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Regulation of IL-17 production in human lymphocytes

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Abstract

The discovery of a new lineage of helper T cells that selectively produces interleukin (IL) - 17 has provided exciting new insights into immunoregulation, host defense and the pathogenesis of autoimmune diseases. Although the factors that promote murine Th17 differentiation have been intensively examined, there has been much less information on the regulation of this cytokine in human T cells. IL-17 is readily produced by human memory T cells, which we now know express distinct patterns of chemokine receptor expression and may differentiate in response to selective pathogens. Recently it has been shown that IL-1, IL-6 and IL-23 are important in driving human Th17 differentiation. However, TGF β -1 which is important for the differentiation of murine Th17 cells and inducible regulatory T cells (iTregs), is not required and even inhibits for human Th17 differentiation. In addition, human Th17 cells also produce other proinflammatory cytokines. Further characterization of the transcription regulation of human IL-17 expression, and the epigenetic regulation of human *IL17* locus should improve our understanding the lineage commitment of human Th17 cells. Targeting the production and action of this cytokine is also likely to be beneficial therapeutically for autoinflammatory and autoimmune diseases.

1. Introduction

IL-17A is a proinflammatory cytokine initially identified in mouse cytotoxic T cells [1]. Later human IL-17 was cloned and the cDNA encodes a 155-amino acid polypeptide with an N-terminal hydrophobic signal sequence typical of cytokines [2]. Now we know that this family includes 6 family members: IL-17 (also denoted IL-17A), IL-17B, IL-17C, IL-17D, IL-17E and IL-17F [1–4] that share 16–50% amino acid identity but apparently have different tissue expression patterns. IL-17A and IL-17F appear to be important in host defense against extracellular bacteria and fungi [5–7]. Additionally, a number of autoimmune diseases are associated with overproduction of these cytokines and interference with IL-17 production or action attenuates autoimmune disease [8–14].

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Although it has been known for more than 10 years that IL-17 is a product of activated CD4⁺T cells, it was not until recently that it was recognized that a subset of helper T cells exists, Th17 cells, which preferentially produces IL-17 [15–17]. Conversely, it was also recognized that polarized Th1 and Th2 cells generally do not produce IL-17 and in fact, IFN- γ and IL-4 inhibit Th17 differentiation. Thus, it was proposed that IL-17-producing helper T cells or Th17 cells represent a new lineage of CD4⁺ T cell, although it should be borne in mind that cells producing both IFN- γ and IL-17 are readily detectable in physiologic and pathologic settings. During the past two years, cytokines and signaling pathways involved in regulating this new lineage differentiation, as well as its importance in the pathogenesis of autoimmune disease, have been intensively investigated in various mouse models. Given the pathogenic relevance of IL-17, it is obviously important to understand how this cytokine is controlled in human T cells and to define the conditions under which human naïve CD4⁺ T cells might become Th17 cells. Despite a great deal of information on the regulation of IL-17 in the mouse, until recently there has been a paucity of information of the control of IL-17 in human lymphocytes. Recent advances in our understanding of the similarities and differences in the regulation IL-17 in mice and humans will be discussed in this review.

2. Overview of murine Th17 regulation

Like other CD4⁺ T cell subsets, Th17 differentiation is largely controlled by products of dendritic cells (DCs) and other antigen presenting cells. Specifically, inflammatory cytokines like IL-6 in conjunction with TGF β -1 are important initiators of the program that drives differentiation of naïve CD4⁺ T cells to become Th17 cells [18][19][20]. Accordingly, IL-6^{-/-} mice have reduced but not absent Th17s [21]. Another product of DCs, IL-23, serves to expand and maintain Th17s in vivo. The current view is that IL-23 is not sufficient to drive Th17 differentiation of naïve cells principally because naïve CD4⁺ murine T cells lack receptors for this cytokine. Nonetheless, IL-23 is important for driving production of IL-17 in vivo [22–24][25]. Th17 cells preferentially produce IL-21, which has an important role as an autocrine positive regulator of Th17 differentiation and a negative regulator of Th1 differentiation [21, 26–29]. Thus, IL-21 acts in a manner analogous to IL-4 in that the lineage specific product promotes differentiation to the subset that produces this factor while simultaneously inhibiting other fates. Accordingly, both IL-21 and IL-21R-deficient mice also have significant impairments IL-17 production [26][21].

