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REVIEW

Targeting Th17 Effector Cytokines for the Treatment of Autoimmune Diseases

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Abstract Interleukin (IL)-17-producing T cells, especially T helper (Th)17 cells, play a critical role in the pathogenesis of a variety of autoimmune inflammatory diseases. The pathogenic function of Th17 cells results from their production of Th17 effector cytokines, namely IL-17 (or IL-17A), IL-17F, IL-22 and IL-26. The importance of IL-17 has been demonstrated by antibody neutralization studies in both animal models of autoimmune diseases as well as in human clinical trials. This review highlights the current knowledge of the clinical aspects of the Th17 cytokines as well as therapeutic antibodies against IL-17, IL-17F, IL-17 receptor, IL-22, IL-26 and granulocyte macrophage colony-stimulating factor for the future treatment of autoimmune inflammatory diseases.

Keywords Th17 · IL-17 · IL-22 · IL-26 · Autoimmune disease

Introduction

Upon antigen stimulation by MHC class II on antigen-presenting cells and with the appropriate cytokine milieu, naïve $CD4^+$ T helper (Th) cells are differentiated into subsets, including Th1, Th2, and Th17 cells. Th1 cells typically produce interferon (IFN)-γ, Th2 cells produce interleukin (IL)-4 and IL-13, and Th17 cells produce IL-17A/F, IL-22, IL-26, IL-21 and granulocyte macrophage colony-stimulating factor (GM-CSF). Th17 cells were identified by and named for their production of IL-17 (now formally named IL-17A). IL-17-producing Th17 cells were first found to be much more pathogenic than IFN-γ-producing Th1 cells in an adoptive transfer model of experimental autoimmune encephalitis (EAE), an animal model of human multiple sclerosis (Langrish et al. 2005).

Th17 cell differentiation from naïve $CD4^+$ T cells is induced by T cell receptor activation and costimulation with the inflammatory cytokines IL-6, transforming growth factor β, IL-21, IL-1β and IL-23 (Bettelli et al. 2006; Veldhoen et al. 2006). The differentiation of Th17 cells requires the retinoic acid receptor-related orphan nuclear receptor RORγt (Ivanov et al. 2006), which is induced in activated naïve T cells upon stimulation with the STAT3-activating cytokines IL-6 and IL-1β (Acosta-Rodriguez et al. 2007). In addition to Th17 cells, RORγt expression has been described in $CD8^+$ Tc17 cells and subsets of γδ T cells characterized by IL-17 expression. T cells lacking RORγt (*Rorc*$^{-/-}$) or STAT3 fail to generate Th17 cells (Ivanov et al. 2006). Several other transcription factors also contribute to the regulation of Th17 cell development. For example, BATF and IRF4 cooperatively contribute to the initial chromatin accessibility, and in combination with STAT3 initiate a transcriptional program that is tuned by RORγt (Ciofani et al. 2012). RORγt has been demonstrated to be the master transcription factor of Th17 cells. RORγt small molecular inhibitors have been generated for the treatment of several autoimmune diseases (Skepner et al. 2014, 2015; Yang et al. 2013).

Th17 cytokines are important not only for protective immunity against extracellular pathogens including *Klebsiella pneumonia* and *Pneumocystis carinii* (Happel et al. 2005; Rudner et al. 2007; Ye et al. 2001a), but also for the clearance of intracellular pathogens such as *Mycobacteria tuberculosis* (Khader et al. 2007). IL-17R-deficient mice have been used to demonstrate that IL-17A is involved in

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the host defense to *Candida albicans* and *K. pneumonia* fungal infections (Huang et al. 2004; Ye et al. 2001b).

In addition to the important role in protective immunity, Th17 cells and Th17 effector cytokines play a critical role in the pathogenesis of a variety of autoimmune inflammatory diseases. In this article, we review the role of Th17 effector cytokines in the pathogenesis of autoimmunity and the current progress and strategies of targeting the Th17 effector cytokines IL-17A, IL-17F, IL-22 and IL-26.

