Persistence, Pathogenicity and Plasticity: The Role of IL-23 in Th17 Fate

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Abstract

For a long time Th1 cells were considered the key players in the induction of inflammation and progression of disease in autoimmune diseases. With the discovery of IL-17-producing CD4⁺ T cells (Th17) being abundant at inflammation sites, this soon changed. Investigating this new T helper subset, it became clear that in comparison to Th1 and Th2 cells, Th17 cells have an increased tendency to change their phenotype and therefore become either more pathogenic or immunoregulatory. This makes them an attractive target for therapeutic interventions. As plasticity of Th17 cells differs between different autoimmune diseases, understanding its drivers is complex. This review focusses on the role of plasticity within Th17 cells in induction, aggravation and resolution of disease and points out IL-23 as a potential key player in controlling Th17 fate. Finally, current treatments targeting IL-23 and Th17 plasticity are highlighted and an outlook on future therapeutics is given.

Keywords: Th17, T cell adaptation, IL-23, IL-17, T cell subsets

Abbreviations: CD: Cluster of differentiation; cGN: Crescentic Glomerulonephritis; EAE: Exogene Autoimmune Encephalitis; GM-CSF: Granulocyte Macrophage Colony Stimulating Factor; HIES: Hyper IgE Syndrome; IBD: Inflammatory Bowel Disease; IFN-γ: Interferon-γ; IL: Interleukin; IL-23R: Interleukin 23 Receptor; IL6R: Interleukin 6 Receptor; NTN: Nephrotoxic Nephritis; SC: Single Cell; seq: Sequencing; Tfh: T follicular helper cell; TGF-β: Transforming Growth Factor β; Th1: T helper cell type 1; Th2: T helper cell type 2; Th9: T helper cell type 9; Th17: T helper cell type 17; Th22: T helper cell type 22

Introduction

Focusing on adaptive immunity there is a humoral and a cellular immune response. The humoral response is executed by antibodies acting via antigen specific binding. These antibodies are produced by activated B-lymphocytes in order to bind and neutralize antigens. The cellular response is performed via effector CD4⁺ and CD8⁺ T-lymphocytes. It was previously assumed that CD4⁺ T-lymphocytes only consist of Th1 and Th2 cells [1]. But over the last decades with the introduction of new T-helper subsets and more studies revealing grades of plasticity within CD4⁺ T-lymphocyte populations, this classic view was exposed to be lacking. Added subsets include regulatory T cells, Th17, Tfh, Th9 and Th22 cells [2]. Regarding these added subsets, Th17, Th9 and Tfh cells acquire their phenotype under the effect of master transcription factor RORγt, Etv5/PU.1 and Bcl6 respectively. The transcriptional program of Th1 and Th2 cells is also defined through a specific master transcription factor, the former by T-bet and the latter by GATA3 [3,4]. In order to polarize into
specific effector subsets naïve CD4⁺ T cells are dependent on cytokine signaling. These cytokines are produced by immune, epithelial and stromal cells in physiological conditions or as a response to pathogens. Therefore, the current composition of the cytokine milieu is what determines the fate of naïve CD4⁺ T cell. Furthermore, the different subsets of T cells are not only polarized through a certain cytokine environment but can also be defined through their cytokine output [1]. Differentiation of naïve CD4⁺ cells is also impacted by commensals and pathogens within the intestinal microbiome. The pathogen Delta arao Salmonella enterica triggers an IFN-γ dominated response, while Citrobacter rodentium leads to a Th2 response [6]. This work focuses on the recently discovered Th17 cells and the plasticity within this subset. In addition, the role of IL-23 in these processes will be highlighted.

