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Potential route of Th17/T_{reg} cell dynamics in targeting type 1 diabetes and rheumatoid arthritis: an autoimmune disorder perspective

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ABSTRACT

Cytokines, small secreted proteins, have a specific effect on the interactions and communications between cells. They play a pivotal role in the pathogenesis of autoimmune diseases. Factors in the breakdown of self-tolerance and the subsequent events leading to the induction of pathogenic responses remain unclear for most of the autoimmune diseases. Large numbers of studies have revealed a general scheme in which pro-inflammatory cytokines contribute to the initiation and propagation of autoimmune inflammation, whereas anti-inflammatory cytokines facilitate the regression of inflammation and thereby recovery from the disease. The interleukin (IL)-17/IL-23 axis that emerged as the new paradigm has compelled us to critically re-examine the cytokine-driven immune events in the pathogenesis and treatment of autoimmunity. T-helper 17 cells and Regulatory T cells are two lymphocyte subsets with opposing action. In this review, we discuss the mechanism that promotes development of these cells from common precursors and specific factors that impact their cell numbers and function. Also presented are findings that suggest how the equilibrium between pre-inflammatory T helper and regulatory T-cell subsets might be pharmacologically restored for therapeutic benefit, emphasising type-1 diabetes and rheumatoid arthritis. Furthermore, the emerging clinical data showing anti-IL-17 and anti-IL-23 treatments for their efficacy in treating immune-mediated inflammatory diseases are presented.

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Introduction

Until recently, T-helper 1 (Th1)/Th2 cytokine balance was examined and analysed in the pathogenesis of autoimmune diseases, with the two T-cell subsets mutually cross regulating each other.[1–3] Here, cytokines produced by Th1 cells [e.g. interleukin 2 (IL-2), interferon (IFN)-γ and tumour necrosis factor (TNF)-α and macrophages (e.g. IL-1, IL-6, IL-12 and TNF-α) mediate the Th1-driven responses, whereas Th2-driven responses are mediated by cytokines such as IL-4, IL-5 and IL-13.[1,4] Accordingly, autoimmune diseases could be categorised as predominantly Th1-driven if the major events were cell-mediated in nature, or predominantly Th2-driven if antibodies and/or immune complexes served as the main mediators. Because of the cross regulation between Th1 and Th2, various immunomodulatory regimens were developed that were aimed at restoring the cytokine balance.[3,5,6] For these reasons, the Th1/Th2 regulation has been the cornerstone of the mechanistic and therapeutic aspects of autoimmune diseases over the past two decades. However, there are contradictions in mechanisms underlying the pathogenesis of autoimmunity that need additional understanding for their resolution. Therefore, in this review, we have presented the role of Th17/Treg and implications of its imbalance in autoimmunity. The clinical data shows anti-IL-17 and anti-IL-23 treatments for their efficacy in immune-mediated inflammatory diseases throwing light on probable correlation between rheumatoid arthritis and type-1 diabetes mellitus, two autoimmune disorders. Also, we present a unique graphical representation simplifying the entire gamut of inflammatory imbalance that triggers autoimmunity and also developmental evolution of IL-17 and IL-23.

A major paradigm shift in the Th1/Th2-centric view of autoimmunity occurred just over a decade ago with the realisation that many of the effector responses previously assigned to IL-12 and IFN-γ were indeed mediated *in vivo* by IL-23 and IL-17 (the IL-17/IL-23 axis).[7] An important turning point was that heterodimeric cytokines IL-12 and IL-23 shared a common chain (p40), while possessing a distinct second chain, p35 and p19, respectively. Therefore, previous studies that were performed in p40-knockout mice were interpreted in the context of IL-12 and researchers had inadvertently missed the contribution of IL-23 to the immune events during autoimmune inflammation.[8] The latter was further clarified

