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The effects of IL-6 on CD4 T cell responses

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Abstract

Cytokines have long been known to profoundly influence the adaptive immune response by determining CD4 T cell differentiation. Although IL-6 has been initially characterized as a B cell growth factor and inducer of antibody production research from our lab and others has revealed over the last years that IL-6 also plays a significant role in CD4 T cell differentiation. This review highlights the variety of ways in which IL-6 affects CD4 effector functions and how this may contribute to different types of diseases.

Keywords

IL-6; IL-6R; CD4 T cell differentiation; T helper response; Th1/Th2/Th17; IL-21; autoimmune disease; allergic airway inflammation

Introduction

In a search for factors that promote plasma cell differentiation and antibody production of B cells, one cytokine now known as IL-6 was discovered in 1986 [1]. In addition to its effects on antibody production, IL-6 has a strong stimulatory effect on the growth of mouse plasmacytoma and human myeloma cells [2]. Together with TNFα and IL-1, IL-6 is also considered a major proinflammatory cytokine important in the protection from pathogens during an infection. Proinflammatory cytokines are also known to play an important role in disease progression and tissue damage of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus. In the last years, it has become increasingly clear that IL-6 is an important modulator of CD4 T cell effector functions thereby shaping the immune response and contributing to inflammation.

The IL-6 receptor and its signaling pathways

IL-6 is a pleiotropic cytokine expressed by antigen presenting cells (APCs) such as dendritic cells, macrophages and B cells among other cells of the hematopietic system but is also produced by a variety of non-hematopoietic cells including keratinocytes, fibroblasts, epithelial cells, and astrocytes [3]. IL-6 production is induced in response to a number of external stimuli like IL-1, tumor necrosis factor (TNF)α, LPS, and platelet-derived growth factor (PDGF) [3]. IL-6 binds to a receptor complex consisting of the specific IL-6R and the common signaling component gp130 which is also shared by other cytokines of the IL-6 family (e. g. oncostatin

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M, leukemia inhibitory factor (LIF), IL-11) [4]. X-Ray crystallography has shown that two heterotrimers of IL-6, IL-6R and gp130 associate to form a hexameric complex [5]. Through formation of this complex members of the cytoplasmic Janus kinase (Jak) family of tyrosine kinases bind to gp130 inducing their kinase activity resulting in phosphorylation of downstream targets. Jak1 is thought to be most relevant for IL-6 signaling although Jak2 and Tyk2 also transduce some of the IL-6 signals [4]. The best described substrate for Jaks in IL-6 signaling is the Signal Transducer and Activator of Transcription (STAT)3, a transcription factor that in its inactive state remains in the cytoplasm but after phosphorylation through Jaks forms homodimers that are actively being transported to the nucleus to induce gene transcription [6]. To a lesser extent, STAT1 has also been involved in IL-6 signaling [7]. Other than STAT family members, IL-6 stimulation activates the transcription factor CCAAT/enhancer binding protein (C/EBP)β through the ras-Erk MAPK cascade and further upregulates the expression of C/EBPδ [4,8]. C/EBP family member are therefore important mediators of IL-6-induced changes in gene expression. Lastly, phoshpatidyl-inositol (PI)3-kinase has been described as a signal transducer of IL-6 triggering the activation of Akt and subsequently promoting survival in many cell types [9].

While gp130 is ubiquitously expressed, IL-6R is present mostly on leukocytes and hepatocytes [10]. In accordance with its expression pattern, IL-6 regulates acute phase protein production in the liver as well as proliferation, survival and function of many leukocyte populations [3]. Surprisingly, it was observed that cells lacking IL-6R expression were responsive to IL-6 stimulation especially during inflammatory conditions. This finding led to the discovery of a soluble form of the IL-6R that lacks the transmembrane domain but retains its ability to bind to IL-6 and gp130 to form a functional complex in a process called transsignaling of IL-6 [11]. Soluble IL-6R (sIL-6R) can be generated by two mechanisms: 1) Metalloproteinase mediated cleavage (“shedding”) of the membrane bound form of the IL-6R [12], and 2) expression of an alternatively spliced IL-6R variant that lacks the transmembrane domain [13]. Little is known about the regulation of the full-length IL-6R cleavage versus expression of the alternatively spliced receptor and which cells are the sources of sIL-6R. Neutrophils and macrophages in addition to some cell lines have been shown to produce sIL-6R [13,14,15]. We have recently demonstrated that human CD4 T cells also produce sIL-6R upon T cell receptor activation primarily through cleavage of the cell surface IL-6R by the ADAM family of metalloproteinases [16]. Thus, CD4 T cells at the site of inflammation can not only provide cytokines but also exert effector functions through release of sIL-6R. In conjunction with cells that produce high levels of IL-6 such as macrophages and fibroblasts, the presence of the sIL-6R renders cells lacking the IL-6R, but expressing gp130, responsive to IL-6.