**Th17 Cells**

IFN-γ producing Th1 cells were considered to be the driver of inflammation within autoimmune disease. However, research revealed the substantial pathogenic role of a not yet described T cell subset within different types of autoimmune disease, which is now known as Th17 cells [7,8]. Th17 cells are crucial in eliciting inflammation in response to bacterial or fungal pathogens penetrating the mucosa [9,10]. In the multisystemic disorder HIES mutations in Stat3 occur [11]. Stat3 is an important transcription factor for the induction of Th17 cells. Patients suffering HIES have less Th17 cells and suffer mucocutaneous candidiasis [12]. Th17 cells are defined through their expression of the master transcription factor RORγt, the chemokine receptor CCR6 and production of the cytokines IL22 and IL17A-F. IL17A-F production can also be found in other cell types such as macrophages, γδT-cells and NK cells [13,14]. IL17A-F, RORγt, RORα, and IL-21 are expressed in a Stat3 dependent manner, while Th1 cells continue production of IFN-γ in Stat3 knockout mice [15,16]. For naïve CD4⁺ T cells to become Th17 cells, the cytokines IL1-β, TGF-β1 und IL-6 are necessary [17]. IL-23 was also believed to play a role in Th17 polarization, but as it only induces IL17 secretion in CD4⁺ CD62L⁻ memory T cells and not in naïve CD4⁺ CD62L⁺ T cells its role is rather limited to maintaining Th17 fate. This is because naïve T cells do not express IL-23R [18]. IL6 and TGF-β1 also increase IL17 secretion in these naïve cells [15]. Once polarized Th17 cells do not show a stable IL-17-producing phenotype but rather display a certain degree of plasticity. Depending on the environment they can differentiate into regulatory T cells, Th1 cells or Thf [19-21]. Apart from Stat3 another signal transducer and activator of transcription, Stat4, seems to affect Th17 cells. Stat4 knockout mice stimulated with IL-23 show decreased IL-17 output in comparison to WT mice, suggesting IL-23 exercises its Th17 stabilizing effect partly through Stat4. However, this is limited to IL17 output and no difference in RORγt expression could be found [15]. A more recent study came to the conclusion that IL6 acts upstream of IL-23 signaling in Th17 polarization. Only the IL6-IL6R interaction keeps a steady RORγt expression, which is required for IL-23R. Hence without IL6, IL-23 has no binding site [22]. This finding indicates that IL6 is not only crucial for induction of Stat3 and therefore inhibiting Foxp3 and a possible Treg fate, but is also a key regulator of stability of Th17 cells [22,23]. GM-CSF knockout mice did not develop severe EAE, underlining the importance of GM-CSF production by Th17 in order to elicit their pathogenic potential [24]. GM-CSF production in Th17 cells is dependent on RORγt, which in turn is negatively regulated by IFN-γ [24]. So called non-classical Th17 or Th1 like Th17 cells expressing IFN-γ are prevalent in active inflammation [25]. These proinflammatory cells express the master transcriptions factors of Th1 (T-bet) and Th17 (RORγt) cells at the same time and are believed to play a part in the induction of autoimmune disease [9].

**IL-23 and Its Receptor**

The cytokine IL-23 was first described by Oppmann et al. in the year 2000. Structural analysis revealed its composition of two different subunits p19 and p40. The latter also forms a part of interleukin 12, while the p19 subunit is unique for IL-23 [26]. The close structural relation of IL12 and IL-23 is reflected in their receptor affinity, as both cytokines bind to the receptor subunit IL12Rβ1 (Figure 1). Even though they have a mutual binding site, IL12 and IL-23 elicit their distinct effects in vivo by the means of a ligand specific subunit. For IL-23 the specific binding site is IL-23Rα [26]. A therapy targeting p19 or IL-23Rα can therefore specifically eliminate IL-23 signaling without interfering with the IL-12 signal [27]. Binding of IL-23 to IL-23Rα induces signaling via receptor associated JAK2 and Tyk2. This leads to phosphorylation and dimerization of Stat3 and Stat4 [18].