Interleukin 17

IL-17 Cytokine Family and IL-17 Receptors

IL-17 was first cloned two decades ago as CTLA-8 from T cells by Rouvier et al. (1993). Later, Yao et al. (1995a) discovered that CTLA-8 acts as a novel cytokine and binds to a novel cytokine receptor. CTLA-8 was then named IL-17. IL-17 is believed to be a proinflammatory cytokine since it stimulates epithelial, endothelial, and fibroblastic cells to express the proinflammatory molecules IL-6, IL-8, granulocyte colony-stimulating factor, prostaglandin E2 and intracellular adhesion molecules-1 (Fossiez et al. 1996; Yao et al. 1995b). IL-17 was re-named IL-17A since there are at least six IL-17 family members: IL-17A, IL-17B (also known as IL-20), IL-17C, IL-17E (also known as IL-25) and IL-17F. These cytokines bind to different receptors IL-17RA, IL-17RB, IL-17RC, and IL-17RE. IL-17A is most similar to IL-17F, sharing 60 % amino acid identity. In addition, the signaling of both IL-17A and IL-17F requires both IL-17RA and IL-17RC (Gaffen 2009; Miossec and Kolls 2012). The importance of IL-17 was significantly emphasized after the discovery of IL-17-producing Th17 cells (Langrish et al. 2005).

Source of IL-17

IL-17A and IL-17F are mainly expressed in T cells whereas IL-17B, IL-17C, and IL-17E are more broadly expressed in other cell types. In cells involved in the adaptive immune response, $CD4^+$ Th17 cells produce both IL-17A and IL-17F (Korn et al. 2009; Langrish et al. 2005; Leppkes et al. 2009; Seiderer et al. 2008). In addition to Th17 cells, some subset of $CD8^+$ T cells express Th17 cytokines such as IL-17A, IL-17F and IL-22 (Kondo et al. 2009; Res et al. 2010; Skepner et al. 2014), and these cells are defined as Tc17 cells. In the cells of innate immunity, γδ T cells produce IL-17 upon stimulation with IL-1β and IL-23 (Sutton et al. 2009). IL-17-producing γδ T cells share characteristic features with Th17 cells, such as expression of chemokine receptor 6 (CCR6), RORγt, and IL-23 receptor (Martin et al. 2009). Lymphoid tissue-inducer (LTi) cells also express RORγt and produce IL-17A and IL-22 upon stimulation with IL-23, yeast cell wall product zymosan, or Toll-like receptor (TLR)2 (Crellin et al. 2010; Cupedo et al. 2009; Takatori et al. 2009), indicating LTi cells play important roles in host defense and inflammation. Further, IL-17 can be produced by invariant NKT cells upon synthetic [α-galactosylceramide (α-GalCer) or PBS-57] as well as natural (lipopolysaccharides or glycolipids derived from *Sphingomonas wittichii* and *Borrelia burgdorferi*) ligand stimulation (Michel et al. 2007). In the absence of IL-10R signaling, macrophages express high level of IL-17 and IL-22 (Gu et al. 2008). Synovial mast cells in rheumatoid arthritis have been reported to release IL-17 (Suurmond et al. 2011). For further reading regarding innate IL-17-producing cells, see the review by Daniel Cua (Cua and Tato 2010).

IL-17 and Autoimmune Diseases

Th17 cells and IL-17A are critical for the development of EAE (Ivanov et al. 2006). Microarray analysis of multiple sclerosis lesions obtained at autopsy revealed an increase in IL-6 and IL-17 transcripts (Lock et al. 2002). In mice, an anti-IL-17A auto-vaccine prevented the development of EAE (Uyttenhove and Van 2006). In rheumatoid arthritis (RA), numerous reports have demonstrated a correlation between disease activity, IL-17 cytokine level and the number of Th17 cells. IL-17 is increased in RA sera and synovial fluid, and is present in the T cell-rich areas of the synovium (Lubberts 2015). Increased levels of IL-17 and tumor necrosis factor (TNF)-α mRNA expression in synovium from early stage RA are predictive of more severe joint damage progression (Sarkar and Fox 2010). Overexpression of IL-17 in the knee joint of collagen type II immunized mice promotes collagen-induced arthritis and aggravates joint destruction (Lubberts et al. 2002). IL-17 receptor deficiency results in impaired synovial expression of IL-1β and matrix metalloproteinases 3, 9, and 13, and prevents cartilage destruction during arthritis (Koenders et al. 2005). Th17 cells and Th17 cytokines are also important for the pathogenesis of several other inflammatory diseases including psoriasis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, systemic lupus erythematosus, asthma and chronic obstructive pulmonary disease (for review, see reference Miossec and Kolls 2012 and Robinson et al. 2013). Thus, blocking IL-17/IL-17R pathway is believed to be effective ways for the treatment of autoimmune inflammatory diseases.