IL-6 in T cell survival and proliferation

IL-6 was initially cloned as a growth factor for B cells and inducer of plasma cell differentiation [1]. Over the years it has become increasingly clear that IL-6 has also a profound effect on CD4 T cells. Resting, naïve CD4 T cells undergo apoptosis in *in vitro* cell culture soon after isolation from lymphoid mouse tissues suggesting the presence of survival factors *in vivo*. IL-6 has such anti-apoptotic properties as it prolongs CD4 T cell survival *in vitro* most likely by retaining Bcl-2 expression in the isolated T cells [17].

Soon after its discovery, IL-6 was described as a costimulatory molecule for T cell activation enhancing proliferation independently of IL-2 gene expression [18]. It further protects CD4 T cells from activation induced cell death (AICD) due to downregulation of FasL expression again without an involvement of IL-2 [19,20]. Antigen specific CD4 T cells also expand more vigorously *in vivo* when IL-6 is present during immunization due to reduced apoptosis suggesting that IL-6 may increase the effector/memory T cell population [21]. Likewise, the memory response against a second, heterologous influenza infection is impaired in IL-6 gene

deficient mice which coincides with reduced T cell numbers in the lung [22]. Interestingly, IL-6 stimulation has been linked to increased migration of activated T cells *in vitro* [23] which could explain their inability to enter the infected lungs in the absence of IL-6 during an infection. In the light of recent findings regarding the role of IL-6 in T cell differentiation it may be interesting to revisit the effects of IL-6 on CD4 T cell survival and correlate it to the different T helper subsets generated in the presence of IL-6.

IL-6 in the Th1/Th2 decision

Since IL-6 is rapidly produced by professional APCs in response to different stimuli it was possible that it may act similar to IL-12 in determining the differentiation of naïve CD4 T cells in effector cells. Our group was the first to show that indeed IL-6 can modulate the Th1/Th2 balance towards Th2 [24]. IL-6 present during antigen stimulation of CD4 T cells promotes autocrine IL-4 production which further enhances Th2 differentiation through an auto-feedback loop [24](Fig. 1). The IL-6 mediated IL-4 expression requires upregulation of Nuclear Factor of Activated T cells (NFAT)c2 expression which is largely absent in unstimulated naïve CD4 T cells [25,26]. Nuclear accumulation of NFATc2 results in increased IL-4 expression. It is unclear how IL-6 promotes NFATc2 expression but activation of C/EBP family members is a likely mechanism as sequence analysis predicts potential C/EBP binding sites within the NFATc2 promoter and C/EBP-mediated NFATc2 expression has been demonstrated in hepatocytes [27]. In addition to NFATc2, IL-6 activates IL-4 expression through early upregulation of the transcription factor c-maf in a STAT3 dependent pathway [28]. c-maf is specifically expressed in Th2 cells and contributes to IL-4 expression via binding to its promoter but is not required for IL-5 expression [29]. Interestingly, CD4 T cells differentiated to Th2 in the presence of IL-6 are similarly unable to produce IL-5 although they express high amounts of IL-4 [25]. How IL-6 orchestrates the effects of c-maf and NFATc2 has not been addressed yet but the fact that c-maf alone is insufficient to mediate IL-4 expression suggests a synergistic collaboration between both transcription factors. Given its enhancing effects on Th2 differentiation, IL-6 may play a role in the development and exacerbation of Th2 mediated diseases such as allergic airway inflammation and asthma. High IL-6 and sIL-6R levels have been found in the bronchoalveolar lavage fluid of asthmatic patients as well as in mouse models of allergic airway inflammation [30]. IL-6 has been suggested to play a protective role in disease progression since IL-6 gene deficient mice exhibit increased inflammation compared with their wild type littermates in a mouse model of allergic asthma [31]. On the other hand, inhibition of IL-6R signaling by neutralizing antibodies against the IL-6R diminished disease progression in a mouse model of OVA-induced allergic airway inflammation [32]. Although it is not clear yet whether the IL-6 mediated effects in Th2-type diseases such as asthma are through upregulation of IL-4 those results indicate that it could be a potential target for a therapeutic intervention.