What these cytokines, IL-6, IL-21 and IL-23, all have in common is that they activate the transcription factor Stat3. Stat3 directly binds the *Il17* and *Il21* genes [30] [27]. Stat3 is also a positive regulator of another transcription factor, the orphan retinoid receptor, Ror γ t, which is a critical regulator of Th17 differentiation [31]. Conversely, retroviral overexpression of constitutively active Stat3, results in increased production of IL-17 production [32]. Stat3 also regulates expression of IL-23R [26, 28, 33]. Suppressor of cytokine signaling (SOCS3) is a cytokine-inducible negative regulator of Stat3. Interestingly, deletion of *Socs3* is associated with enhanced Stat3 phosphorylation and increased IL-17 production, and widespread inflammatory disease consistent with dysregulation of IL-17 production [30, 34].

In their original studies of murine Th17 differentiation, Stockinger's group pointed out that LPS-stimulated DC cells were potent inducers of Th17 development[18]. In addition to IL-6 and TGF β -1, they showed that inflammatory cytokines such as IL-1 and tumor necrosis factor (TNF) are contributors to murine Th17 differentiation. Although in vitro differentiation of Th17 cells can occur in the absence of IL-1, IL-1RI^{-/-} mice have impaired Th17 cell differentiation and reduced incidence of EAE associated with failure to induce autoantigen-specific Th17 cells [35].

Given the intense inflammatory actions of IL-17, it is no surprise that there are also many negative regulators of IL-17 production. IL-2, IL-27, IFN- γ , and IL-4 all inhibit IL-17 production. Additionally, another DC product, retinoic acid (RA), inhibits IL-17 production [36–39]. The precise mechanism by RA inhibits IL-17 production is unknown. However, it is known that RA is selectively produced by CD103⁺ mucosal DCs and binds to retinoic acid receptors (RAR) to positively regulate Foxp3, and thereby inducing a Treg phenotype [38][40]. Whether there are endogenous ligands for Ror γ produced by immune cells, which positively regulate Th17 differentiation, is not known but is an intriguing possibility.

3. IL-17-producing human memory cells are readily detectable

IL-17 has been reported to be overproduced not only in mouse models of diseases, but also in several human autoimmune diseases including: multiple sclerosis, inflammatory bowel disease, psoriasis and rheumatoid arthritis [8][10][11][41]. Therefore, it is important to identify the cellular sources of IL-17 and the regulation of this cytokine in humans.

Although the conditions required to polarize naïve human CD4⁺ T cells to become selective IL-17 producers has been elusive, it has been readily apparent that human memory T cells are very effective producers of IL-17. This occurs by stimulation with anti-CD3 and anti-CD28 alone, although there is considerable individual variation in the propensity of IL-17 production[33][42]. Also of note is that IL-17- and IFN- γ -double producers are consistently detected in memory CD4⁺ T cells [33]. One marker of memory T cells that produce IL-17 is the IL-23 receptor [42]. Additionally though, both memory and effector IL-17-producing cells in peripheral blood and inflamed tissues express the chemokine receptor CCR6 cells [6][43]. However, it appears that T cell which express CCR6 and CCR4 only produce IL-17 whereas T cells that express CCR6 and CXCR3 and produce both IL-17 and IFN- γ [6].

