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Role of IL-6 in the commitment of T cell subsets

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ABSTRACT

IL-6 gained much attention with the discovery that this cytokine is a non-redundant differentiation factor for Th17 cells and T follicular helper cells. Adaptive immune responses to fungi and extracellular bacteria are impaired in the absence of IL-6. IL-6 is also required for the induction of ROR-γt^{+} Treg cells, which are gatekeepers of homeostasis in the gut lamina propria in the presence of commensal bacteria. Conversely, severe immunopathology in T cell-mediated autoimmunity is mediated by Th17 cells that rely on IL-6 for their generation and maintenance. Recently, it has been discovered that the differentiation of these distinct T helper cell subsets may be linked to distinct signaling modalities of IL-6. Here, we summarize the current knowledge on the mode of action of IL-6 in the differentiation and maintenance of T cell subsets and propose that a context-dependent understanding of the impact of IL-6 on T cell subsets might inform rational IL-6-directed interventions in autoimmunity and chronic inflammation.

1. Introduction

A pro-proliferative impact of IL-6 on T cells has long been recognized. However, with the extensive increase in knowledge on the commitment of T helper cells in response to antigenic, co-stimulatory, and cytokine stimuli in the peripheral immune compartment, the effect of IL-6 on distinct subsets of T helper (Th) cells has become a cornerstone in the understanding of their functional phenotypes. We are only beginning to understand how the distinct modes of IL-6 signaling determine the generation and function of Th17 cells, T follicular helper (Tfh) cells, and regulatory T (Treg) cells. While these are the T cell subsets that are most directly shaped by IL-6, IL-6 also influences memory T cell responses in perhaps any T cell lineage in a context and tissue-specific manner. In this review, we will give a concise overview of the impact of IL-6 on T cell subsets and summarize the role of IL-6 on inflammatory T cell-mediated disease paradigms.

2. Modes of IL-6 signaling

Both subunits of the IL-6 receptor complex, i.e. IL-6Rα and gp130, exist in a membrane bound version and in a soluble version [1]. Soluble IL-6Rα (sIL-6Rα) is mostly generated by proteolytic shedding while a minor fraction (less than 20%) of sIL-6Rα in the serum might be directly secreted after translation of an alternatively spliced mRNA [2–4]. The concentration of sIL-6Rα in the serum is already high in steady state (around 50 ng/ml) and is increased in inflammation [1]. Soluble gp130 (sgp130) is generated by alternative splicing of the gp130 transcript, and sgp130 reaches steady state concentrations in the serum as high as 300 ng/ml [5]. Since IL-6 does not only bind to membrane bound IL-6Rα but also to sIL-6Rα, it has early on been proposed that the soluble complex of IL-6 and sIL-6Rα might be bioactive [1]. Different modalities of IL-6 signaling have been suggested, and T cells can indeed sense IL-6 by different modes (Fig. 1). In classic IL-6 signaling, the soluble cytokine binds to its membrane ankered IL-6Rα, which then associates with gp130 resulting in the homodimerization of gp130. Gp130 has no measurable affinity for IL-6 but is the signal transducing subunit of the IL-6 receptor complex. Virtually all body cells (except perhaps granulocytes [6]) express gp130. Cells that lack membrane bound IL-6Rα are still able to sense IL-6: here, a preformed soluble complex consisting of IL-6 and IL-6Rα binds to gp130 on the target cell, which leads to gp130 dimerization and subsequent signal transduction. This process has been termed IL-6 trans-signaling [1]. IL-6Rα can be shed from the cell surface by the action of metalloproteases (ADAM10 and ADAM17) [7], and as a soluble protein (sIL-6Rα) then binds IL-6 to form the IL-6Rα/IL-6

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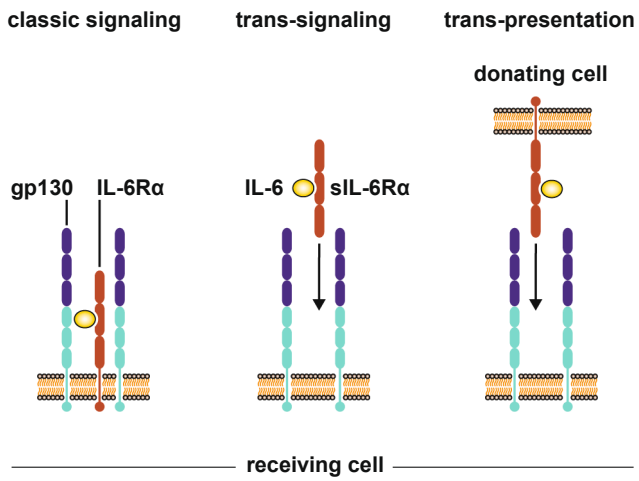