In addition to promote Th2 differentiation directly by upregulating IL-4 production, IL-6 contributes also in another, IL-4 independent way to Th2 differentiation of CD4 T cells. The presence of IL-6 during the activation of CD4 T cells induces the expression of Silencer of Cytokine Signaling (SOCS)1 thereby interfering with IFNγ signaling and production [33]. Without a positive feedback loop through endogenous IFNγ, CD4 T cells stimulated in the presence of IL-6 produce less IFNγ and show a diminished Th1 phenotype. IL-6 has therefore two independent ways to shift the Th1/Th2 balance of an immune response towards Th2, by promoting early IL-4 expression and by rendering CD4 T cells unresponsive to IFNγ signals.

IL-6 in the regulation of Th17 differentiation

The effect of IL-6 on promoting Th2 and inhibiting Th1 differentiation does not correlate with the high levels of IL-6 found in some autoimmune diseases such as rheumatoid arthritis which had been associated with a Th1-type inflammatory response. This discrepancy was resolved

with the discovery of two new T cell subsets, T regulatory (Treg) and Th17 cells, which both play a major role in inflammatory processes and are affected by IL-6 stimulation. Th17 cells are a recently described subset of differentiated T effector cells which preferentially expresses IL-17 while Th1 and Th2 cytokines are virtually absent in those cells [34]. Several studies have now shown that the de novo differentiation of Th17 cells from naïve mouse CD4 T cells is achieved by the simultaneous treatment with IL-6 and low doses of transforming growth factor (TGF)β during antigen stimulation [35,36,37]. This function of IL-6 is completely dependant upon TGFβ as IL-6 alone is unable to induce IL-17 expression. The contribution of TGFβ to Th17 differentiation in human CD4 T cells remains controversial. Initial studies suggested that a synergistic collaboration between IL-6 and IL-1β as well as IL-23 achieves Th17 differentiation while the presence of TGFβ was not required [38,39]. However, recent studies have shown a requirement for low doses of TGFβ together with various combinations of IL-1β, IL-6, IL-21, and IL-23 in Th17 differentiation of human naïve CD4 T cells [40,41,42]. Since IL-21 and IL-23 can induce STAT3 similar to IL-6 there may be some functional redundancy between these cytokines which may explain why they all achieve IL-17 expression.

TGFβ has been known for a long time as an immunosuppressive cytokine and was described to differentiate naïve CD4 T cells into inducible T regulatory (iTreg) cells [43]. As naturally occurring Treg cells that arise in the thymus, iTreg express the transcription factor Foxp3 which downmodulates IL-2 production and promotes immunosuppressive functions of Treg cells. These studies now show a direct link between the differentiation of iTreg and Th17 cells through the absence or presence of IL-6 during antigen stimulation. The first hint that IL-6 may play an important role in overcoming Treg mediated immune suppression was demonstrated by a study showing that dendritic cells activated by toll-receptor stimulation secrete cytokines that inhibit the Treg mediated suppression of activated T cells [44]. Further analysis revealed that IL-6 was required for blocking Treg function although it was suggested that it has to work in conjunction with some other cytokine(s) as its sole presence could not abrogate the negative regulatory effect of Treg cells [44]. Likewise, transsignaling via the soluble IL-6 receptor abrogates the induction of Foxp3 and the generation of iTreg in naïve CD4 T cells through upregulation of the TGFβ signaling inhibitor Smad7 [45]. Thus, IL-6 has a pivotal role in switching the immune response from a tolerant state to active inflammatory conditions.