By assessing memory T cell responses to various antigens, it has been possible to correlate responsiveness to certain pathogens with selective IL-17 production. That is, *C. albicans* – responsive T cells were noted to be selective IL-17 producers whereas *M. tuberculosis*– specific cells produced both IL-17 and IFN- γ . Interestingly, this pattern of cytokine production also correlated with specific chemokine receptor expression. That is, *C. albicans* – responsive T cells were primarily CCR6+CCR4⁺ (i.e. IL-17 producers) and *M. tuberculosis*–specific cells were mainly CCR6+CXCR3⁺ (IL-17, IFN- γ dual producers). As CCR6 and CCR4 are important for localization to mucosa and skin, the findings also suggest that different helper T cell subsets have distinct homing capacity. Whether murine Th17 cells have the similar pattern of chemokine receptor expression has not been reported; however, the majority of Ror γ -expressing cells in the mouse reside in the gut [31]. In

humans, IL-17-producing cells have been detected in the gut in patients with Crohn's disease; however, some of these IL-17-producing cells also produce IFN γ [43]. Notably, these IL-17 producing cells are CD45RO+ memory T cells.

As indicated, occupancy of the TCR alone is sufficient to induce large amounts of IL-17 in human memory T cells [33, 42]. TCR signaling activates a number of pathways and transcription factors, but one major pathway activated by the TCR, which appears to be very relevant to IL-17 regulation, is the production of intracellular calcium and the activation of the transcription nuclear factor of activated T cells (NFAT). Not surprisingly, the proximal promoter of the human *IL17A* gene contains two NFAT binding sites which appear to be important in regulation of IL-17 [44]. In addition, TCR occupancy in human memory T cells also upregulates ROR γ expression although the regulation of expression of this transcription is not well understood [33].

One common feature of many studies of human T cell differentiation, is their increased flexibility or plasticity compared to mouse T cells [45]. This feature is also observed in human Th17 cells. Although clearly Th17 differentiation is inhibited by Th1 and Th2 polarizing conditions, after one week culture, restimulation with anti-CD3/CD28 nonetheless resulted in IL-17 production in these cells suggesting more plasticity than mouse cells [33]. Additional evidence of plasticity is the coexistence of dual IL-17- and IFN- γ -producing memory T cells (see above) [6][33, 42][43]. Whether IL-17-producers and IL-17+IFN- γ + double producers represent distinct two subsets or are developmentally related is not clear. Functional study of these two subsets showed similar cytotoxic capability, suppression by Treg cells, and ability to help B cells, Furthermore, both subsets reportedly express similar levels of ROR γ t and T-bet [43].

Thus, it is clear that like the mouse, there are circumstances in which human memory cells can arise that preferentially produce IL-17. This appears to be relevant to the pathogenesis of autoimmune disease and presumably in normal host defense. This begs the question, how do human Th17 cells arise?

4. Human Th17 differentiation – lessons learned

As discussed above, IL-6, IL-21, and IL-23, cytokines that activate Stat3, are now recognized to be a key regulators of IL-17 production. Additionally, in murine studies inflammatory cytokines such as IL-1 were also important in driving IL-17 production. Therefore, it was logical to explore whether combinations of such cytokines are capable of promoting human Th17 differentiation. In fact, it appears that these cytokines do promote Th17 differentiation of naïve human CD4+ T cells; however, not all groups agree on all of the details.

In the recent studies by Acosta-Rodriguez et al and Wilson et al, the authors report that IL-6 alone fails to induce either the expression of Ror γ t or IL-17 [42][46]. Furthermore, IL-1 alone is not sufficient to induce sustained IL-17 expression and only transiently induces expression of ROR γ . Sallusto's group has found that IL-1 synergizes with IL-6 to induce human Th17 development with sustained Ror γ expression [42, 46]. Of note, is that this

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cytokine combination induces substantial numbers of cells producing both IL-17 and IFN- γ [46]. Studies from Sallusto's group also examined the ability of different types of antigen presenting cells (APCs) to drive Th17 differentiation. They showed that LPS-activated DCs produce large amounts of IL-12. Unsurprisingly, such cells promoted Th1 cell differentiation rather than Th17 differentiation. By using various ligands of toll-like receptors with different APCs, these investigators found that activation of monocytes with peptidoglycan (a ligand for TLR2) resulted in high level IL-6 production with little IL-12 production, thereby providing a particularly effective stimulus for generating cells that selectively produce IL-17 [46].