Fig. 1. Modalities of IL-6 signaling. Soluble IL-6 can be directly sensed by cells that express both subunits of the IL-6 receptor complex, i. e. IL-6Rα and gp130 (classic signaling). IL-6Rα is also expressed as a soluble protein (splice variant) or cleaved from the cell surface of IL-6Rα expressing cells (hepatocytes and subsets of myeloid cells and lymphocytes [105]). Soluble IL-6Rα can bind IL-6 and this complex is able to trigger dimerization (and signaling) of gp130 on receiving cells that do not express their own IL-6Rα (trans-signaling). Finally, the IL-6/IL-6Rα complex can also be presented *in trans* in a cell bound form to receiving cells (trans-presentation or cluster signaling).

complex. Since gp130 is ubiquitously expressed (while IL-6Rα is not), virtually any cell can respond to IL-6 trans-signaling. The affinity of IL-6 for IL-6Rα is high (0.5 to 1 nM). Therefore, a third modality of IL-6 signaling has been described: IL-6 trans-presentation (also called IL-6 cluster signaling) [8]. In IL-6 cluster signaling, a donating cell presents IL-6 via its own membrane bound IL-6Rα *in* trans to a receiving cell. For instance, SIRP1α$^+$ DCs (DC2) are able to perform this trans-presentation by loading IL-6 on their IL-6Rα before IL-6Rα is displayed on the cell surface [8]. The receiving cell needs to be in close proximity to the donating cell so that it can sense the donating cell's IL-6Rα/IL-6 complex through its gp130. Similar to the scenario of trans-signaling, the receiving cell is not required to express IL-6Rα in order to pick up an IL-6 signal by trans-presentation. The downstream pathways induced by productive IL-6 signaling have been extensively reviewed (e.g. [9]).

Besides potentially different biological outcomes for the receiving cell (see below), the efficacy and mechanisms of IL-6 signaling blockade are likely different for the various modes of IL-6 signaling. For instance, while monoclonal antibodies to IL-6 block classic IL-6 signaling and trans-signaling, IL-6 trans-presentation is resistant to anti-IL-6 [8]. In contrast, monoclonal antibodies to IL-6Rα target all three modes of IL-6 signaling. Finally, sgp130 buffers the soluble IL-6Rα/IL-6 and thus prevents trans-signaling [10,11]. Whether sgp130 also blocks IL-6 trans-presentation (cluster signaling) may be context-dependent [8,12,13].

3. Sensing of IL-6 by naive T cells

3.1. IL-6 as "homeostatic" cytokine

Both subunits of the IL-6 receptor complex are expressed in naive CD4$^+$ T cells. Naive T cells express particularly high levels of IL-6Rα and gp130 (CD130) [14]. Upon sensing of IL-6, IL-6Rα is downregulated in naive T cells. In fact, the expression level of IL-6Rα in T cells is linked to the expression of CCR7 and CD62L [15]. While shedding of IL-6Rα might be the main mechanism [16], ligand dependent internalization of IL-6Rα has been described [17]. However, more recent reports also suggest IL-6 independent modes of IL-6Rα internalization [18].

Downregulation of cytokine receptor expression in response to cytokine sensing in naive T cells is a hallmark of "homeostatic" cytokines. For example, within the group of γc cytokines, the paradigmatic homeostatic cytokine IL-7 leads to downregulation of its receptor in naive T cells while "inflammatory" γc cytokines including IL-2, IL-4, and IL-21 induce their own receptors and thus create feedforward loops in an inflammatory environment. Since IL-6 signaling results in downregulation of IL-6Rα in naive T cells, IL-6 has been tested for its potential to induce homeostatic proliferation of T cells, and overexpression of IL-6 in IgH deficient mice (to prevent plasmocytosis) indeed results in an enlarged T cell compartment, most likely due to the induction of survival factors (including Mcl-1) by IL-6 [19].