In several recent studies, the mechanisms by which IL-6 promotes Th17 differentiation have been further elucidated. IL-6 together with TGFβ upregulates expression of the transcription factor retinoic-acid receptor related orphan nuclear receptor (ROR)γt which is required for IL-17 expression and has been postulated as Th17 lineage determining transcription factor similar to T-bet for Th1 and c-maf and GATA3 for Th2 cells [46]. RORα is a close homologue to RORγt and may play a similar role in Th17 differentiation [47]. It has been shown recently that RORγt binds to a consensus motif in the IL-17 promoter but a direct interaction with Foxp3 inhibits its transcriptional activity [48]. IL-6 upregulates RORγt expression through STAT3 and downregulates Foxp3 thereby shifting the balance from Treg towards Th17 differentiation.

IL-6 promoting IL-21 production

In an effort to determine IL-6 induced changes in gene expression early upon antigen stimulation of CD4 T cells we found that among many genes affected by the IL-6 treatment the cytokine IL-21 was the only gene upregulated over 200-fold by IL-6 (Dienz, O., unpublished data). IL-21 is a common γ-chain dependant cytokine whose expression is restricted to CD4 T cells and natural killer (NK)T cells [49,50]. It was first described as a cytokine produced primarily by effector T cells, especially Th2 cells, but not by naïve CD4 T cells [51]. However, our recent studies show that IL-21 can be readily produced by naïve and memory CD4 T cells when IL-6 is present during antigen stimulation (Dienz, O., unpublished

data). No other cytokine appears to have an effect similar to IL-6. Recent studies have shown that Th17 cells are high producers of IL-21 [52,53,54] and it is now believed to be a cytokine specific for this T cell subset. However, the high production of IL-21 in Th17 cells could just be the result of the presence of IL-6 during their differentiation. The fact that IL-6 induces IL-21 expression prior to IL-17 expression and does not require the presence of TGFβ supports this alternative model (Dienz, O., unpublished data). Furthermore, intracellular cytokine stain of Th17 cells revealed that only a small percentage of cells co-express IL-17 and IL-21 while the majority produces only one of the two cytokines (Dienz, O., unpublished data and [55]). In addition, a recent study has shown that vasoactive intestinal peptide (VIP) together with TGFβ induces the generation of Th17 cells that produce IL-17 and IL-22, but lack IL-21 expression [56]. Thus, IL-21 production appears to be dissociated from IL-17 production and is highly dependant upon IL-6 stimulation. The induction of IL-21 expression in CD4 T cells by IL-6 is independent of RORγt but requires binding of STAT3 to the IL-21 promoter [52, 57](Fig. 2). Initial studies proposed IL-21 as an autocrine factor further enhancing Th17 differentiation since it can promote IL-17 expression in the presence of TGFβ [52,53,54]. However, more recent studies show no requirement for IL-21 in mouse models of Th17-associated diseases challenging the perception of IL-21 as a Th17 cytokine [58,59]. Thus, IL-21 may have some contribution to Th17 differentiation especially *in vitro* but other factors such as IL-6 seem to play a much more important role *in vivo*. Whether IL-21 mediates some of the effector functions of Th17 cells in certain diseases has become even more questionable when there is only little overlap in the expression of IL-17 and IL-21. In summary, the combination of IL-6 and TGFβ remains pivotal for the de novo differentiation of Th17 at least in mice.

Does IL-6 promote the differentiation of a unique T helper subset?

While IL-6 in the presence of TGFβ can generate Th17 cells, IL-6 by itself is also capable of inducing additional types of effector cytokines and suppressing the production of others. The question remains whether these CD4 T cells activated in the presence of IL-6 represent a different subset from the currently well established Th1, Th2, and Th17 cells. Only recently, a new CD4 T cell subset has been defined providing B cell help in germinal centers of B cell follicles and therefore aptly termed T follicular helper (Tfh) cells [60]. They are characterized by the expression of the chemokine receptor CXCR5 whose ligand CXCL13 is expressed by lymphoid stromal cells attracting Tfh cells to lymphoid follicles [60]. Microarray analysis revealed a very distinct gene expression profile of Tfh cells compared with Th1 and Th2 differentiated effector cells with IL-21 being a characteristic Tfh cytokine [61]. IL-21 is most likely the main effector molecule of Tfh cells to mediate the generation of plasma cells and antibody production in germinal center B cells. On the other hand, the factor(s) promoting the Tfh phenotype have not been discovered yet. Since IL-6 is a major inducer of IL-21 production in CD4 T cells it is possible that IL-6 contributes to the differentiation of the Tfh subset. This model is supported by the fact that IL-6 differentiated effector cells retain their ability to produce IL-21 even when cultured under Th1, Th2 or Th17 conditions [55]. Although IL-6 has been initially described as B cell growth factor and has long been known to play a role in antibody production this might be a mostly indirect effect through its upregulation of IL-21 production in CD4 T cells.