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As discussed previously, IL-23 was initially thought to be the driver of Th17 differentiation in murine cells; however, it is now thought that this cytokine does not act on naïve murine T cells. This is consistent with the idea that naïve murine T cells express low levels of IL-23R [33, 42]. However the role of IL-23 in regulating human Th17 differentiation is a bit more controversial. Both Wilson et al and Chen et al showed that IL-23 alone is quite effective in driving human Th17 differentiation. In addition, IL-23 is a potent inducer of another inflammatory cytokine-IL-22 [42][33]. In contrast, Sallusto and colleagues reported that IL-23 alone was a poor inducer of IL-17. It should be noted that temporally, IL-23 has small effects on IL-17 induction at early stages of Th17 differentiation, which can be explained by minimal IL-23R expression on naïve T cells [33]. However IL-23R expression can be upregulated by TCR stimulation, IL-6, IL-21 and even IL-23 itself [26, 33, 47]. It is therefore not surprising that IL-23-dependent IL-17 production was apparent at later stages of Th17 differentiation [33][42]. Both Sallusto's and de Waal Malefy's groups did show that the combination of IL-1 and IL-23 generates more IL-17-producers than does IL-1 alone. Cells stimulated with IL-23 alone or in combination with IL-1 generated a mixed population of IL-17 single producers and IL-17-IFN- γ 'double-producing' cells. This contrasts sharply with mouse data in which IL-23 is not an effective inducer of Th17 differentiation in naïve CD4+ T cells.

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One explanation for the difference between mouse and human T cell responsiveness could simply be the regulation of expression of IL-23R. It is possible that naïve human T cells have higher levels of expression of IL-23R or that it is more easily inducible. An alternative explanation is that it is harder to be certain that human T cells are completely "naïve" compared to mouse cells in which this can be more carefully ascertained. While this distinction between converting naïve into Th17 cells vs. maintaining and expanding Th17s is an interesting conceptual distinction, with respect to targeting this pathway therapeutically it may not be an important practical distinction. Moreover, the recent finding of the relationship between IL-23R polymorphisms and the prevalence of inflammatory bowel disease and other autoimmune diseases clearly argues for relevance of this cytokine in human autoimmune disease [48, 49].

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IL-21 has recently emerged to be another key regulator of Th17 cells, analogous to the role of IL-4 in Th2 cells. However, relatively little work has been done on IL-21 and human Th17 cells. Whether this cytokine has similar effect on naïve and memory helper T cells has not been addressed. How is this cytokine involved in human Th17 differentiation has not been systematically studied.

5. Species-specific differences in the regulation of Th17 differentiation

TGF β -1 has pleiotropic functions in immune responses and in many respects, TGF β -1 is viewed as a critical immunosuppressive cytokine. However, all studies in murine cells agree that it is an important in vitro and in vivo regulator of Th17s [18][19][20]. Nonetheless, despite the critical role of TGF β -1 in murine Th17 differentiation, TGF β -1 has not only been reported to be dispensable for human Th17 differentiation; in fact, it inhibits IL-17 production in human cells in a dose-dependent manner [33, 42, 46].

This is especially perplexing and may simply point to species-specific differences in regulation of the *Il17* gene. While this may certainly be the case, it is not an especially appealing explanation at this point. The explanation is particularly unappealing because TGF β -1 is also a critical regulator of another subset of helper T cells-Treg cells – principally for their in vitro differentiation [50]. For murine T cells, functional Tregs, with high level expression of the transcription factor Foxp3, can be readily generated from naïve CD4+ T cells by the combination of IL-2 and TGF β -1. The effects of TGF β -1 in the context of a different cytokine milieu (i.e IL-6) have been an argument for the potential relatedness of Th17 and Treg cells. More recent data directly document the ability of Foxp3+ positive cells to convert to Th17s. Foxp3+ cells obtained from mice can be changed to IL-17-producing cells by in vitro culture with IL-6 and LPS- activated bone marrow derived DC [51]. This results in loss of Foxp3 expression and induction of IL-17 expression. The possibility that Tregs and Th17s might interconvert is a fascinating possibility, which could have immense implications with respect to immunoregulation; in such scenarios, TGF β -1 would be a major player for both of these fates.