IL-23 is a proinflammatory cytokine of particular relevance for Th17 effector cells [7]. Different mouse models with an IL-23p19 knockout, a knockout particularly targeting IL-23 signaling, subline this finding. IL-23p19 knockout mice are protected from disease in models of EAE, collagen induced arthritis or IBD [7,28,29]. The protection from EAE was due to a lack of GM-CSF production in Th17 cells and not to a reduced IL17 expression [24]. GM-CSF production in Th17 cells is dependent on RORγt, which in turn is negatively regulated by IFN-γ [24]. In contrast IL-23 upregulates GM-CSF expression explaining the non-present inflammation in IL-23 knockout-mice [30]. In line with this finding stimulation with IL-23 resulted in exacerbated disease and increased IL17 production [31]. Transgene mice ubiquitously expressing p19 show elevated levels of inflammation in various organs and growth disturbances. Inflammation markers such as IL1 and TNFa were elevated in these animals [32]. These findings put targeting of IL-23 and its receptor on the map for the development of new pharmaceuticals for treatments of autoimmune
diseases and potentially hyperinflammation in infection [33,34]. Genome wide association studies could associate mutations in components of the IL-23 signaling pathway with several immune mediated diseases [35-37]. A regulator of IL-23 activity is the suppressor of cytokine signaling 3 (Socs3). At low Socs3 levels the phosphorylation frequency of Stat3, induced by IL-23, is amplified. Therefore, in the presence of Socs3 less Stat3 can bind to the promotor region of IL17A-F and when absent significantly more naïve CD4+ T-cells polarize into Th17 cells [38]. Th17 cells polarized under the influence of IL1β, IL6 and IL-23 expressed Tbx21 mRNA and T-bet protein, while cells stimulated with IL1β, IL6 and TGFβ1 did not [39]. Furthermore, polarization with IL-23 leads to significantly more IL22 production [39]. Elevated levels of IL22 can be found in psoriasis patient, correlating with the degree of inflammation. Furthermore, IL22 only affects digestive, epidermal and respiratory epithelial cells but not immune cells, lacking IL22R [40]. IL-23R is only expressed in memory T-cells therefore IL-23 is unable to directly affect naïve CD4+ cells [15]. Cultures of Th17 cells either with or without IL-23 revealed a role for IL-23 in stabilizing the Th17 phenotype. Cells cultured with IL-23 kept their Th17 phenotype over time [20]. IL-6 knockout mice showed less IL-23R expression suggesting a role for IL-6 not only in inducing RORyt but also IL-23R [4]. IL-23 promotes a more pathogenic Th17 subset compared to IL6 and TGFβ1 primed more immunoregulatory Th17 cells (Figure 2). This is due to the inability of IL-23 primed cells to produce IL10, splitting Th17 cells into a rather pathogenic IL10- subset and a nonpathogenic IL10+ subset [41]. The nonpathogenic Th17 cells showed upregulation of transcription factors related to IL-10 production like MAF and the Aiolos encoder IKZF3 [25,42]. While IL10+ Th17 cells stimulate M2 macrophages, linked to immunoregulatory tasks, IL10 Th17 cells prime M1 macrophages driving inflammation [42].

Th17 Plasticity (Figure 3)

In comparison to Th1 and Th2 cells which are rather stable Th17 cells display a high level of plasticity. Plasticity means that cells start to express markers (cytokines or transcription factors) that are known to define other T-helper subsets. With the finding that Th17 subsets can also secrete IFN-γ, the signature cytokine of Th1 cells, or IL-4, one of the signature cytokines of Th2 cells, it has been shown in vitro that definition of rigid subsets based on their cytokine expression may be lacking. In vitro studies with isolated IL-17 high cells from TGFβ+ IL6+ IL1β primed naïve CD4+ cells showed that adding IL-23 and IL1-β keeps IL17 production, while adding IL-12 or IL-4 reduced IL-17 output with cells starting to respectively produce IFN-γ and IL4 [20]. In order to further investigate the fate of Th17 cells in vivo a mouse model permanently marking IL17 producing cells has been developed. Cre-recombinase expression is linked to IL17 production and leads to a following permanent labeling of the cell with a fluorochrome. These

**Figure 2: Role of IL-23 in Th17 polarization.** A naïve T cell activated in an environment lacking IL12, IFN-γ and IL4 while supplying IL6, ILβ and TGF-β is predestined to become a Th17 cell. IL-23 induces IL-23R resulting in a positive feedback loop. IL-23 drives pathogenicity in Th17 cells by inducing IL22, GM-CSF and TGF-β3 while restricting IL10 production.

**Figure 3: Th17 plasticity.** Cytokines driving Th17 cells towards Th1, Tr1, Tfh and a regulatory Th17 subset and transcription factors and cytokines upregulated in the arising subsets. (Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).
cells can then be sorted based on their fluorochrome marking, making further investigation on their current cytokine output and their reaction to certain stimuli possible [43]. Possible subsets Th17 cells can transdifferentiate into are Tregs, Th1 cells, Tr1 and follicular T cells [19,43-45]. With this amount of possible differentiation and resulting effector functions encoding the drivers of Th17 plasticity is immensely important to understand disease and derive treatment options. An overlap of loci bound by master TF of Th17 cells RORyt and the targets of TF like STAT4, GATA3 and FOXP3 has been shown, which points at a central role of RORyt in influencing other subsets [46]. This overlap of targets further hints at a high grade of plasticity within the Th17 subset.