Conclusions

From its discovery as a B cell growth factor more than 20 years ago, our knowledge about the functions of IL-6 has improved greatly. IL-6 is now considered as an important mediator of the immune response especially by directly acting on CD4 T cells and determining their effector functions. It remains an open question how IL-6 orchestrates all these different functions but the presence of other factors will probably be a likely explanation. While TGFβ alone induces Treg differentiation, IL-6 reduces Foxp3 expression and enhances RORγt expression, thereby

generating Th17 cells [48]. Thus, IL-6 is an important switch determining whether Th17 or Treg cells are generated when TGFβ is present. Since IL-6 alone already upregulates the expression of RORγt [52] the lack of IL-17 expression in IL-6 stimulated CD4 T cells suggests that another critical signal is provided by TGFβ to achieve Th17 differentiation. Accordingly, IL-6 generated effector cells are distinct from Th17 cells as they express high levels of IL-21 but not IL-17 [55]. IL-21 is the signature cytokine of Tfh cells suggesting a role of IL-6 in the differentiation of this T helper cell subset but that remains to be further investigated [60]. IL-6 has also been reported to promote Th2 differentiation [24,25] and at first it seems difficult to imagine how IL-6 stimulation could mediate the generation of two distinct T cell subsets. Nevertheless, full differentiation of Tfh cells could require an additional signal which may be provided by germinal center B cells or follicular dendritic cells which are in close contact to Tfh cells during an immune response [60]. Another possibility is a linear model where IL-6 induced potential Tfh cells are an intermediate step in the differentiation of Th2 cells. In support of such a model, IL-6 promotes IL-21 production before IL-4 can be detected and IL-6 induced effector cells co-express both cytokines when exposed to Th2 conditions similar to IL-4 differentiated Th2 cells [25,55](Fig. 3). A further characterization of Tfh cells is necessary to reveal their relationship to Th2 cells and how IL-6 affects their differentiation. Since both subsets are thought to play an important role in providing B cell help an understanding of their generation and maintenance may help in the design of efficient vaccines to promote long-lasting protective antibody production.

Given the various responses elicited by IL-6 in CD4 T cells, therapies using humanized antibodies against the IL-6R yielded promising results in several diseases so far. In fact, anti-IL-6R therapy has already been approved in some countries for Castleman's disease and shows very good responses in clinical trials for rheumatoid arthritis and Crohn's disease [2]. Since Th17 cells are thought to play a major role in other autoimmune diseases such as multiple sclerosis and psoriasis additional clinical applications for an anti-IL6 therapy may be worth testing in the future, given the important role of IL-6 in Th17 differentiation. In addition, the various ways of IL-6 in contributing to CD4 T cell effector functions suggests that other, more Th2-type diseases like allergic asthma may benefit from a therapy targeting IL-6. One future emphasis will be to define the molecular mechanisms of how exactly IL-6 contributes to disease progression and CD4 T helper cell differentiation in various diseases. Although much progress has been made lately in revealing the importance of IL-6 in CD4 T cell functions, there is still more to be learned until the diverse functions of IL-6 in the immune response are understood.