3.2. IL-6 in the commitment of Th17 cells

During antigen specific priming, besides TCR signaling strength and co-stimulatory signals [20], the cytokine milieu contributes to and sometimes determines the commitment of naive T cells to a distinct T helper cell lineage. The concept of distinct T helper cell lineages has been widely accepted after the functional relevance of such a classification had been shown by Mosmann und Coffman and many other investigators [21]. While Th1 cells produce IFN-γ and communicate with macrophages in order to harness them for the elimination of intracellular pathogens, Th2 cells produce IL-4 and promote antibody responses in order to deal with pathogens that are too large to be phagocytosed. The T cell extrinsic cytokine IL-12 is required for the full differentiation of Th1 cells. Conversely, IL-4 (initially likely also from T cell-extrinsic sources) is necessary to induce the Th2 program in naive T cells (for review see [22]). IL-6 is irrelevant for the commitment of Th1 cells or Th2 cells. However, early work suggested that IL-6 was a proliferative stimulus for T cells, and especially naive T cells require exogenous IL-6 for proliferation while the proliferation of memory T cells has been reported to depend on autocrine IL-6 provided by T cells [23]. Upon antigen-specific stimulation, T cells still differentiate into effector T cells even in the genetic absence of master transcription factors required for the commitment to Th1 cells and Th2 cells [24,25], and this finding kindled the discovery of a new T helper cell lineage that was later termed Th17 cells since – among others – IL-17 is one of the cytokines produced by these cells. Interestingly, only in the presence of LPS stimulated monocytes and Foxp3$^+$ Treg cells could Th17 cells be differentiated from naive T cells [26]. Here, Treg cells were a source of TGF-β and LPS stimulated monocytes were a source of IL-6. Together with two other reports [27,28], these data supported the idea that IL-6 is an essential differentiation factor for Th17 cells. The differentiation of T helper cell subsets is mutually cross-inhibitory. However, the initiation of Th17 differentiation is not only inhibited by IFN-γ and IL-4, but also by IL-2 (at least in early phases of the differentiation process) [29]. Mechanistically, IL-2 down-modulates the expression of both gp130 and IL-6Rα on conventional T cells and thus decreases their responsiveness to IL-6 [30].

Since the establishment of Th17 cells as a T helper cell lineage independent of Th1 and Th2 cells, the knowledge on this T helper cell subset grew exponentially but also created conceptual problems that have not yet been solved [31,32]. In fact, Th17 cells rely on IL-6 for their differentiation, and STAT3 and ROR-γt are indispensable transcription factors to establish the functional phenotype of Th17 cells. However, Th17 cells are also exquisitely plastic [22] and can co-express both IFN-γ and IL-4 [33], which are signature cytokines of Th1 and Th2 cells, respectively.

The function of Th17 cells is most likely host defence at barrier tissues including gut, skin and lung, and due to the receptor distribution of many of their products including IL-17 and IL-22, Th17 cells are designed to communicate directly with tissues. It has been difficult to conceive that Th17 cells can have functions in host protection and tissue regeneration but at the same time also induce severe tissue destructive immunopathology. Therefore, some efforts have been undertaken to define subgroups of Th17 cells according to their potential to induce immunopathology [34]. Although "pathogenic" Th17 cells have been functionally defined according to their capacity to induce severe disease

in models of autoimmunity [34], co-expression of ROR-γt together with T-bet, expression of IL-18R1 and Cxcr3, and lack of IL-10 expression might determine the phenotype of these cells [35]. Sensing of IL-23 has been suggested to be a criterion for Th17 cells to acquire the potential for immunopathology [35]. However, perhaps the mode of IL-6 sensing is the upstream determinant for whether the priming of Th17 cells *in vivo* results in the capacity of these cells to become tissue-protective or tissue-destructive. In fact, while classic IL-6 signaling is sufficient to suppress the TGF-β-mediated induction of Foxp3^{+} in naive T cells, IL-6 cluster signaling, i. e. the trans-presentation of IL-6 by the antigen-presenting cell that also delivers the antigen-specific signal in the context of MHC class II is required for the generation of pathogenic Th17 cells *in vivo* [8] (Fig. 2).