**Th17/Th1 axis**

Th-1 like Th17 cells co-express the master transcription factors of the Th17 and Th1 lineage and produce IFN-γ and IL17. These RORyt+ and T-bet+ double positive cells seem to display a link between what used to be considered terminally differentiated populations and therefore are the key player, when talking about the Th17/Th1 axis [44]. Th1 like Th17 cells can be found in several types of autoimmune disease like colitis [21,47], rheumatoid arthritis [48,49], multiple sclerosis [50] and EAE [43], where they have been linked to pathogenicity. Some Th17 cells, while starting to express IFN-γ, completely stop expression of IL17 and are therefore named Th1-like ex Th17 cells [44,51]. Stimulation of *in vitro* polarized Th17 cells with IL12 and IL-23 results in upregulation of T-bet and Stat4 and therefore arising IFN-γ expressing Th17 cells. When transferring polarized Th17 into Rag-/- mice, IFN-γ Th1 like Th17 cells emerged and induced colitis, proving that the *in vitro* findings translate to *in vivo* experiments [21]. Previous studies proved that transducing CD4+ T-cells with a retrovirus expressing RORyt lead to expansion of the Th17 population, while on the other hand transduction with T-bet blocked this expansion [52]. Yet combination of both failed to induce the “intermediate” Th1-like Th17 subset. Therefore, there may be inducers of IFN-γ apart from T-bet that lead to the formation of these IL-17A+ IFN-γ+ double positive cells [52]. Transcription factors upregulated in Th1-like Th17 cells stimulated with IL12 are T-bet, Runx1, Runx3 and Eomes. Especially Runx1 and Runx2 proved to be capable of inducing an IFN-γ and IL17A double positive population [53]. Chip analysis revealed an enrichment of Runx1 binding at the IFN-γ promoter in these IL12 treated Th17 cells [53]. In a T cell transfer model of colitis Harbour et al. showed that polarized Th17 cells transferred into Rag-/- mice, induce IBD. The majority of these Th17 cells became double positive for IL-17A and IFN-γ or acquired IFN-γ production combined with stagnation of IL17 expression. Since IFN-γ Th17 cells did not induce wasting disease, these Th1 like Th17 cells and Th1 like ex Th17 cells appear to be crucial for disease induction [47]. The transformation of IFN-γ Th17 to IFN-γ Th17 cells was STAT4 dependent, and it could be shown that the downstream effects of an IL12rb2- knockout in mice did not have a significant effect on this conversion. Due to the fact that this knockout targets only IL12 signaling, IL-23 which also is known to signal through STAT4, was proposed as the key player for Th17/Th1 plasticity [47]. However, there is a lack of direct evidence for this and further research is required. Th17 cells generated without TGF-β signal are RORyt+ T-bet+ double positive and express IL-23. They further expressed GM-CSF and IFN-γ at the same time [43]. This hints at a possible generation of Th1 like Th17 cells in a cytokine environment lacking TGF-β. It has been shown that TGF-β inhibits T-bet and IFN-γ in Th1 cells, but further studies on its role in plasticity are required [54]. Considering the crucial role of Th1 like cells in autoimmune disease it is surprising that investigating mice with cGN, another immune disease model highly dependent on Th17 cells, this generation of Th1-like cells could not be observed. Although previous studies hinted at a possible generation of Th1-like cells more recent studies have proven that Th17 are quite stable within this model [43,55,56]. Th1-like Th17 cells could form a smaller population within cGN and be less relevant for disease than in IBD and EAE. Another explanation is, that the disease microenvironment in cGN lacks factors driving the transdifferentiation towards Th1 cells, which are present in other autoimmune models. This discrepancy between the models of EAE and colitis, with a lot of Th17 to Th1 plasticity and the missing one in cGN remains unexplained. Therefore, it will be interesting to further investigate the fate of exTh17 cells in cGN using the means of scRNA seq.