Blocking IL-17/IL-17R Pathway

There are several ways to block the IL-17 pathway. Neutralizing IL-17 is an obvious choice since IL-17 is a

dominant Th17 cytokine. Indeed, Secukinumab (AIN457), Ixekizumab (LY2439821), SCH-900117, and RG4934 have been developed as neutralizing monoclonal antibodies against IL-17. Since IL-17A and IL-17F can form IL-17A/IL-17F heterodimers, RG7624 was developed to interact with both IL-17A and IL-17F, and theoretically might also target IL-17A and IL-17F homodimers as well as IL-17A/IL-17F heterodimers. Targeting IL-17 receptor is another way to block the IL-17/IL-17R interaction. Brodalumab (AMG827) binds to IL-17RA, a subunit of functional IL-17R together with IL-17RC, and inhibits IL-17 binding to the functional receptor complex. Figure 1 illustrates different approaches of targeting Th17 effector cytokines.

Targeting the IL-17/IL-17R pathway with these antibodies in different autoimmune diseases has allowed for the assessment of the pathogenic role of this cytokine pathway in each disease. In psoriasis, a Phase II study with a single injection of Secukinumab reduced the surface area covered by skin lesions as well as the number of IL-17A-positive cells in skin biopsy samples (Hueber et al. 2010). Another Phase II psoriasis study with multiple injections of Ixekizumab showed significant effect as early as 1 week and the effect was sustained through 20 weeks (Leonardi et al. 2012). Targeting IL-17RA with Brodalumab also showed significant improvement in plaque psoriasis at 12 weeks (Papp et al. 2012). Phase III studies have been completed for Secukinumab (Langley et al. 2014), Ixekizumab (ClinicalTrials.gov Identifier: NCT01597245) and Brodalumab (ClinicalTrials.gov Identifier: NCT00975637) with the results still pending release. The consistent results from Phase II trials indicate that the IL-17/IL-17R pathway has clear pathological role in psoriasis (Mease 2015). In ankylosing spondylitis, a Phase II trial with Secukinumab rapidly reduced clinical and biological signs of moderate-to-severe ankylosing spondylitis, and demonstrated significant improvement in ASAS20 at 6 weeks (Baeten et al. 2013).

In an animal model of RA, treatment with a neutralizing anti-murine IL-17 antibody after the onset of collagen-induced arthritis reduced joint inflammation, cartilage destruction, and bone erosion (Lubberts et al. 2004). In a proof-of-concept study with RA patients, Secukinumab injection significantly reduced inflammation in the joints, and demonstrated improvements in ACR20, DAS28 and CRP scores (Hueber et al. 2010). These effects were seen rapidly after the first infusion, and the improvements sustained for up to 13 weeks after the second infusion, indicating that neutralizing IL-17A has the potential to rapidly suppress inflammation as well as provide sustained effect. A Phase I study with Ixekizumab in combination with oral disease-modifying antirheumatic drugs improved the signs, symptoms and DAS28 scores of RA, with no strong adverse safety signal. Percentages of ACR20, ACR50, and ACR70 responses as well as improvements in