3.3. IL-6 in the commitment of T follicular helper cells

Besides Th17 cells, the differentiation of Tfh cells is dependent on IL-6 (and IL-21 as well as STAT3) [36]. This model of Tfh generation suggested that similar to other T helper cell lineages, Tfh cells can be generated from naive T cells in the presence of IL-6 and IL-21 but (in contrast to Th17 cells) in the absence of TGF-β. Similar to other T helper cell subsets, the TCR signaling strength is a determinant of Tfh cell development: while during acute antigen exposure, low TCR avidity drives Tfh development at the expense of effector T cell commitment [37], higher TCR avidity favors Tfh cell development as compared to effector T cell commitment in chronic antigen availability (e.g. during chronic viral infection) [38,39]. Perhaps, the initiation of a Tfh cell program is a way for some high affinity clones to escape from T cell exhaustion during chronic viral infections. It is now widely accepted that Tfh cells develop independently of alternative T helper cell subsets. However, Tfh cells do not develop in the absence of B cells. Therefore, after a DC-dependent priming event that – besides TCR engagement – requires sensing of IL-6, ICOS expression and production of IL-21 by T cells, full commitment to the Tfh lineage (with high expression of Bcl6) only occurs after a subsequent interaction of Tfh precursor cells with B cells [40]. Notably, when both IL-6 and IL-21 are missing, Tfh cells are not generated [41]. On the other hand, it has been questioned whether IL-6 is a differentiation factor for Tfh cells: IL-6-deficient mice show a strong reduction of Tfh cells upon protein immunization but T cell conditional *Il6ra* $^{-/-}$ mice only have a slight reduction in Tfh cells. Yet, their function is fundamentally impaired resulting in reduced germinal center B cells and specific antibody titers (in particular IgG2c) [42]. In accordance with this finding, the generation and function of Tfh cells in later phases of viral infections (here LCMV) appear to be dependent on IL-6 with reduced levels of antigen-specific IgG1 and IgG2 responses in *Il6* $^{-/-}$ mice in chronic LCMV infection [43]. Mechanistically, sensing of IL-6 by T cells enhances the expression of ICOS that is required for the DC-mediated initiation process of Tfh commitment [42]. The establishment of a functional Tfh cell population is driven by B cell-derived IL-6 and follicular dendritic cell-derived IL-6 in acute and chronic phases of the infection, respectively. In both scenarios IL-6 is sensed by T cells that – in response to IL-6 – provide IL-21 to further promote the differentiation of Tfh cells in an autocrine feedforward loop.

4. Sensing of IL-6 by committed T cells

4.1. IL-6 in the maintenance of Th17 cells

While established as a differentiation factor for Th17 cells, it has been unclear whether Th17 cells depend on sustained IL-6 sensing in order to maintain their identity. This is a relevant question since Th17 cells are considered to be more plastic than alternative T helper cell lineages with diverse options to further differentiate into effector and regulatory T cell species. Sensing of IL-6 by T cells results in Jak1, Jak2, and Tyk2 activation and phosphorylation of STAT3 (and STAT1). Committed Th17 cells express the IL-23R that is also linked to STAT3 activation, and IL-23 has been described as a T cell-extrinsic factor to stabilize a pathogenic phenotype in Th17 cells. However, IL-23 (as IL-12) most likely due to simultaneous activation of STAT4 promotes the loss of ROR-γt expression and upregulation of T-bet and IFN-γ in Th17 cells. Therefore, even though promoters of pathogenic potential, IL-12 and IL-23 destabilize the bona fide Th17 phenotype. In contrast, sustained IL-6 signaling into Th17 cells is required to maintain ROR-γt expression and a bona fide Th17 cell transcriptome and Th17 cell identity [44].

Given the shedding of IL-6Rα by activated T cells, it is a matter of debate whether activated T cells with a transcriptional program already committed to a distinct T helper cell lineage are still able to respond to