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through the use of mice deficient in p35 or p19. Thereafter, the role of IL-23 in driving IL-17 response was revealed,[9] and a new subset of T cells (Th17) that produced IL-17 but was distinct from Th1 subset was identified.[10–12] Early studies in animal models of rheumatoid arthritis (RA)[13,14] as well as in patients with these diseases spearheaded the appreciation for the role of IL-17 in these autoimmune diseases. The activity of Th1 and Th17 can be effectively down modulated by a diverse group of regulatory T cells[15–17], e.g., Th2 (secreting IL-4, IL-5 and IL-13), Tr1 (secreting IL-10) and $CD4^+$ $CD25^+$ forkhead box p 3 (Foxp3) + T regulatory cells (Treg) [secreting transforming growth factor (TGF)-β and IL-10]. There is a reciprocal developmental pathway between Th17 and Treg, with TGF-β facilitating the development of Treg, whereas TGF-β in the presence of a pro-inflammatory cytokine (IL-6/IL-1) favouring Th17 induction. [18–20] The reciprocal differentiation between Treg vs. Th17 can be influenced by various molecular switches/mediators such as Foxp3, retinoic acid-related- γt (ROR-γt), IFN-regulatory factor-4 and aryl hydrocarbon receptor.[21] In 2010, it was shown that IL-23 (in the absence of TGF-β) in the presence of IL-1/IL-6 can drive the differentiation of Th17 that express both ROR-γt and T-bet. This subset of Th17 is more pathogenic than the Th17 subset (expressing ROR-γt) generated in the presence of TGF- β and IL-6/IL-1 Th22, Th9 and TfH represent additional T-cell subsets that display specific cytokine secretion profiles and other unique attributes[22] (Figure 1).

Method

Electronic searches were conducted to explore relevant publications till December 2015. Medline, Embase, Cochrane, Central Register of Controlled Trials, Science Direct, Web of Science, PubMed, Sci Finder and Scopus databases were explored using predetermined search strategies. Exclusion criteria were in accordance with the reading of abstracts and articles. Out of 328 pertinent research papers, 87 were found to be more appropriate and interpretations from the studies were used as data for thematic analysis and synthesis of findings.

Cytokines that promote Th17-cell development

TGF-β and IL-6 drive initial lineage commitment but also restrain the pathogenic potential of $T(H)^{-}17$ cells. The cumulative impact of $ROR\gamma t^+$ Th17 cells is a function of the effector cytokines they produce and these $ROR\gamma t^+$ Th17 cells can be broadly divided into two groups: host protective cells that express both IL-17 and IL-10 [23,24] and a highly inflammatory population that express IL-17, IL-22, IFNγ and granulocyte-macrophage colony-stimulating factor (GM-CSF).[25] The

