6 gene were identified in patients with asthma. These were then used to screen 108 families with at least two children diagnosed with the disease. None of the SNPs showed any linkage association with asthma [39]. However, one SNP in intron 18 of the STAT6 gene showed a significant correlation with increased IgE levels, a predictor of asthma. Additionally, one allele of the dinucleotide polymorphism (GT repeat) in the first exon of STAT6 showed a significant association with another asthma related phenotype, namely eosinophil count [39]. Thus, while STAT6 polymorphisms are not associated directly with asthma, they can correlate with some clinical predictors of asthma. Interestingly, an SNP in the 3' UTR region of the STAT6 gene was associated with increased susceptibility to food allergy [40].

While STAT6 polymorphisms seem to predispose patients to eosinophilia and food allergy, GATA-3 polymorphisms might contribute to asthma and atopic eczema. Three novel GATA-3 haplotypes were found to be associated with asthma-related phenotypes [41]. Furthermore, an SNP in the third intron of GATA-3 (rs444762) associated with atopic eczema [42].

Like T_H2 cells, T_H9 cells are proposed to be effectors that drive allergic responses in the lung and gastrointestinal tract. In the case of T_H2 cells, the specific cytokines produced and their downstream effects have been well-defined. However, the precise functions of T_H9 cells remain poorly understood. While human data is lacking in the gastrointestinal tract, mouse studies support a role for IL-9 in intestinal anaphylaxis [43, 44]. More is known regarding the role of T_H9 cells in human patients with asthma. Several studies have implicated IL-9 in asthma pathogenesis. Increased production of IL-9 and/or expression of IL-9R has been documented in human bronchial biopsy sections from asthmatic patients [45-48]. Furthermore, overexpression of IL-9 in mice causes lung inflammation and airway hyperresponsiveness [49]. Following the initial descriptions of T_H9 cells in 2008, and the association of IL-9 with allergic inflammation, there has been significant interest in targeting IL-9 therapeutically to treat patients with asthma. A human anti-IL-9, MEDI-528, is being developed by MedImmune, LLC. MEDI-528 was recently analyzed in randomized, placebo-controlled Phase II studies [50]. The results were promising as the study showed a favorable safety profile with some clinical improvements in asthmatic patients. This supports the need for continued studies in larger patient cohorts with asthma and other allergic disease [50].

CONCLUSIONS

It is clear that IL-4 and TGF-β can antagonize one another during the development of T_{reg} or T_H2 cell differentiation, respectively. The recent description of T_H9 cells shows that these two cytokines can coordinate their actions to orchestrate an entirely different T_H cell profile. Since most of these studies are performed *in vitro* with super-physiologic concentrations of cytokine, it remains unclear the extent to which local concentrations of IL-4 and TGF-β influence the outcome of the T_H cell differentiation program *in vivo*. How other cytokines and chemokines in the local cytokine milleu counteract or cooperate with each of the signaling pathways are also unknown. Future studies are warranted to fully understand the dynamic nature of cytokine signaling and the function outcomes. Such studies will not only improve our understanding of T cell subsets and their function, but will likely reveal new therapeutic approaches with which to treat allergic diseases.

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