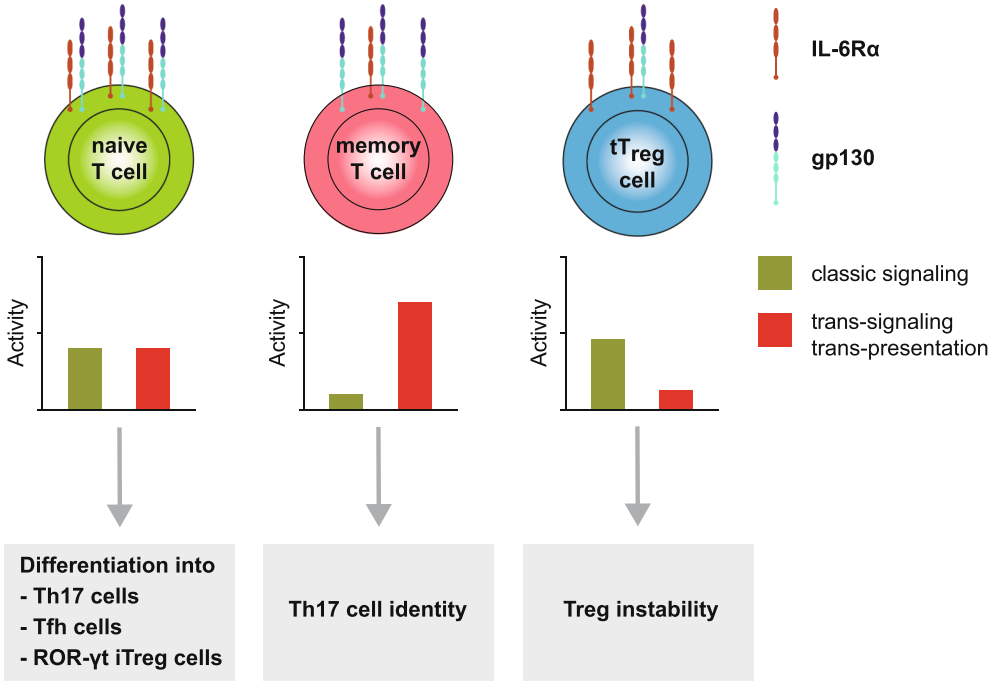

Fig. 2. T cell responses to IL-6. In naive T cells – depending on the cognate antigen, the costimulatory context, and further cytokine signals – IL-6 can drive the differentiation of Th17 cells, Tfh cells or ROR-γt^{+} iTreg cells. The differentiation of other T helper cell subsets (like Th22 cells in human skin) might also dependent on IL-6 (plus TNF and plasmacytoid dendritic cells) [106]. However, the firm establishment of these cells as an independent T cell lineage is pending. In activated/memory T cells and thymus derived Treg (tTreg) cells, IL-6 stabilizes and destabilizes the pre-imprinted cell identity, respectively. Depending on the receptor outfit of these various T cell subsets, different IL-6 signaling modalities might be operational.

classic IL-6 signaling. Early work suggested that IL-6 only has a minor role in the maintenance of the Th17 phenotype as compared to TGF-β [45]. However, certain effector functions of activated T cells (including resistance to apoptosis [46] and trafficking [47]) are reverted by the blockade of IL-6 trans-signaling. In addition, soluble gp130 (a selective inhibitor of IL-6 trans-signaling) blocked the maintenance of Th17 cells in a model of S. epidermidis cell-free supernatant-induced peritonitis, suggesting that soluble IL-6Rα is required for the identity of Th17 cells that are low in membrane bound IL-6Rα. Yet, in transfer colitis, *Il6ra* $^{-/-}$ T cells lost their Th17 identity despite an unimpaired capacity to sense IL-6 via trans-signaling [44]. Therefore, the significance of classic vs trans-signaling of IL-6 for the identity and function of committed T helper cells might be dependent on the tissue environmental context.

4.2. IL-6 in memory T cell responses

IL-6 signaling is dispensable for the generation of Th1 cells. However, Th1 cells lacking IL-6Rα contract rapidly after an immune response and fail to re-expand after antigen-specific challenge, suggesting a functional deficiency in memory responses in the absence of IL-6 signaling [48]. Since genetic ablation of *Il6ra* was performed in both conventional and regulatory T cells, it is unclear whether the absence of Th1 memory responses is a feature intrinsic to conventional T cells deficient in IL-6Rα. Alternatively, exaggerated Treg responses in the absence of IL-6 signaling or increased susceptibility of conventional T cells to Treg-mediated suppression could explain this phenotype. In support of this idea, Th1 recall responses are in part rescued in T cell conditional IL-6Rα-deficient mice upon transient depletion of Treg cells [48]. Conversely, highly activated wild type effector T cells in the target tissue of inflammatory responses are resistant to Treg cell-mediated suppression due to enhanced sensing of IL-6 [49].

4.3. Interpretation of IL-6 signals by committed T helper cells

The differential interpretation of the IL-6 signal by naive and memory T cells has been investigated to some detail on the molecular level. While naive T cells respond to IL-6 with tyrosine phosphorylation of STAT3 but also STAT1, pY-STAT1 is reduced in activated and memory T cells while the pY-STAT3 response is unchanged as compared to naive T cells. The reduced pY-STAT1 response in memory T cells is due to the TCR-induced activation of PTPN2, a phosphatase that preferentially dephosphorylates STAT1 (but not STAT3). STAT3 activation in the absence of a relevant STAT1 signal in response to IL-6 leads to the expression of transcriptional modules in memory T cells that are associated with increased survival (Hmox1, Myc, Cd83) [50]. The ratio of STAT3/STAT1 activation might also be the molecular mechanism to translate the sensing of the different IL-6 signaling modalities into different cellular outcomes in the receiving T cell.

5. Sensing of IL-6 by Treg cells

Foxp3^{+} Treg cells express both components of the IL-6 receptor complex. While IL-6Rα expression equals the expression of IL-6Rα in conventional T cells, gp130 expression is one order of magnitude lower in Treg cells than in conventional T cells [14]. In human Treg cells this pattern of IL-6 receptor complex expression results in a lower activation of STAT3 in response to IL-6 in Treg cells as compared to conventional T cells.