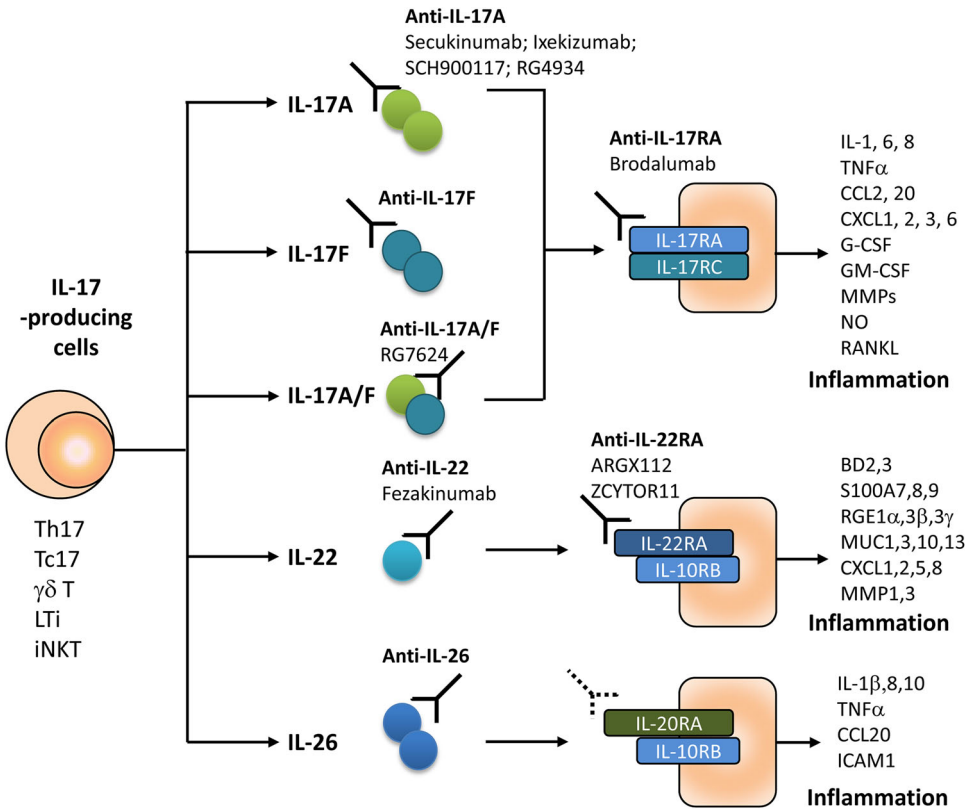

Fig. 1 Antibodies targeting major Th17 signature cytokines and their related receptors. The antibodies against these molecules block the binding of the cytokines to their receptors and inhibit the downstream signalings and proinflammatory gene expression responses. The antibodies with names are being developed or in the clinic. The antibodies without names are potential targets for specific inhibitions. Antibodies against IL-20RA could block IL-26 binding to the receptor, but may also block other cytokines using this receptor such as IL-19, IL-20 and IL-24

the ACR core set of measures were greater in Ixekizumab-treated patients than in placebo-treated patients at multiple time points (Genovese et al. 2010). Exploratory efficacy analyses in Phase IB with Brodalumab using ACR20 and DAS28 scores did not reveal significant clinical responses with moderate-to-severe RA patients (Martin et al. 2013). Further, the Phase II study with Secukinumab on RA patients with inadequate response to methotrexate did not achieve significant ACR20 response at 16 weeks (Genovese et al. 2013). Thus, the role of IL-17-IL17R pathway in RA warrants further studies (Lubberts 2015).

In inflammatory bowel disease (IBD), clinical trials of Brodalumab and Secukinumab for Crohn's disease failed to improve disease symptoms, and even increased disease activity likely because IL-17 is involved in maintaining intestinal epithelial barrier function (Hueber et al. 2012; Symons et al. 2012). Thus, most anti-IL-17 monoclonal antibody trials now exclude IBD.

Taken together, preclinical and clinical evidence demonstrate a strong pathogenic role for the IL-17A/IL-17R pathway in psoriasis and ankylosing spondylitis, modest to equivocal role for RA, and a protective role in IBD. The role of the IL-17A/IL-17R pathway in other autoimmune/inflammatory diseases remains to be further investigated (Li et al. 2015).