**IL-23/Th17axis**

Mice transferred with CD4+ T-cells stimulated with IL6, TGF-β and IL-23 or only IL6 and TGF-β did not suffer EAE, while IL-23 stimulated cells induced EAE in all specimens. This supports a role for IL-23 in producing a pathogenic Th17 phenotype while TGF-β and IL6 polarize an immunoregulatory subtype. Furthermore, it indicates that TGFβ and IL6 signaling is dominant to IL-23 [41]. Uproadization of IL-23R by IL-23 implies a positive feedback loop and further augments pathogenic potential of IL-23 [41]. IL22 is another Th17 effector interleukin driving inflammation, which is upregulated by IL-23 [41]. Further investigation on the influence of IL-23 on nonpathogenic Th17 cells revealed TGF-β3 to also be an IL-23 induced cytokone. Th17 cells induced by TGF-β3 and IL6 showed higher phosphorylation levels of Smad1 and Smad5, while polarization with TGF-β1 and IL6 lead to phosphorylation of Smad2 and Smad3 [57]. Transfer of these TGF-β3 and IL6 polarized cells resulted in severe disease and even mortality [57]. With RBPJ (Recombining binding protein suppressor of hairless), Meyer zu Horste et al. proposed a key regulator of IL-23 signaling, both transactivating IL-23R and repressing IL10 in Th17 cells [58]. T-bet, the master TF of the Th1 program, is suspected to upregulate IL-23R and vice versa T-bet upregulation following IL-23 signaling has been shown [59]. The upregulation of IL-23R by T-bet is in line with the necessity of both Th17 and Th1 cells in order to elicit pathogenicity in autoimmune disease. IL-23 stimulation

leaves to more pathogenic IL10 Th17 cells while TGF-β and IL6 promotes immunoregulatory IL10+ Th17 cells [41].

**Th17 to regulatory T cells**

When facing a pathogen, the induction of an immune response and the following inflammation are advantageous for the organism. Nevertheless, at some point the inflammation has to be opposed in order to restore homeostasis. Here two regulatory cell types, Foxp3 expressing regulatory T cells (Tregs) and the regulatory type 1 cells (TR1), play a crucial role [19]. Th17 triggered inflammation within autoimmune disease is not beneficial for the host, yet the subsets opposing Th17 cells are comparable to the ones in acute infection [19]. While Th17 cells are considered a pathogenic T cell subset they still share TGF-β as a differentiation marker with the immune regulatory T-regs [60]. In 2008 Lochner et al. observed that Tregs can co-express RORγt and Foxp3 [61]. There are three hypotheses on the origin of these double positive cells, 1) they could form an independent cell type 2) they could be transdifferentiated from regulatory T cells 3) they have their origin in Th17 cells. The fate of Th17 cells can be investigated with IL17A-fate reporter mice, where cells expressing IL17A are permanently marked as YFP+. It could be shown that under homeostatic conditions almost 50% of YFP+ CD4+ lymphocytes of the colon stop IL17A expression [19].

Some of these so called exTh17 cells started to produce IL10 and express Foxp3 [19]. LAG3 a marker for Tr1 cells was also increased in exTh17 cells and similar to Tr1 cells, exTh17 cells displayed downregulated expression of CCR6 and RORγt. Th17 cells being able to downregulate Th17 markers and acquire regulatory markers, points at an axis between pathogenic Th17 cells and immunoregulatory T cells. Formation of exTh17 Tr1 cells correlates with the ongoing immune response [19]. A study following up on Th17 cell transdifferentiation in the kidney in cGN found no plasticity towards RORγt Foxp3 double positive cells. This led to the assumption that these double positive cells resemble an independent population [62]. Kannan et al. recently reported that IL-23 induced inflammation in psoriasis leads to higher amounts of IL17 producing Tregs and to more Tregs entering cell cycle [63]. Around 11% of these IL-23 induced IL17A+ Tregs where double positive for Foxp3 and RORγt [63]. These cells were most likely generated from IL17A Foxp3+ Tregs suggesting a transdifferentiation from Treg to Th17 cells [63]. Kannan et al. therefore proposed IL-23 as a potential inducer of instability in the Treg lineage further exacerbating disease [63].

**TH17/Tfh axis**

Compared to previously described axes there is not that much known about the Th17/Tfh axis. Tfh cells interact with B cells in the germinal center and are important for their differentiation. Sorting of Payer’s patch derived IL17 fate positive cells expressing Tfh markers (CXCR5+, PD-1high) revealed downregulation of RORc and IL-17a together with an upregulation of Tfh markers IL21 and Bcl6 [64]. IL-23 was not necessary for transdifferentiation of Th17 cells towards Tfh cells, as there were similar amounts of Th17 cells expressing Tfh markers in IL17 fate reporter mice and p19 deficient IL17 fate reporter mice [64].