So why does TGF β -1 have such seemingly strange effects on human Th17 differentiation? It is worth bearing in mind in this context that Foxp3 expression is less tightly controlled in human T cells compared to mouse T cells. Foxp3 is widely expressed in activated human T cells and its pattern of expression is not necessarily indicative of a population of cells with suppressive activity [52]. However, this does not explain the seemingly strange effects of TGF β -1 vis-à-vis Th17 difference – indeed, it adds to the puzzle. Curiously, by studying the expression of IL-17 and Foxp3 in human T cells, we observed the coexistence of IL17⁺Foxp3⁺ cells and IL17⁺Foxp3⁻ cells in response to TGF β -1 and IL-6 stimulation [33]. Therefore, exactly what the functional significance of such Foxp3⁺IL-17⁺ cells remains to be determined.

TGF β -1 inhibits both Th1/Th2 differentiation, downregulating both T-bet and Gata3, so it is possible that indirect actions are important aspects of the action of this cytokine in murine T cells [53, 54]. Thus, it is possible that *Il17* or *Rorg* transcription *per se* may not be directly regulated by TGF β -1 signaling – TGF β -1 may primarily acting to inhibit other fates. Another possibility – also somewhat unappealing - is that “naïve” human T cells obtained from peripheral blood may not be the appropriate counterparts of naïve murine CD4+ T cells generally obtained from primary or secondary lymphoid organs.

6. Negative regulation of human Th17 cells

As discussed above, given the highly inflammatory effects of IL-17, it comes as no surprise that Th17 cell differentiation is tightly regulated; there is no shortage of cytokines that negatively regulate murine Th17. Indeed, IFN- γ and IL-4, the signature cytokines of Th1 or Th2 cells, inhibited both human Th17 differentiation, but the repression of IL-17 production is incomplete [16, 17, 29, 55].

IL-2 is a well-known T cell growth factor *in vitro*, but the deficiency of IL-2 is severe multi-organ autoimmune disease characterized by overproduction of IL-17. These observations led to the finding that IL-2 inhibits Th17 differentiation while promoting Treg differentiation [56, 57]. Whether the effect of IL-2 is due solely to induction of Foxp3 is unknown. Nonetheless, IL-2 does appear to have similar effects on human Th17 differentiation, although there are also clear temporal considerations. Sallusto and colleagues assessed at this issue systematically in their study and showed that early on, high dose of IL-2 inhibits early Th17 differentiation of human CD4+ T cells [46]. However, they also show that IL-2 will ultimately lead to the population expansion of Th17 cells. Similarly, the study by de Waal Malefyt's group shows that cells treated with IL-2 produce more but not less IL-17, at least in some donors. They concluded that this is another example of species-specific regulation [42]; however, in view of the data from Sallusto's group, it seems likely that this represents an effect on differentiated cells. The effects of IL-2 are also consistent with another study showing that IL-17-producing memory T cell populations are expanded by IL-2 in both species [55]. IL-27 is another potent negative regulator of mouse Th17 differentiation, but whether this cytokine also has directly inhibitory effects on human IL-17 production is less clear [55].

7. Unanswered questions in human IL-17 regulation

As should be evident, there is still much to be learned about IL-17 regulation in humans. Although, much emphasis has been placed on the production of IL-17 by CD4+ T cells, they are clearly not the only cell that produces IL-17. Certainly invariant NK T and $\gamma\delta$ T cells can rapidly produce IL-17 [58][59]. Clearly, it will be important to carefully assess the production of IL-17 in immunologically relevant cells in health and disease in humans, assessing the capacity of both adaptive immune and innate immune cells. Recent evidence points to distinct chemokine receptor expression of IL-17-producing cells. It will be important to understand how different pathogens elicit such cells and how these cells traffic. The identification of IL-17- and IFN- γ -dual producing cells with distinct chemokine receptor expression, which are apparently induced by different microorganisms is also fascinating. What the relationship (if any) between these two populations of IL-17-producing cells will be important to dissect.