5.1. Role of IL-6 for peripherally induced Treg cells

The functional consequence of IL-6 sensing by Treg cells is context dependent. For instance, sensing of IL-6 might have different outcomes depending on which type of Treg cell senses IL-6: overall IL-6 is a suppressor of Foxp3 and other core signature genes of Treg cells by transcriptional and post-transcriptional mechanisms [51–53]. Therefore, peripherally induced Treg (pTreg) cells are reciprocally linked to the development of Th17 cells, for which IL-6 is a non-redundant differentiation factor [28]. However, a subset of pTreg cells that is induced in the gut and co-expresses Foxp3 and ROR-γt to regulate immune responses to commensal bacteria is dependent on IL-6. In fact, *Il6*$^{-/-}$ mice exhibit significantly reduced fractions of ROR-γt^{+} Treg cells in the gut lamina propria [54], and a very recent report suggests that enteric neurons are a relevant source of IL-6 for the induction of ROR-γt^{+} Treg cells [55]. ROR-γt^{+} Treg cells and Th17 cells share similar cytokine cues for their development, yet are differentially dependent on vitamine A, which promotes Treg induction but not Th17 cell development [54].

5.2. Role of IL-6 for thymus-derived Treg cells

While IL-6 is a key factor in the decision of naive T cells to differentiate into effector T cells or Tfh cells vs induced Foxp3^{+} Treg cells in the peripheral immune compartment, the commitment of thymocytes to the conventional T cell or to the Treg cell compartment within the thymus is believed to be independent of IL-6/STAT3 signaling [56]. Once generated, thymus-derived Foxp3^{+} Treg (tTreg) cells keep their identity both during homeostatic proliferation but also in inflammatory environments. Epigenetic imprinting of key Treg cell loci warrants this stability. For instance the CNS2 of the *Foxp3* locus is fully demethylated in tTreg cells [57]. However, STAT3 dependent signaling is able to compromise the expression of Foxp3 in tTreg cells (e. g. [58]). Since STAT3 may not directly inhibit the transcription of *Foxp3*, a major mechanism of IL-6 in the destabilization of tTreg cells is to compromise the epigenetic status of the *Foxp3* locus. Indeed, the methyltransferase Dnmt3a is a target of STAT3, and Dnmt3a is induced in tTreg cells in a STAT3 dependent manner unless tTreg cells express high levels of Blimp1 [59]. Loss of Blimp1 in Treg cells initiates a cascade of IL-6/STAT3-driven destabilization of tTreg cells. Other STAT3-dependent Treg-destabilizing events have been described as well [60,61], and activation of STAT3 in Treg cells may not only lead to a loss of identity or function of Treg cells but also to a “toxic” gain-of-function since Treg cells may convert into effector T cells [58], which is particularly dangerous since the T cell receptor repertoire of Treg cells is biased towards autoantigens [62–64]. For example, IL-6 from fibroblasts in inflamed joints has been identified to promote the conversion of Treg cells into pathogenic Th17 cells [65]. Notably, the mode of IL-6 sensing by Treg cells is under debate and some investigators have suggested that Treg cells do not only lose IL-6Rα but also downregulate gp130 in highly inflammatory milieus to become resistant to any type of IL-6 signaling [66]. However, overall the IL-6/STAT3 signaling pathway has clearly been identified as a major pathway to dismantle Treg cell identity [60,61,67].

6. IL-6 in T cell-mediated host defence

Due to its profound effects on myeloid cells and stromal cells, the function of IL-6 in host defence is complex. The net effect of IL-6 in infectious diseases will probably at least as strongly be determined by these functions of IL-6 as by the role of IL-6 in priming and modulating T cell subsets. In fact, exaggerated immunopathology in host defence is likely primarily dependent on non-lymphoid cell targets of IL-6. In contrast, productive and long-term host protection in some infections is orchestrated by antigen-specific Th17 cells and Tfh cells, whose generation depends on IL-6.

Th17 cells are a cornerstone in host defence against some bacterial and most fungal infections (also in humans [68]). In bacterial infections with *Klebsiella pneumonia*, Th17 cells are essential to contain the infection by producing IL-17A that acts on non-immune cells in infected tissues and in turn leads to the production of antimicrobial proteins, cytokines, and chemokines [69]. IL-17A fate mapping showed that Th17 cells in an acute fungal infection with *Candida albicans* produce high levels of IL-17 early on. While IL-17 production is reduced over the

course of the infection, ex-IL-17 producers do not switch their cytokine profile to Th1 cytokines, as is observed in chronic inflammation, like experimental autoimmune encephalomyelitis (EAE) [70].