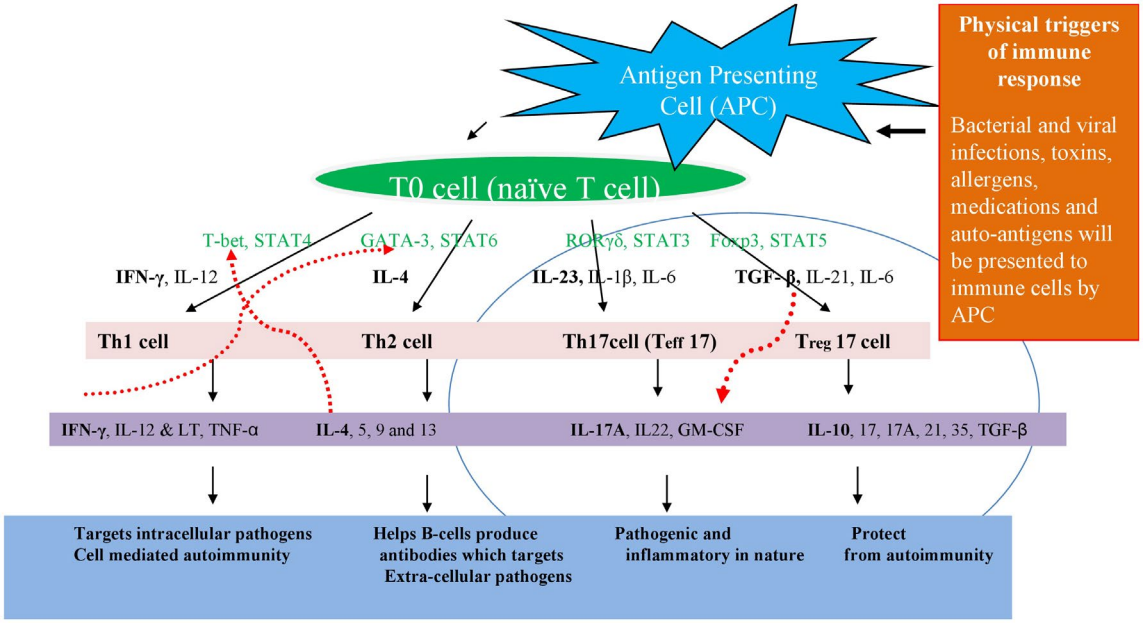

Figure 1. Steps involved in IL-17 activation.

Notes: Immature or naïve T cell under the influence of respective transcription factors along with presence of locally involved cytokines are differentiated into various forms of T helper cells. These T helper cells (Th1, Th2, Teff 17 and Treg 17) once stimulated release increased levels of various cytokines. The master transcription factor of Th1 cells is T-box transcription factor expressed in T cells (T-bet) and it is inhibited by IL-4. In contrast, GATA-binding protein 3 (GATA-3) is necessary for Th2 differentiation and it is inhibited by IFN-γ. The cross regulation of the two Th subsets is the hallmark of the Th1–Th2 paradigm. Though IL-1β and IL-6 can induce IL-17 from naive T cells, it is IL-23 that up-regulates GM–CSF expression in Th17 cells and is therefore responsible for its pathogenic activity. TGF-β suppresses the production of GM–CSF and thereby a balance is maintained between Teff 17–Treg 17 cells. Given Treg broad suppressive action, it is unclear how the activity of Tregs is regulated to ensure that beneficial immune responses to infectious stimuli proceed unabated, while other responses are suppressed. *GM–CSF – Granulocyte macrophage colony-stimulating factor, IL-interleukin, IFN-Interferon, LT-leucotoxin, ROR – retinoic acid receptor-related orphan receptor, STAT – signalling transducer and activator of transcription, TGF – transforming growth factor.*

final outcome of Th17-cell activity is determined by the balance of these effector functions. Th17 cells activated by TGF-β and IL-6 promote mucosal defence, barrier tissue integrity and curtail immunopathogenic responses, whereas IL-23-activated Th17 cells promote chronic tissue inflammation during infection and autoimmunity. [26,27]