Obviously, a practical aspect of understanding what cells make IL-17 and what factors regulate its production is the possibility of targeting such factors in autoimmune disease. In the mouse, considerable effort is devoted to understanding lineage commitment and there are some apparent puzzling differences in the control human Th17 differentiation. However, these subtleties (e.g. does IL-23 act on naïve or memory human T cells) may

be less important in considering target IL-17; targeting molecules is likely to be beneficial regardless of the details of how such a cytokine might be acting. While there may be benefit of targeting IL-17 in immune-mediated pathogenesis, it will also be important to keep a close eye on the role of IL-17 in normal host defense against extracellular bacteria in considering the risk/benefit ratio of targeting IL-17.

Th17 cells are also reported to be high producers of another important proinflammatory cytokine, IL-22. In human CD4⁺ T cells, IL-23 is an also potent inducer of not only IL-17 and IL-22, but also IFN- γ , TNF and IL-26 - cytokines that all participate in inflammation and autoimmune diseases [33, 42, 46, 60–62]. Additionally, IL-22 may also be produced by cells other than Th17 cells. While this seemingly cacophonous pattern of cytokine production may not fit neatly with the lineage commitment model of mouse helper T cell differentiation, it nonetheless offers opportunities for therapeutic intervention. That is, the concept that a major driver of autoimmune diseases can be explained solely by a discrete IL23/IL-17 connection is likely may be an oversimplification in humans, but that does not take away for the potential therapeutic benefit of targeting IL-23.

The negative regulation of IL-17 production, is clearly another important area of investigation, particularly with respect to the development of new therapeutic strategies. A series of recent studies on mouse model show that RA, the active metabolite of vitamin A produced by mucosal DC reciprocally regulates Th17 and Treg differentiation [36–39] [40, 63]. That is, RA downregulates expression of ROR γ t, and enhances the expression of Foxp3, arguing that the balance of Treg vs. Th17 differentiation might be influenced by engagement of RAR and ROR γ t. Despite this intriguing possibility, the role of RA in human cells has not been studied. We also do not know whether RA can act on cells that are already polarized to be IL-17-producers and downregulate production of this cytokine in memory T cells – this, of course, has important therapeutic implications. Currently it is not clear whether and how RA-regulated expression of ROR γ t and Foxp3 might influence Th17 and Treg function in human cells, but this will surely be an important area for future investigation. Indeed, further investigation of the apparent relationship of Th17 cells and Tregs is clearly of great importance. Considering the immense effort devoted to bringing Treg-based cellular therapy to the clinic, it is more than a little disturbing that thymic derived-Tregs can apparently convert to Th17s cells [51]. Adding to this consternation are the observations that human CD4⁺ T cells seem to be much more plastic than their mouse counterparts. Moreover, Foxp3 expression is a less reliable marker of cells with immunosuppressive capability in human than in mice. Clearly, these issues will need to be carefully considered in human Treg trials.

Further investigation of the basic biology of human Th17 cells is also warranted. Epigenetic regulation of the *IL17* and other cytokine loci is clearly a critical area for future research. One would imagine that many aspects of T cell memory will ultimately be explained by epigenetic modifications of cytokine loci. One might further speculate that some of the vexing differences between mouse and human cells might be explained by differences in these modifications. The *IL17a* gene is linked to the *IL17f* gene on mouse chromosome 1 and human chromosome 6 in a tail-to-tail configuration. Most data point to coordinate expression of these two cytokines; although IL-17F regulation has not been intensively