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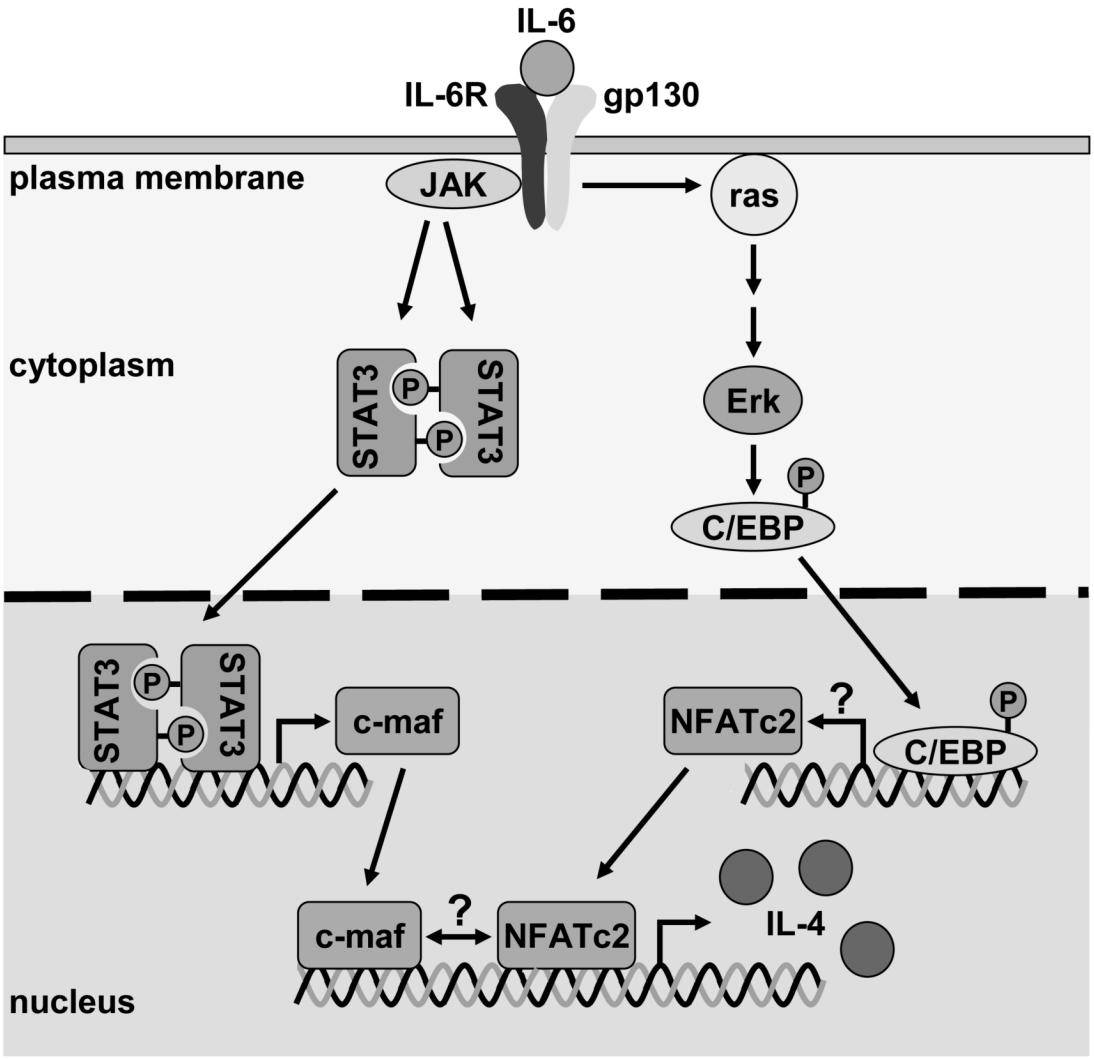

Figure 1.
Molecular mechanism of IL-6 induced IL-4 production. Stimulation by IL-6 activates the transcription factors STAT3 through JAKs and C/EBP through the ras-ERK MAPK cascade. STAT3 upregulates c-maf expression while C/EBP may mediate upregulation of NFATc2. c-maf and NFATc2 activate in a potentially synergistic manner the expression of IL-4. Autocrine production of IL-4 will subsequently promote Th2 differentiation.