Initiating cytokines

Studies in 2005 showed that IL-23 promotes the development and expansion of a pathogenic T-cell population with a unique inflammatory gene signature.[28] However, additional factors are required for their lineage fate determination as IL-23 alone cannot drive differentiation of Th17 cells from naïve CD4 + T cell precursors. Shortly thereafter, Stockinger, et al., showed that addition of TGF-β and IL-6 during initial T-cell recognition of cognate antigen promotes Th17-cell differentiation. [29–31] The Betelli et al., Mangan et al. and Veldhoen et al. papers showed the importance of TGF-β plus IL-6 in the lineage specification of Th17 cells. IL-6 has an essential role in this process by activating signal transducer and STAT3, which directly drives transcription of Th17 lineage-specific genes[31] including Rorc, IL17 and IL23r. STAT3 also suppresses TGF-β-induced forkhead box P3 (FOXP3) expression and thereby inhibits the generation of regulatory T (TReg) cells. Consequently, $Il6^{-/-}$ mice are unable to generate Th17 cells and are protected from developing experimental autoimmune encephalomyelitis (EAE)[32] and collagen-induced arthritis (CIA).[33] Although IL-6 was identified as a therapeutic target long before the recognition of Th17 cells, the recent advances have validated IL-6 as a target for the treatment of rheumatoid arthritis and other inflammatory conditions. IL-1β signalling also has a critical role during the initial stages of Th17-cell differentiation. $IL1r1^{-/-}$ mice fail to develop antigen-specific Th17 cells and are resistant to EAE.[34] Expression of IL-1 receptor type 1 (IL-1R1) by Th17 cells is induced by IL-6, and signalling through the IL-1R promotes the transcription factor IFN-regulatory factor 4 (IRF4), which reinforces the expression of RORγt. [35] Mechanistically, IL-1β induces phosphorylation of the mammalian target of rapamycin (mTOR) in Th17 cells and thereby enhances the metabolic fitness of rapidly dividing Th17 cells during inflammation. Indeed, rapamycin treatment or mTOR-deficiency completely abolishes IL-1β-induced Th17-cell proliferation.[36] These results suggest that IL-6 functions to direct differentiation of Th17 cells, whereas IL-1β functions to enhance expansion of Th17 cells in competition with other T-cell subsets in the context of a resource-limited tissue environment. In contrast to IL-1β and IL-6, the role of TGF-β in Th17-cell differentiation is more complex. Genetic approaches that used a dominant negative TGF-β receptor II, which inhibits the formation of a functional TGF-β signalling complex, and a T-cell-specific deletion of TGF-β confirmed that endogenous TGF-β induces Th17-cell development *in vivo*.[37–39] However, deletion of TGF-β also led to excessive production of IFNγ and IL-4, which inhibited Th17-cell development and expansion. Thus, TGF-β can either function as an obligate Th17-inducing factor or could indirectly suppress alternate cell fates. Notably, in the absence of TGF-β, IL-6 alone can promote Th17 development in T cells that lack transcription factors Tbet (T-box transcription factor) and STAT640 (signal transducer and activator of transcription), which suggest that TGF-β represses Th17 differentiation indirectly by repressing T-bet and transcription factor GATA-binding protein 3 (GATA-3). This complexity is further highlighted by human studies; three separate research groups show that TGF-β is required for *in vitro* Th17-cell development, whereas two other research groups found that a cocktail of IL-1β, IL-6 and IL-23 is sufficient to drive Th17 differentiation.[40–48] These discrepancies could be due to the source of the human T cells (e.g. peripheral blood vs. umbilical cord blood), which may influence their developmental status and hence, the requirement for TGF-β. However, under *in vivo* inflammatory conditions, the presence of TGF-β is probably necessary for optimal Th17-cell differentiation. Although the combination of TGF-β and IL-6 efficiently generates Th17 cells *in vitro*, the cells generated by this cocktail are only weakly pathogenic, and subsequent exposure to IL-23 is essential to drive pathogenicity.[23] A further study supported the notion that TGF-β is not always required for *in vitro* Th17 differentiation, as Th17 cells could be generated in response to IL-1β, IL-6 and IL-23 in a TGF-β-independent manner.[22]

IL-17 signal transduction

Cells that respond to IL-17 are mainly, though not exclusively, non-haematopoietic and the effects of IL-17 are most similar to other innate inflammatory effectors, especially those that belong to the IL-1 family of cytokines and TLR ligands.[49] In particular, IL-17 is a potent regulator of neutrophils, which is mediated by IL-17-induced downstream genes such as those that encode the granulocyte colony-stimulating factor (G-CSF) and CXC chemokines. The IL-17 receptor (IL-17R) has many unique and/or unexpected properties in terms of structure and signalling, and ultimately, a detailed understanding of these events may reveal potential novel drug targets or avenues for therapeutic intervention. Positive activation of signalling when IL-17R was cloned in 1995 was noteworthy for its striking lack of similarity to known receptor families.[50] Subsequently, it became clear that the IL-17R (now known as IL-17RA) was the founding member of a new subclass of cytokine receptors, which comprises five receptor subunits, IL-17RA–IL-17RE, that have homology to one another but not to other receptor families. All subunits of the IL-17R family exhibit a broad expression pattern; IL-17RA is most highly expressed in

hematopoietic cell types and IL-17RC in non-haematopoietic cells.[51] Most of the homology within the IL-17R family is located in the conserved cytoplasmic motif SEF/IL-17R (SEFIR), which suggests a common mode of signalling that is probably distinct from other cytokine receptors. A landmark bioinformatics study demonstrated that this domain was related to the Toll/IL-1R (TIR) domain. Recent studies have revealed that the IL-17RA subunit is shared among several members of this family. IL-17RA is essential for signalling through IL-17E (also known as IL-25) when partnered with IL-17RB, and also for signalling through IL-17C when partnered with IL-17RE.[52,53]

