Minireview

IL-12 and IL-23/Th17 axis in systemic lupus erythematosus

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Impact statement

Our article is focused on emerging pathogenetic pathways in systemic lupus erythematosus (SLE). Notably, IL-12 and IL-23 have been described as emerging cytokines in SLE pathogenesis. We know that IL-23 stimulates Th17 cells to produce IL-17. We try to point out the importance of IL-23/Th17 axis in SLE and to focus on the interaction between this axis and IL-12. Ustekinumab, a fully human IgG1κ monoclonal antibody directed towards the p40 shared subunit of IL-12 and IL-23, has been recently investigated in SLE, suggesting a potential novel therapeutic strategy in SLE. To our knowledge, there are no reviews which simultaneously focus on IL-12 an IL-23/Th17 axis in SLE. Thus, we believe our work will be of interest to the readers.

Abstract

Systemic lupus erythematosus (SLE) is a very complex disease where multiple immunological pathways can concur in inducing tissue damage. Cytokines are key mediators in this process and among them the role of interleukin (IL)-12 and the IL-23/Th17 axis has recently emerged. IL-12 and IL-23 have a heterodimeric structure with a common subunit, named p40. Although they share a partially common structure, their functions appear slightly different. Indeed, IL-12 is a key cytokine in inducing an efficient T helper 1 (Th1) response and in Th differentiation, while IL-23 plays a crucial role in chronic inflammation and Th17 cell activation, which results in IL-17 secretion. The increasing knowledge on the interaction between IL-12 and IL-23/Th17 axis in the development of autoimmune diseases has led to the identification of new therapeutic strategies targeting these immunological pathways. IL-23/Th17 axis has recently been suggested to be essential in developing lupus nephritis, both in mice and in humans. In keeping with these observations, ustekinumab, a fully human IgG1κ monoclonal antibody (mAb) directed towards p40 subunit, has been investigated in SLE. Promising data from a phase II randomized controlled trial in SLE patients suggest that this mAb might be a potential novel therapeutic strategy in SLE. In this review, we summarize the complex interaction between IL-12 and IL-23/Th17 axis in SLE with a special focus on drugs which affect this immune pathway.

Keywords: SLE, immune response, Th1 response, IL-23/Th17 axis, IL-12, ustekinumab

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Introduction

Systemic lupus erythematosus (SLE) is a rheumatic autoimmune disease characterized by a loss of self-tolerance leading to the development of autoantibodies (auto-Abs) directed towards ubiquitous nuclear self-antigens, which in turn can induce immune complex (IC) formation, and eventually organ damage.[1] The production of auto-Abs is enhanced by several mechanisms, including abnormal clearance of apoptotic material.[1,2]

Studies on animal models have recently provided novel insights into the mechanisms leading to SLE occurrence (Table 1). It has been shown that the interleukin (IL)-17/interferon (IFN) type 1 interplay is crucial in the recruitment of immune cells into the kidney and in the formation of the inflammatory infiltrate in lupus nephritis (LN): indeed, lupus-prone IL-17A receptor (IL-17RA) deficient mice develop an IFN type I-dependent LN milder than control mice.[3,4]

The interaction between IL-12 and IL-23/T helper 17 (Th17) axis has recently been shown to be involved in SLE progression, which could pave the way for new therapeutic targeted strategies in SLE.

To our knowledge, no reviews simultaneously focusing on the interaction between Il-12, IL-23, and IL-17, as well as

Table 1. Summary of murine studies using genetically modified mice by targeting IL-12, IL-23, and IL-17.

Mouse strain	IL-12 p35–/–	IL-12 p40–/–	IL-23 p 19 –/–	IL-23R deficient	Anti-IL-17	IL-17–/–	IL-17R A–/–	IL-17R E–/–
C57BL/6 mice	Highly susceptible to the induction of EAE;[5] Highly susceptible to CIA[6] Enhanced EAU is associated with increased systemic and local IL-17 responses[7] Develop less severe cGN than wild-type animals[8]	Administration of IL23 to p40$^{-/-}$ mice infected with T. gondii result in a decreased parasite burden and enhanced resistance[9] Mice are resistant to CIA induction[6]	High resistance to CIA induction[6] More severe cGN than wild-type animals on day 21[8]	NA	NA	Protected from renal injury;[8] when cGN is established, disease is enhanced in IL-17A(–/–) mice[8] IL-17F–deficient nephritic mice have fewer renal infiltrating neutrophils than wild-type nephritic mice; neutrophil depletion does not affect the course of GN in IL-17F–deficient mice[10] In experimental GN IL-17C deficiency significantly ameliorates the course of GN[11]	NA	Deficiency of the unique IL-17C receptor IL-17 receptor E (IL-17RE) provides protection against cGN[11]
BALB/c mice	NA	Rapidly succumb to toxoplasmosis[9]	NA	NA	NA	NA	NA	NA
B6/lpr mice	NA	NA	NA	Reduced numbers of CD3+CD4−CD8− cells and IL-17A–producing cells in the lymph nodes; less anti-DNA Abs production[12]	NA	NA	Reduced renal inflammation[3]; protected from IFN-I-dependent cGN[3]	NA
B10.RIII mice	NA	NA	NA	NA	Anti-IL-17 prevents and reverses EAU[7]	NA	NA	NA
Fcgr2b-deficient mice	NA	NA	NA	NA	NA	Largely protected from GN[13]	NA	NA