Interleukin 22

IL-22 and IL-22 Receptors

IL-22 belongs to the IL-10 cytokine family and is mainly produced by T cells and innate lymphoid cells (ILCs) in humans. Th17 cells are believed to be the major source of T cell derived IL-22 (Liang et al. 2006; Zheng et al. 2007). Further studies characterized IL-22-producing cells as a new subset of Th cells name as Th22 cells (Duhen et al. 2009; Eyerich et al. 2009; Trifari et al. 2009). A subset of Th1 cells has also been shown to express IL-22 (Wolk et al. 2002). In addition, $CD8^+$ T cells, γδ T cells and NKT cells have also been reported to express IL-22 (Witte et al. 2010).

IL-22 signals via a transmembrane receptor complex composed of two subunits: IL-22RA and IL-10RB (Kotenko et al. 2001; Xie et al. 2000). The IL-22RA subunit is not only utilized for IL-22 signaling, but is also used as a receptor subunit for two other members of the IL-10 cytokine family: IL-20 and IL-24. Unlike other cytokines secreted by Th17 cells, IL-22 (and IL-26) mainly targets non-hematopoietic cells. IL-22 exerts its effects mainly on epithelial cells that confer barrier function, such as skin, lung and intestine (Sonnenberg et al. 2011).

Physiological Role of IL-22

IL-22 binding to the IL-22 receptor complex induces the phosphorylation of STAT3. In addition to STAT3, weak activation of STAT1 and STAT5 has also been observed after IL-22 stimulation of cells expressing the IL-22 receptors (Lejeune et al. 2002; Wolk et al. 2004). Further, phosphorylation of MEK1/2, ERK1/2, p90RSK, JNK, and p38 kinase can be induced by IL-22 stimulation (Lejeune et al. 2002). IL-22 induces the expression of anti-microbial proteins of the β-defensin family (BD2, BD3), S100A family (S100A7, S100A8, S100A9), and regenerating islet-derived protein (REG) family (REG3β, REG3γ and REG1α) in keratinocytes, and epithelial cells from bronchia and intestine (Wolk et al. 2006; Zheng et al. 2008). In tracheal and colonic epithelial cells, IL-22 induces the expression of mucus-associated proteins, including mucin 1 (MUC1), MUC3, MUC10 and MUC13 (Aujla et al. 2008; Sugimoto et al. 2008). Further, IL-22 induces the expression of specific chemokines in epithelial cells, particularly chemokines with neutrophil-attracting properties including CXC-chemokine ligand 1 (CXCL1), CXCL2, CXCL5 and CXCL8 (Wolk et al. 2009). In addition, IL-22 may facilitate the epithelial repair process by increasing the expression of the extracellular matrix-degrading enzymes matrix metalloproteinase 1 (MMP1) and MMP3 (Boniface et al. 2005; Wolk et al. 2006), inhibiting the terminal differentiation of keratinocytes, and enhancing the proliferation of epithelial cells from the respiratory tract and the gut (Kumar et al. 2013).

IL-22 in Autoimmune Inflammatory Diseases

In psoriasis, IL-22 is increased in the blood of patients and its level strongly correlates with the disease severity (Wolk et al. 2006). IL-22 is highly expressed in psoriatic lesional skin but not in non-lesional skin or in the skin of healthy individuals (Wolk et al. 2004). The skin alterations observed in psoriasis are caused by inflammation-induced hyper-proliferation (i.e., acanthosis) and impaired differentiation of keratinocytes, consistent with observations of the biological activity of IL-22 in vitro. This alteration is attributed to the excess activity of IL-22 to regenerate the breached barrier (Wolk et al. 2004). Induction of neutrophil recruitment to the lesion contributes to the further destruction of tissue structure (Wolk et al. 2009). IL-22-deficient mice have shown reduced acanthosis and skin infiltration of granulocytes induced by intradermal injection of IL-23 (Zheng et al. 2007).

In RA patients, high levels of plasma IL-22 and increased numbers of IL-22-expressing T cells have been observed (Leipe et al. 2011). The increased plasma IL-22

level positively correlates with disease severity and disease progression (Da Rocha et al. 2012; Zhang et al. 2011). Furthermore, IL-22 mRNA is expressed in synovial tissues and mononuclear cells in the synovial fluid of RA patients (Ikeuchi et al. 2005). However, the pathogenic contribution of IL-22 in experimental models of arthritis is not well established (Sarkar et al. 2013).