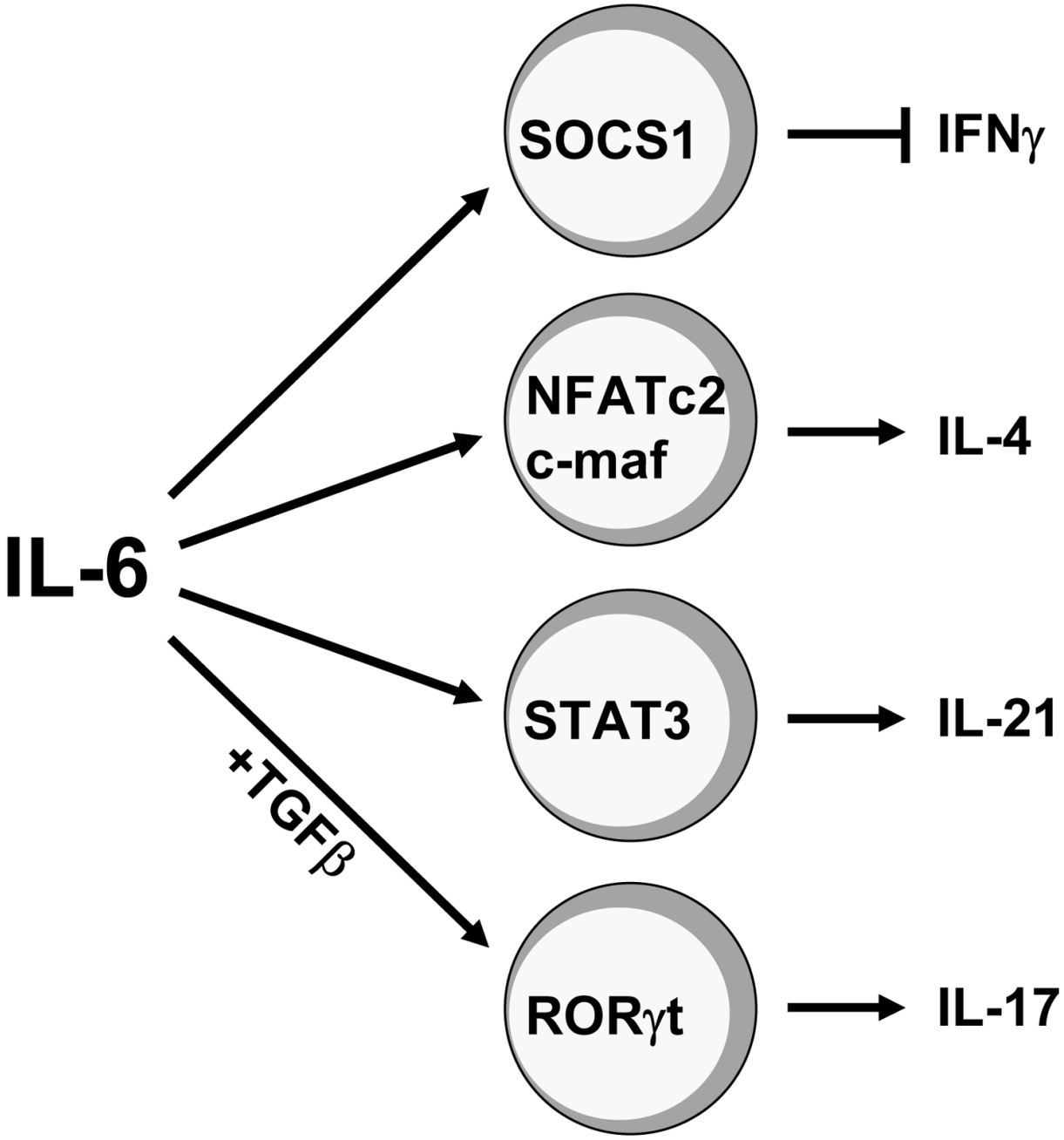

Figure 2.
IL-6 exerts its effects on cytokine production through a diverse set of key molecules. Upregulation of SOCS1 expression inhibits IFNγ signals thereby diminishing additional IFNγ production. IL-4 production is mediated through the induction of NFATc2 and c-maf expression. STAT3 directly regulates IL-6 induced IL-21 expression, which therefore precedes expression of the other cytokines. Simultaneous stimulation through IL-6 and TGFβ induces high level expression of RORγt which mediates IL-17 production.