studied in humans [33]. In mouse *Il17* locus, the promoter regions of both the *Il17a* and *Il17f* genes undergo histone H3 acetylation and K4 tri-methylation in response to TGFβ-1 and IL-6, implying increased accessibility of the locus [64]. In addition, there are eight conserved noncoding sequences in this locus, four of which reside in the intergenic region. These sites also appear to undergo preferential histone acetylation. Human memory T cells clearly maintain the capacity to promptly generate IL-17 indicating that this locus remains accessible in memory CD4⁺ T cells – even under the circumstances which favor IFN-γ and IL-4 production [33]. However, there have been no studies of the epigenetic regulation of the *Il17a/f* loci in human cells. Remodeling of the IL-17 locus in memory cells might allow for efficient production of this cytokine, and may also explain some aspects of the plasticity of human CD4⁺ T cells, but this area has not been explored.

Aside from Stat3, which is known to bind the *Il17a* gene, we know essentially nothing about the details of the regulation of the *Il17a/f* locus. Whether and how RORγt and Stat3 might contribute to the chromatin remodeling of *Il17a/Il17* locus have not been assessed, but based on what we know about the regulation of the Th2 and *Ifng* loci it is likely that this is a strong possibility. Since there are interchromosomal interactions between the *Ifng* and Th2 loci, one wonders whether interactions between *Il17a/f* and *Foxp3* loci also exist and how interchromosomal and intrachromosomal interactions might change with activation and differentiation of T cells [65]. Brustle and colleagues have recently reported that interferon regulatory factor (IRF)-4 is a positive regulator in Th17 differentiation [66]; however, the expression of this transcription in human Th17 has not been explored. IRF4 is known to interact with NFAT and this may be one mechanism through which it could regulate IL-17 production [67, 68].

8. Conclusions

Unquestionably, our sophisticated understanding of mouse immunology and the tools provided by genetic manipulation have provided enormous insights into immunologic mechanisms. However, the gap between the knowledge obtained from the mouse its applicability to human immunology is disturbingly vast. One of the more striking discrepancies recognized in recent studies relates to the function TGFβ-1 in mouse vs. human cells. In the mouse, this is clearly a critical cytokine that links Treg and Th17 differentiation. Its function in human T cell differentiation is clearly more enigmatic. A second lesson is that despite the elegant work on mouse T helper T cell lineage commitment, human CD4⁺ T cells appear to be much more plastic and much less “terminally differentiated”. The molecular mechanisms underlying these fascinating differences is unclear, but one can speculate that epigenetic modifications are likely to be at the heart of these differences. Clearly this will be important to dissect. Despite these puzzles, the advances in understanding IL-17 regulation offer many opportunities for increasing our sophistication in dissecting immunological mechanisms in autoimmune disease. Furthermore, these advances should offer many new therapeutic opportunities.