In IBD, the plasma level of IL-22 and the number of IL-22-producing $CD4^+$ T cells in the blood were found to be elevated in Crohn's disease and were correlated with disease severity (Wolk et al. 2007). The number of IL-22-producing $CD4^+$ T cells in the blood was also correlated with the extent of mucosal inflammation (Dige et al. 2013). Thus, IL-22 expression correlates with Crohn's disease. However, studies in mice have demonstrated mixed effects of IL-22 in the pathogenesis of colitis. In a Th2 cell-mediated ulcerative colitis-like model, the increased expression of IL-22 conferred a protective effect (Sugimoto et al. 2008). A similar effect was observed in a mouse model of colitis induced by the transfer of naive $CD4^+$ T cells into mice deficient in RAG expression. Transfer of IL-22-deficient naive $CD4^+$ T cells into $IL22^{-/-}Rag1^{-/-}$ mice exacerbated the colitis, suggesting protective role of IL-22 secreted from T cells (Zenewicz et al. 2008). However, in a similar model, transfer of IL-22-deficient memory $CD4^+$ T cells into $Rag1^{-/-}$ mice resulted in amelioration of the phenotype, suggesting a pathogenic role for IL-22 (Kamanaka et al. 2011). Accordingly, the precise role of IL-22 in colitis may be context-dependent.

Targeting IL-22/IL-22R Pathway

Blocking IL-22/IL-22R appears to be a legitimate path (Fig. 1) for the treatment of psoriasis. In the imiquimod (TLR7 and TLR8 agonist)-induced skin inflammation model, the tissue alteration was significantly reduced in both IL-22-deficient mice and mice treated with neutralizing IL-22 antibodies (Van Belle et al. 2012). Clinical trials have been conducted with an anti-human IL-22 antibody [ILV-094 (fezakinumab), Pfizer] on healthy subjects, followed by a small number of psoriasis subjects. Unfortunately, the study was discontinued in 2011 for not being able to meet the primary end points (ILV-095) (ClinicalTrials.gov Identifier: NCT01010542). The anti-IL-22 antibody ILV-094 is currently being tested in atopic dermatitis patients (ClinicalTrials.gov Identifier: NCT01941537). There was also an effort to target IL-22R by developing an anti-IL-22R antibody (ZCYTOR11) for the treatment of psoriasis, but the development has ceased. Another attempt to block IL-22R signaling was ARGX112, an antibody that neutralizes both IL-20 and IL-22 mediated signaling through blockade of their common receptor, IL-22RA. This antibody has proven to be highly effective in preclinical models of chronic skin inflammation (http://www.argen-x.com/argx-112/). Thus, the effect of inhibiting the IL-22/IL-22R pathway in psoriasis remains to be determined.

A clinical trial has been conducted with the anti-human IL-22 antibody ILV-094 (fezakinumab) in RA patients on a stable background of methotrexate. The study was completed in 2011 but the results have not been published (ClinicalTrials.gov Identifier: NCT00883896). The contribution of IL-22 in the pathogenesis of RA remains to be explored. Furthermore, IL-22 was recently suggested to be involved in pathogenesis of enthesitis based on data from a mouse model (Sherlock et al. 2012). Therefore, targeting IL-22/IL-22R pathway might be efficacious for the treatment of enthesitis, with a safety profile already obtained from the competed clinical studies.

Interleukin 26

IL-26 and IL-26 Receptors

IL-26 belongs to IL-10 family of proteins which includes IL-10, IL-19, IL-20, IL-24, IL-22, IL-26, IL-28 and IL-29. IL-26 is mainly expressed by RORγt-positive/IL-17-producing Th17 and γδ T cells. IL-26 is often co-expressed with IL-22 in activated T cells, especially Th17 cells (Donnelly et al. 2010; Ouyang et al. 2011; Pene et al. 2008; Wilson et al. 2007). It is also expressed in a cell population called NK-22 cells, which seem to play a role in human mucosal immunity (Cella et al. 2009). A recent study revealed that ILC3 cells from human tonsil expressed high level of *Il26* mRNA (Montaldo et al. 2014). In addition, synoviocytes from RA patients were reported to express IL-26 (Corvaisier et al. 2012).