**Treatments Targeting IL-23**

As previously described, IL-23 is critical for maintaining the Th17 phenotype and furthermore linked to plasticity towards Th1 cells. With Th1 and Th17 cells both being linked to pathogenicity in different autoimmune diseases, IL-23 appears to be a perfect target for a potential treatment. There are several Abs targeting IL-23 showing promising results. Guselkumab and Tildrakizumab are two of those candidates. Guselkumab targets the IL-23p19 subunit and showed to be viable as a new treatment option for psoriasis [65]. Recently tested in a phase 3 trial, it may be applicable for treatment of psoriatic arthritis in the future too [66]. Tildrakizumab is another humanized monoclonal antibody targeting the IL-23/IL17 axis via the p19 subunit of IL-23. It is approved for the treatment of psoriasis [67].

Another recent approach is a gene-silencing Py-Im polymide that can enter the nucleus and compete with c-Rel for binding at the IL-23p19 promoter, therefore limiting IL-23 expression on DNA level [68]. However, application of previously admitted drugs is still limited to few diseases and further clinical studies to expand treatment options are essential.

**Discussion**

In this review we presented the current understanding of Th17 cells and highlighted the role of IL-23 in polarization and plasticity. Understanding the factors that lead to the development of the Th17 cell subtype and decoding its interactions with tissue and other T helper subtypes remains crucial in order to understand autoimmune diseases. In summary, IL-23 is the key cytokine leading to pathogenicity in Th17 cells. Regulating the key effector molecules IL22 and GM-CSF, IL-23 drives inflammation in autoimmune disease (Coderri et al. 2011). With the findings from recent studies, factors that drive Th17 pathogenicity are better understood, but regarding Th17 plasticity, more studies are needed to illuminate the exact pathways and interactions of Th17 cells [24]. According to our current knowledge IL-23 is a key regulator of Th17 stability. However, there is evidence linking IL-23 to the Th17/Tfh axis as it can upregulate T-bet and Stat4 and therefore IFN-γ [21]. There could be other key regulators of Th17 fate yet to be discovered at this time that are important for stabilizing Th17 fate or pushing them towards another subset. Therefore, these contrary roles of IL-23 could be due to different cofactors. Future comprehensive studies focusing on these points will hopefully help us understand Th17 fate even better and translate findings into the clinic. A lot of the data on Th17 plasticity comes from only a few models of autoimmune...
disease, mainly EAE and colitis rheumatoid arthritis. Hence it is interesting to get more data on Th17 plasticity working with new autoimmune disease models in the future. There may be a bias in Th17 plasticity comparing different animal models, which could be addressed in the future and more studies on human samples are necessary due to the fact that findings in animal models seldom translate optimally to patients. A recent study investigating mice T cells in colitis facing different pathogens came to the conclusion that T cells cluster above all according to the pathogens they face and not to their cell type [6]. Therefore, getting more data on the behavior of T cells under changing microbiomes and pathogens may result in a better understanding of triggers of Th17 plasticity. Plasticity seems to not only be limited to pushing a phenotype towards another T helper subset, but may also play a role in fine-tuning within one subset. A more immunoregulatory Th17 subset producing IL10 and more pathogenic Th17 cells lacking IL10 production are reported [41]. These two subsets may merge. It will be interesting to test if it is more beneficial to push Th17 cells towards Tr1/Treg cells or if pushing them only towards a more IL10 producing Th17 subtype is advantageous. Remaining more Th17 like may combine the beneficial host defense mechanisms with immunoregulatory properties. There is a lot of evidence pointing towards an important role for IL-23 in Th17/Th1 plasticity, however direct evidence is necessary to further prove this [47]. Even though there is a lot of in vitro data and data from mouse models, the mechanisms behind Th17 plasticity in the actual in vivo situation in humans are still incompletely understood. The directions of plasticity in different diseases are still not clear and may differ between models. Th1-like Th17 cells in one disease may arise from the Th17 pool, while in the context of another disease have their origin in Th1 cells. Future studies addressing this question and the exact mechanisms driving Th17 plasticity are necessary. Investigation of Th17 cells with new technologies built on scRNAseq will help understand their properties and interactions [69]. Velocity indicates the direction of differentiation of a single cell within a scRNAseq dataset based on spliced and unspliced mRNA [70]. Using this package on Th17 scRNAseq data from different diseases may answer the questions regarding directions of plasticity. Analyzing the gene expression and all the proteins expressed by a single Th17 cell, will further reveal factors that drive transdifferentiation. This might also indicate the state of Th17 cells, when prone to transdifferentiation. With scRNAseq the future for plasticity research looks promising. Recently introduced bioinformatic evaluation packages, forming trajectories and illuminating interactions between T cell subsets, may fill the gaps in our current understanding of Th17 fate.

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