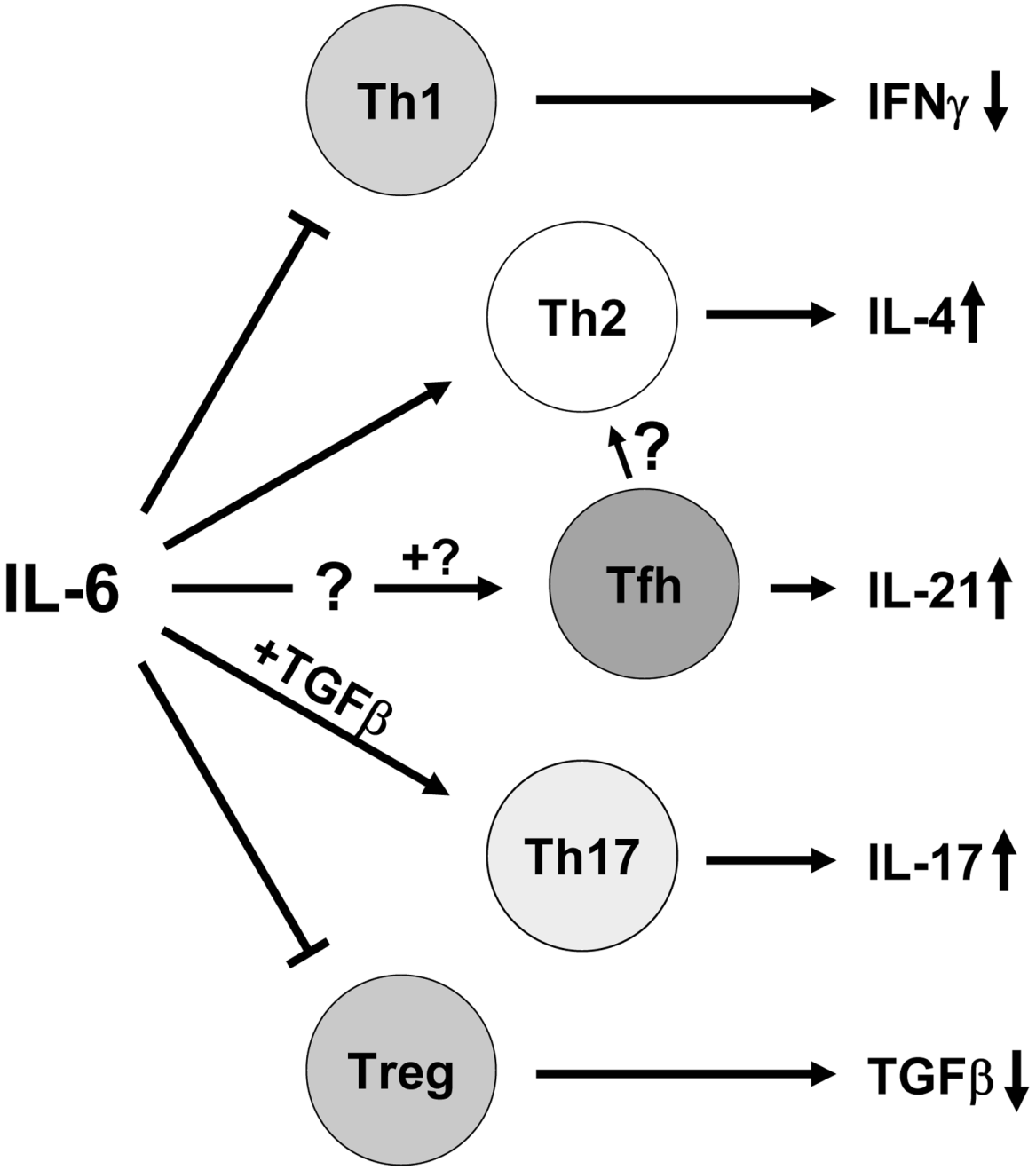

Figure 3.
Contribution of IL-6 to T helper cell differentiation and subsequent cytokine production by various T cell subsets. IL-6 exerts inhibitory activity towards Th1 and T regulatory (Treg) differentiation/function and promotes Th2 and Th17 differentiation either alone (Th2) or together with TGFβ (Th17). The role of IL-6 in T follicular helper (Tfh) cell differentiation is suggested due to its specific upregulation of IL-21 in naïve CD4 T cells.