The *Il26* and *Il22* genes are closely located in tandem orientation on chromosome 12q15, and therefore may explain their overlapping expression pattern in Th17 cells (Donnelly et al. 2010). Both IL-26 and IL-22 share the IL-10RB receptor subunit and induce STAT3 and STAT1 phosphorylation upon receptor binding (Hor et al. 2004; Sheikh et al. 2004) (Fig. 2). IL-26 and IL-22 also share common biological responses in vitro, including activation of phospho-STAT3 and induction of proinflammatory cytokines (Ouyang et al. 2011). The precise difference in their physiological role is poorly characterized largely because of the lack of IL-26 in rodent species (Braum et al. 2012; Shakhsi-Niaei et al. 2013). However, there are a variety of differences between IL-26 and IL-22. Molecularly, the two cytokines share very low amino acid homology (<20 %). IL-26 has a strong cationic nature ($pI = 10.7$) that may allow it to stick to the negatively charged surface of cells and may allow it to function as a

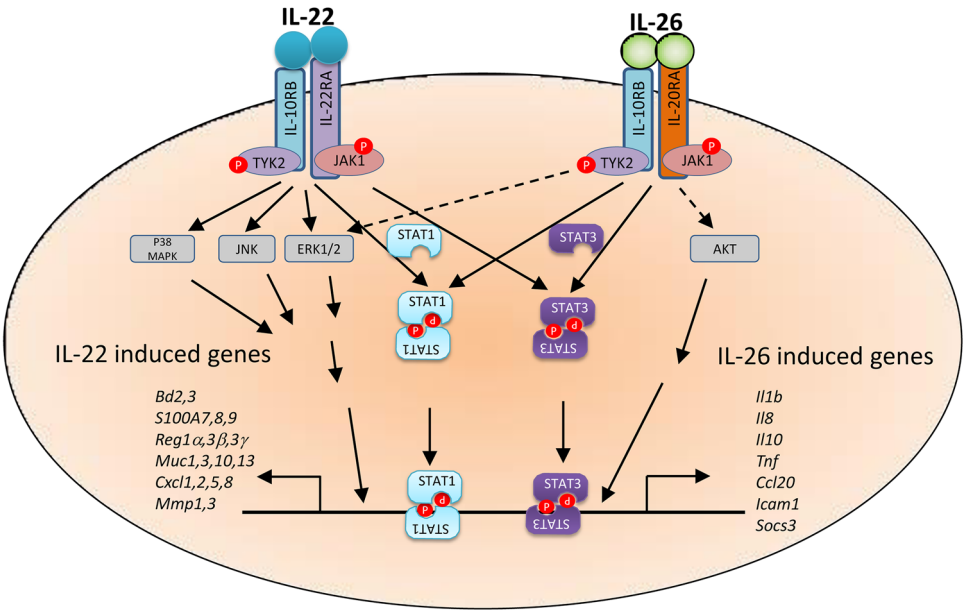

Fig. 2 IL-22 and IL-26 signaling pathways. The two cytokines share the same receptor subunit IL-10RB, but differ in their alpha receptor subunits. Both IL-22 and IL-26 induce the phosphorylations STAT1 and STAT3, but they may trigger other different signaling pathways which result in the induction of different sets of genes