On their own, IL-17 and IL-17F are modest activators of signalling, but they function cooperatively with other pro-inflammatory molecules, particularly TNF-α but also IFNγ, IL-22, lymphotoxin, IL-1β and lipopolysaccharide.[54] The molecular basis for this synergy is not completely understood and probably involves multiple mechanisms. In synovial tissue, IL-17 up-regulates TNFRII expression and thereby enhances responsiveness to TNF-α signalling.[55] For some genes, co-operation between IL-17 and TNF-α occurs at the level of the promoter (for example IL⁻6 and Lcn2) and/or mRNA stability.[56] IL-17 also up-regulates expression of IκBζ, a positive regulator of the NF-κB family, which in turn promotes expression of at least some target genes.[57] The ability of IL-17 to signal cooperatively with other cytokines is probably an important aspect of its biology, since inflammatory environments contain multiple cytokines that can act in concert.

Effector cytokines of Th17 cells

Th17 cells in steady state naturally did not evolve to cause autoimmunity, but to provide effective host defence against pathogens. Experiments using IL-17- and IL-17R-knockout mouse models have demonstrated increased susceptibility to a wide variety of infectious organisms, including bacteria, parasites, fungi and viruses. However, examination of families or individuals with specific mutations in the Th17 pathway indicated a surprisingly limited role for Th17 cells and IL-17 in immunity to infections, with susceptibility to commensal fungi (mainly the commensal *Candida albicans*) by far the dominant disease seen in these settings. Although the reasons for the dichotomy between mice and humans are still unclear, this is similar to findings in MyD88-deficient humans, who show a relative restricted susceptibility to pyogenic bacteria, in contrast to the broadly susceptible MyD88-knockout mice.[58]

Th17 cells in disease states

While Th17 cells did not evolve to cause disease, they are programmed to provide formidable host protective responses – often associated with rapid recruitment and activation of granulocytes and macrophages capable of producing tissue damaging reactive oxygen species (ROS).[59] During prolonged and dysregulated exposure to IL-1 and IL-23, Th17 cells recruit inflammatory myeloid cells to cause severe local tissue injury.[60] Their developmental pathway over the recent years could be seen in Figure 2.

Type–1 diabetes

Type-1 diabetes mellitus (DM) is an autoimmune disease.[61,62] Pranzy et al. [63] suggested that DM can be associated with other autoimmune endocrine disorders and autoimmune impairment of non-endocrine tissue. The associated autoimmune disease may influence the control of diabetes by impairing function of the respective organ. It is now established that patients with type-1 diabetes are at increased risk of other autoimmune diseases as compared to general populations.[64] Singh and