The role of Th17 cells in viral infections is less clear. In a mouse model of west nile virus (WNV) infection, IL-17A-deficient mice show diminished cytotoxic $CD8^+$ T cell responses that can be rescued by application of recombinant IL-17A as late as 6 days after infection [71]. Interestingly, IL-6 dependent T cell responses might also be relevant for proper immune surveillance of the central nervous system in humans as a case of progressive multifocal leukencephalopathy, a lytic infection of oligodendrocytes with JC virus, has recently been reported in a patient that was treated with an antibody to IL-6Rα for rheumatoid arthritis [72]. On the other hand, antigen-specific Th17 responses in Theiler virus infection increase the resistance of infected cells to cytotoxic $CD8^+$ T cell responses and prevent clearance of the virus resulting in chronic demyelination [73]. In viral infections that are controlled by neutralizing antibodies, antigen-specific Tfh cells are key orchestrators of a sterilizing response. In a murine model for chronic viral infection (LCMV clone 13), IL-6 signaling in virus-specific $CD4^+$ T cells up-regulates Bcl6 and induces Tfh responses at late stages of the infection [43]. Moreover, in patients with chronic hepatitis C virus (HCV) infection, a HCV-specific Tfh subset persists after antiviral therapy that might contribute to protection from reinfection with the virus [74].

IL-6 signaling plays also a role in COVID-19 that is caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) and was declared a pandemic by the world health organization in March 2020 [75]. The SARS-CoV-2-induced cytokine storm (with massive systemic elevations of IL-6 and other cytokines [76]) has been identified as a major determinant of mortality in SARS-CoV-2-associated severe acute respiratory syndrome (ARDS) [77]. T cell-specific effects of IL-6 in COVID-19 might include the facilitation of Th17 cell responses and – indirectly – the recruitment of Th17 cells to the infected epithelia. In the tissue, Th17 cells are responsible for the attraction of neutrophils and amplification of immunopathology [78]. In COVID-19 patients an endophenotype of highly activated T cells and circulating Tfh cells is associated with disease severity [79]. Notably, a subset of tissue-resident memory-like Th17 cells has been reported in the lungs of COVID-19 patients that might be contributing to hyperinflammation in severe cases of COVID-19 by the production of IL-17A and GM-CSF and the interaction with lung macrophages and cytotoxic $CD8^+$ T cells [80].

Blockade of IL-6 signaling with monoclonal antibodies to IL-6Rα (tocilizumab) is used in COVID-19 patients with signs of severe systemic inflammation (C-reactive protein) that are hypoxic but are not yet mechanically ventilated. Bacterial or fungal superinfections preclude the application of tocilizumab. A number of randomized placebo-controlled trials support a slight benefit for severely ill COVID-19 patients when treated with tocilizumab [81–83].

7. IL-6 in T cell-mediated autoimmunity

Since Th17 cells have been causally linked to immunopathology in a variety of autoimmune diseases and chronic inflammatory conditions, including psoriasis, inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis and neuromyelitis optica [31,84,85], it is not surprising that strategies to block IL-6 signaling have been tested in clinical trials in some of these conditions. Due to successful pivotal trials, several drugs that intervene with IL-6 signaling pathways have been licensed for rheumatoid arthritis, Castleman disease, and giant cell arteritis [12] while the European Medicines Agency has recently granted a marketing authorization for satralizumab (anti-IL-6Rα) for patients with neuromyelitis optica. However, it needs to be considered that in disease conditions where blockade of IL-6 signaling proved to be beneficial, the relevant cellular targets may not be T cells. For instance, while T cells are clearly required for the pathogenesis of neuromyelitis optica, the eventual damage to astrocytes is mediated by antibodies that recognize the water channel protein AQP4, which is expressed in astrocytes [85]. These antibodies are produced by plasmablasts and plasma cells, for which IL-6 is a direct growth factor. Therefore, it is possible (or even likely) that blockade of IL-6 signaling mainly affects this pathway. In support of this idea, the clinical effects of satralizumab were particularly clear in neuromyelitis optica patients with anti-AQP4 antibodies in the serum while anti-AQP4 negative patients did not benefit [86,87]. Another antibody-mediated autoimmune disease of the central nervous system, i.e. anti-myelin oligodendrocyte glycoprotein (MOG) antibody associated disease (MOGAD), also appears to be responsive to anti-IL-6Rα antibody treatment [88].