long-acting cytokine (Donnelly et al. 2010; Knappe et al. 2000), whereas IL-22 is neutral (pI = 7.2) and could be short lived. IL-26 is predicted to form a dimer structure, while IL-22 acts as a monomer. The receptors of the two cytokines are IL-10RB/IL-20RA for IL-26 and IL-10RB/IL-22RA for IL-22, indicating they share IL-10RB subunit. Both IL-20RA and IL-22RA are expressed on epithelial cells; however, IL-20RA is expressed on skin, lung, and colon, while IL-22RA is highly expressed on liver, kidney, and pancreas. IL-20RA also serves as a receptor subunit for IL-19, IL-20 and IL-24 as well, and there may be interplay between IL-26 and other IL-20RA-binding cytokines. IL-22 can be bound by IL-22 binding proteins, which adds another layer of regulation, while there has been no such proteins identified for IL-26 (Dumoutier et al. 2001). The expression kinetics may also differ between the two cytokines. A recent study in a model of cow mammary gland inflammation suggested a difference in the in vivo kinetics between IL-26 and other Th17 cytokines including IL-22 (Rainard et al. 2013). Thus, it is likely that IL-26 and IL-22 have different roles in both the normal state and in the context of disease.

Blocking IL-26 Pathway for Autoimmune Inflammatory Diseases

IL-26 induces the production of the proinflammatory cytokines such as IL-1β, IL-6, and TNF-α in human monocytes, and also upregulates the expression of the chemokine CCL20 (Corvaisier et al. 2012). It has been shown to induce the expression of IL-8 and TNF-α in a colon epithelial cell line as well (Dambacher et al. 2009). IL-26 expressed by the synovial fibroblasts in the joints of RA patients acts on monocytes to produce IL-1β, which in turn enhances the generation of Th17 cells (Corvaisier et al. 2012). Thus, IL-26 may play a pathogenic role in autoimmune diseases (Figs. 1, 2). Indeed, in ulcerative colitis the single nucleotide polymorphism rs2870946 located in the *Il26* gene showed significant association with the disease (Silverberg et al. 2009), and elevated expression of *Il26* mRNA was observed in the colon in a study of pediatric-onset ulcerative colitis (Kugathasan et al. 2008). In Crohn's disease patients, the number of infiltrating IL-26 positive Th17 cells was increased in the colon; IL-26 mRNA expression was up-regulated, and the expression of IL-26 correlated with the expression of proinflammatory cytokines including IL-8 (Dambacher et al. 2009). Hence, IL-26 may play a pathogenic role in IBD by directly affecting the epithelial cell biology, recruiting neutrophils, and producing proinflammatory cytokines. In RA, a polymorphic marker located 3 kb downstream of the *Il26* gene was significantly associated with RA in women (Vandenbroeck et al. 2003). The synovium from RA patients showed high staining of IL-26 protein in immunohistochemistry, and synovial fibroblasts from RA patients expressed a high level of IL-26 (Corvaisier et al. 2012). In multiple sclerosis, the genetic region of *Il26* and *Ifng* is correlated with susceptibility to the disease in females but not in males (Goris et al. 2002). In Psoriasis, a transcriptional analysis of lesion and non-lesion skin demonstrated that Th17-derived cytokines, including IL-26, were more highly expressed in lesions than in normal skin (Wilson et al. 2007). In summary, these data support that overexpressed IL-26 protein could act as proinflammatory

cytokine and contribute to the development of several autoimmune diseases. Though currently there is no published clinical trial modulating IL-26 activity, accumulating evidence suggests that IL-26 is an interesting drug target to pursue (Fig. 1).

GM-CSF

Beside the cytokines discussed above, there is growing interest in the pathogenic effects of GM-CSF-producing Th17 cells in the development of autoimmune and inflammatory diseases (Shiomi and Usui 2015). Recent studies reported that GM-CSF is critical for the pathogenicity of Th17 cells (Codarri et al. 2011; El-Behi et al. 2011). This has led to the development of anti-GM-CSF and anti-GM-CSF receptor neutralizing antibodies (Burmester et al. 2013; Dale et al. 2014). The results from the future clinical trials of these therapeutics warrant attention.

Conclusion

Th17 cells produce multiple cytokines, and thus exert pleiotropic effects on host protection while playing a pathogenic role in disease pathology. Outcomes from clinical trials targeting individual Th17 cytokines will reveal the differential roles of the cytokines in the context of autoimmune diseases. Thus, targeting the right Th17 cytokines in the right disease contexts should enable effective modulation of the diseases while minimizing adverse effects on host protection.

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