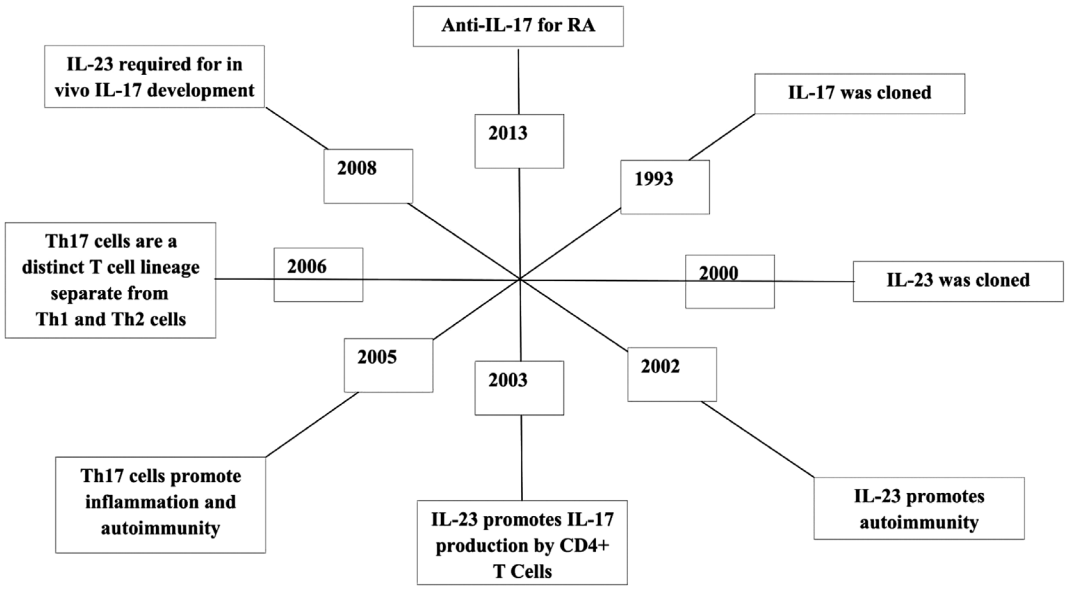

Figure 2. History or developmental evolution of IL-17 and IL-23.

Table 1. Status of various compounds of lead biotech companies in targeting RA and T1D.

Company	Agent	Target	Indications	Phase	Clinical trial ID
Eli Lilly	Ixekizumab (Ly2439821)	IL-17A	Rheumatoid arthritis	Phase 2	NCT00966875
Novartis	Secukinmab (AIN457)	IL-17A	Rheumatoid arthritis	Phase 3	NCT01009281
			Type-1 diabetes	Phase 2	
Abbott Abbvie	ABT-122	IL-17A/TNF-α	Rheumatoid arthritis	Phase 1	NCT01853033
Johnson & Johnson Jansen Biotech	Guselkumab CNTO 1959	IL-23p19	Rheumatoid arthritis	Phase 2	NCT01645280

colleagues [65] have discussed the role of cytokines in the pathogenesis of autoimmune diabetes (type-1 diabetes) in the non-obese diabetic (NOD) mouse model of the human disease. In the process, the authors have presented examples that validate several of the above mentioned attributes of different cytokines and the cells secreting them, e.g., the dual role of cytokines, the plasticity of T-cell subsets, the pathogenic role of IL-27, and the protective role of IL-35. Sadelain et al.,[66] describe the influence of cytokines on rendering the effector T cells refractory to suppression by Treg; the dual role of effector T cells; the balance between IL-2 and IL-21 (both Idd3 locus-linked cytokines) in disease susceptibility; and the role of IL-22 and regenerating (Reg2) genes in the regeneration and maintenance of pancreatic β-islet cells.

Interest in the pathogenicity of Th17 cells began after the demonstration that knocking out IL-23 and its receptor, but not IL-12, is protective in murine models of rheumatoid arthritis and multiple sclerosis.[67–69] Elevated Th17 profiles have been described in rheumatoid arthritis and multiple sclerosis, and there is mounting evidence Th17 cells are pathogenic in murine models of those diseases.[70,71] However, relatively few studies have investigated the Th17 subset in type-1 diabetes. In the NOD mouse model, there have been conflicting reports as to the role of Th17 cells. Neutralising IL-17A at 10 weeks of age, but not at 5 weeks, prevents diabetes onset in NOD mice, highlighting a temporal role in IL-17A action.[72] Similarly, induction of IFN-γ by antigen exposure upon hyperglycaemia, but not prior to insulitis, was necessary to prevent progression to diabetes and was dependent on IL-17A repression.[73] These studies support a role for a Th1 response inhibiting a Th17 response, thereby preventing diabetes. Yet, there are also reports associating Th17 profiles with a protective effect in NOD mice. Transfer of adjuvant-induced splenocytes producing IL-17A into NOD/SCID mice has a protective effect, which is abolished upon neutralising IL-17A.[74] IL-17 neutralisation prevent development of diabetes when given post-initiation of insulitis but not earlier, suggesting interference with the effector phase of the disease.[75]