While Th17 cells have been implicated in the pathogenesis of multiple sclerosis [89–91], the significance of B cells in multiple sclerosis likely does not lie in their function as precursors of antibody producing cells but in their role as antigen presenting cells [92]. Therefore, the blockade of IL-6 signaling will not so much be operational through the elimination of a “B cell growth factor” but through a more direct impact on T cells (and potentially other targets). Since T cells will already have been primed in multiple sclerosis patients with apparent disease, intervening with IL-6 signaling might exert its effects through modulation of T cell trafficking or maintenance of memory/activated T cells (see above). Due to this more complex role of IL-6 in multiple sclerosis, it will have to be determined whether IL-6-directed interventions might be particularly promising in distinct subgroups of patients with multiple sclerosis. However, at the moment, biomarkers to stratify these patients are lacking. As a final caveat, demyelinating lesions have been reported in a patient that did not have multiple sclerosis but was treated with tocilizumab for other reasons [93]. It is unclear at the moment whether this is a relevant safety signal.

8. Concluding remarks

IL-6 is not only produced by a plethora of hematopoietic and non-hematopoietic cells. But IL-6 is also sensed by many cells including hematopoietic cells as well as cells of ectodermal and endodermal origin. In addition, members of the IL-6 family exhibit extensive cross-talk with other cytokine families e.g. by shared usage of receptor subunits [94]. It is therefore not surprising that IL-6 is regulated on many levels including its transcription, RNA stability, secretion, buffering in the extracellular space, sensing, and signaling [95–98] [also refer to Jeff Babon in this issue]. The challenge in understanding the biology of IL-6 has been to assign distinct modes of regulation and distinct modes of action of IL-6 with distinct cellular or systemic outcomes. A very visionary concept has been introduced by the hypothesis that classical signaling of IL-6 would be associated with homeostatic functions of this cytokine (including tissue regeneration) while IL-6 trans-signaling would promote pro-inflammatory responses [99]. Since classical and trans-signaling might be targeted by different interventions [12], this concept holds promise for more selective therapies. A soluble gp130 fusion protein that inhibits trans-signaling (and perhaps cluster signaling) but not classic IL-6 signaling appeared to be safe and efficacious in a phase 2 study of ulcerative colitis (NCT03235752). However, the efficacy and safety of interventions that target IL-6 will also depend on whether myeloid cells or adaptive immune cells including T cells and B cells drive the pathology of the disease. Yet, another level of complexity is associated with the question how directly IL-6 is linked with the respective immunopathology. For instance, IL-6 is a direct growth factor for plasma cells in Castleman disease [100] and for plasmablasts that produce pathogenic antibodies in neuromyelitis optica [101]. Therefore, blocking IL-6 has been very successful in achieving treatment responses in HHV-8 negative Castleman disease and in anti-AQP4 positive neuromyelitis optica [86,100]. More indirect involvement of IL-6 with a certain disease condition or involvement of pathogenic cascades that engage both myeloid responses as well as adaptive immune responses like for example in the tumor microenvironment will be much harder to assess as to beneficial effects of IL-6 targeting strategies. For example, IL-6 has been associated with the differentiation of alternative macrophages (so-

called M2 macrophages) [102]. However in several tumor models, IL-6 not only promotes tumor specific cytotoxic T cell responses but also is required to achieve an M1 phenotype in tumor-infiltrating macrophages that promote tumor regression [103]. Yet, IL-6 dependent Th17 cell responses have been reported to worsen inflammation-associated tumor growth (for review see [104]). Therefore, it will be very challenging (and context-dependent) to design IL-6-directed interventional strategies in cancer therapy unless the contribution of distinct components of the immune response (cytotoxic T cells, Treg cells, myeloid cells) is characterized in more detail for individual tumors.

Finally, with the refined potential of IL-6 interventional strategies (e.g. to target classical vs trans-signaling or even IL-6 trans-presentation), there is an urgent need to better understand whether distinct functions in the adaptive arm of the immune system are linked with distinct signaling modalities of IL-6. For instance, while therapeutic interventions should reduce Th17 cell reactions that are responsible for severe immunopathology in inflammatory skin diseases or multiple sclerosis, an exaggerated impairment of Tfh cell development would jeopardize productive antibody responses in host defence. Selective targeting of the differentiation of T helper cell subsets would be facilitated if it was possible to associate these processes with distinct IL-6 signaling modalities. Therefore, although much progress has been made in the last decade as to the importance of IL-6 for adaptive immune responses, the rational application of a refined armamentarium to target IL-6 calls for a context- and stage-specific understanding of IL-6 in antigen-specific T and B cell responses.

CRediT authorship contribution statement

Thomas Korn: Conceptualization, Writing - review & editing. **Michael Hiltensperger:** Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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