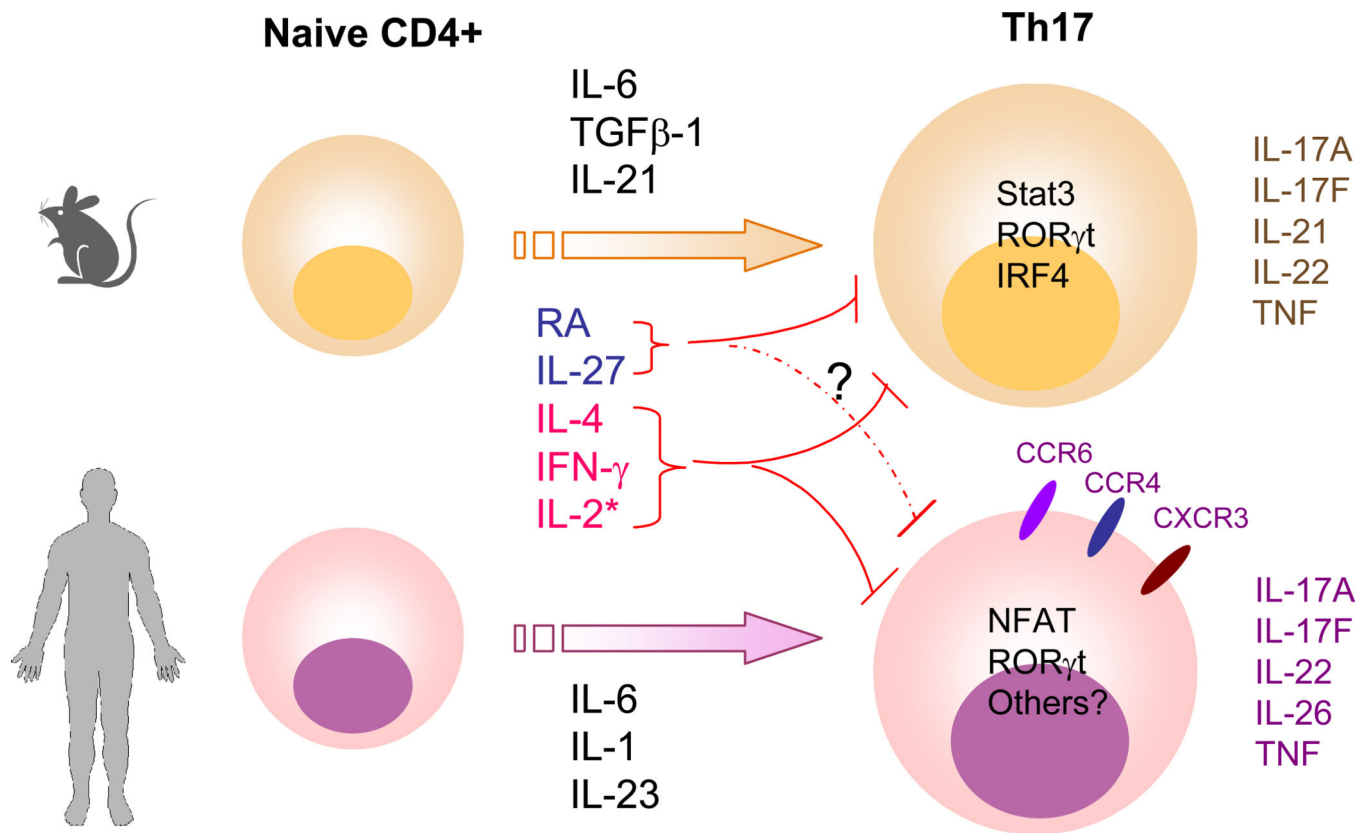
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Divergence and similarity of mouse and human Th17 differentiation.

Upon activation by antigen-presenting cells, in the presence of IL-6, TGF β -1 and IL-21, mouse naïve CD4+ T cells differentiate to Th17 cells, which produce IL-17A, IL-17F, IL-21, IL-22 and TNF α . Transcription factors including ROR γ t, Stat3, and IRF4 are involved in regulating this process. In human naïve CD4+ T cells, cytokines IL-6, IL-1 and IL-23 promote Th17 differentiation but surprisingly, TGF β -1 is not involved. The transcription factors NFAT (from TCR stimulation), ROR γ t have been implicated in regulating human IL-17 expression, although it is also likely that Stat3 is also important. In addition to IL-17A, IL-17F, IL-22 and TNF, human Th17 cells also produce IL-26. Cytokines such as IL-4 and IFN- γ negatively regulate both mouse and human IL-17 production. IL-2 signaling through Stat5 inhibits murine Th17 differentiation but it appears to have distinct temporal effects, especially in regulating human Th17 development (denoted by *). That is, at early points in differentiation, IL-17 production is inhibited. Later on IL-2 appears to expand IL-17 producing effector/memory cells. Retinoic acid (RA) is another negative regulator for IL-17 expression in murine T cells but this effect has not been confirmed in human T cells. Although IL-27 negatively regulates murine Th17 differentiation, it is uncertain if this cytokine directly inhibits IL-17 production in human T cells. Human Th17 cells express chemokine receptors CCR6 and CCR4 whereas cells that produce IL-17 and IFN- γ express CCR6 and CXCR3. Similar chemokine receptor expression pattern has not been characterized in mouse Th17 cells.