Rheumatoid arthritis

The favourable clinical results obtained with inhibitors of TNF-α and IL-1 suggested that the story of the contribution of cytokines to arthritis is almost over. However, additional cytokines that may contribute to joint inflammation have been described later targeting IL-17 as a major proinflammatory cytokine secreted by activated T-lymphocytes that accumulates in the inflamed joints of rheumatoid arthritis (RA) patients.[76] In 2002, IL17, together with TNF-α, induced cartilage degradation in foetal mouse metatarsals *in vitro*. IL17 may, therefore, participate in the development of cartilage destruction associated with RA by enhancing the effects of TNF-α and may provide a potential therapeutic target.[77] Addition of exogenous IL-17 to RA synovium resulted in an increase in the production of IL-6, whereas the introduction of a blocking anti-IL-17 antibody reduced this effect. These first results indicate that IL-17 was present and could contribute to the active proinflammatory and destructive pattern that is characteristic of RA. Some of the effects of IL-17 on articular cartilage can be attenuated by this approach *in vivo*,[78], while blockade of IL-17 abrogates completely the spontaneous development of inflammatory arthritis in IL-1R antagonist-deficient mice,[79] and mice lacking IL-17 are highly resistant to CIA.[80] IL-23 is an essential promoter of end-stage joint autoimmune inflammation, and therefore, specific therapeutic blockade of IL-23 (rather than IL-12 neutralisation) may provide a preferred approach for the treatment of a range of inflammatory autoimmune diseases.[81]

Therapeutic benefits

Since the discovery of the IL-23-Th17 immune pathway a decade ago, immunologists and clinicians have worked diligently to bring this novel therapeutic strategy to the clinic, which is now showing encouraging results for psoriasis, Crohn's disease, rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis.[82,83] However, this treatment strategy is complex. It was initially assumed that IL-23 controls the production of pathogenic IL-17 and that these cytokines are 'duplicate' targets. Recent clinical results suggest that is not the case at all. We are now beginning to appreciate that anti-IL-23p19 vs. anti-IL-17 treatments each has its own beneficial effects as well as unique challenges in different disease settings (Table 1). For example, anti-IL-17 showed good therapeutic efficacy for the treatment of psoriasis—even

surpassing anti-TNF therapy,[84,85] but failed in Crohn's disease. The search for better clinical efficacy biomarkers is critically needed to improve patient stratification and disease indication selection. In addition, better understanding of Th17 biology and cellular mechanisms with Treg-cell therapies for autoimmune disorders [86,87] would allow discovery of additional targets for inflammatory diseases.

To conclude, progress in deciphering IL-17R-mediated signal transduction cascades has advanced considerably in recent years. Data indicate that, although these signalling pathways in many respects overlap with IL-1R and TLR-mediated pathways, there are also distinct processes that seem to be IL-17 specific. Understanding these events may reveal novel treatment strategies. Similarly, new insights into the epigenetics and transcriptional control of Th17 cells have revealed new treatment paradigms. A novel approach could be through destabilising the Th17 lineage to induce reprogramming or functional suppression that could have immense therapeutic potential. Indeed, suppression of JAK (Janus kinase) and TYK2-dependent STAT3 activation as well as direct inhibition of RORγt, using small molecule pharmacologic agents, have demonstrated impressive efficacy in preclinical disease models. It is only a matter of time before these new therapeutic approaches will begin to make a difference in the clinic. The discovery IL-23/IL-17 immune axis has thus brought about major changes in cellular immunology and more importantly improved the quality of life for many patients. Furthermore, with the common IL-17/IL-23 axis, a possible relationship between these two (RA & T1D) autoimmune disorders cannot be ruled out, but needs to be confirmed by more convincing pre-clinical and clinical studies.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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