IL-12: interleukin-12; IL-23: interleukin 23; IL-17: interleukin 17; IL-23R: IL-23 receptor; IL-17RA: IL-17 receptor A; EAE: experimental autoimmune encephalomyelitis; CIA: collagen-induced arthritis; EAU: experimental autoimmune uveitis; cGN: crescentic glomerulonephritis; anti-DNA Abs: anti-double strand DNA antibodies; IFN-I: type 1 interferon; GN: glomerulonephritis; NA: not available.

on their role in SLE, have been published to date. Hence, by considering the pathogenetic role of these cytokines in SLE, we believe this review could pioneer some novel potential therapeutic strategies in SLE.

IL-12

IL-12: Overall characteristics and structure

Firstly identified as a product of Epstein-Barr virus (EBV)-transformed human B-cell lines,[14] IL-12 is composed by an heterodimeric structure of 70 kDa, which includes two covalently linked subunits, namely p40 (IL-12B) and p35 (IL-12A).[15] The expression of the p35 and p40 genes is independently regulated.[15] Indeed, p35 subunit is tightly regulated and requires the expression of p40 for the secretion of the biologically active cytokines.[16] By contrast, the expression of p40 subunit is higher than that required for p35p40 assembly.[17]

IL-12 is released by innate immune cells upon microbial stimulation (discussed below) subsequently binding to IL-12R. The structure of IL-12R includes two different chains, i.e. IL-12β1R and IL-12β2R.[15] The interaction between IL-12 and IL-12R stimulates the non-receptor Janus Kinase 2 (JAK2) and tyrosine kinase 2 (TYK2) activity, leading to the phosphorylation of signal transducer and activator of transcription (STAT) family members, i.e. STAT1, STAT3, STAT5, and mostly STAT4 homodimers.[18]

As demonstrated both in vitro and in vivo,[19,20] free p40 can form homodimers or persist as free monomers, both of which have been proposed as natural inhibitors of IL-12.[21]

Some differences in p40 homodimers have been found between human and mice.[14] In mouse models, p40 homodimers are not biologically active, but they bind the β1 subunit of IL-12 receptor (IL-12 β1R) with an affinity similar to p40 heterodimers; hence, p40 homodimers and heterodimers can compete for IL-12-β1R[21] and homodimers can be considered as natural inhibitors of IL-12 activity.[14,21] However, in humans, p40 homodimers bind IL-12β1R with a lower affinity compared with heterodimers; hence, IL-12p40 homodimer cannot be considered a physiological antagonist of IL-12 in humans.[14]

IL-12 functions in immune response

IL-12 accomplishes different functions as summarized in Figure 1, and represents the "bridge" between the innate and the adaptive immune system.[15]

IL-12 is a pro-inflammatory cytokine which induces Th cells differentiation into Th1 cells.[14,22] However, the absolute requirement of IL-12 in Th1 induction was questioned,[3,23] suggesting that it may rather be part of a broader machinery leading to Th1 differentiation through induction of IFN γ[24] as well as of T-bet,[23] in the frame of overlapping pathways finally culminating in a robust Th1 expansion.[24]

Several authors observed the inhibition of Th1 cell response in animals treated with neutralizing Abs targeting IL-12p40, IL-12p35, IL-12β1R, IL-12β2R or STAT4.[14]

IL-12 has an important role in the defense against microbial agents, particularly in the protection from intracellular

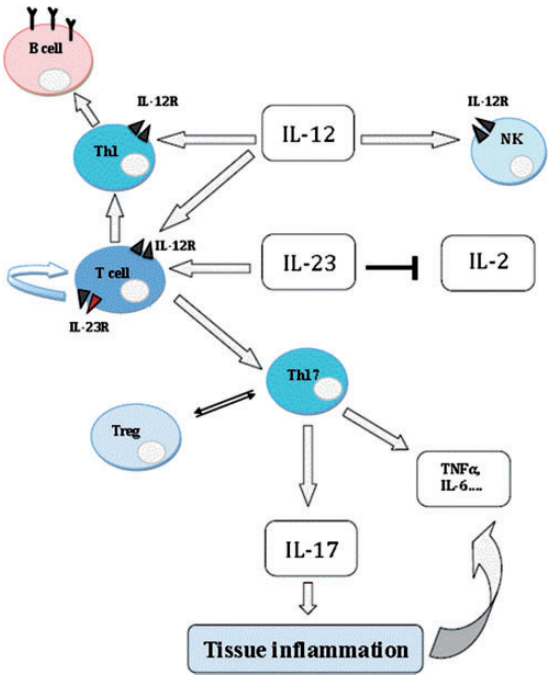

Figure 1. Once secreted by DCs, macrophages, and monocytes, IL-12 targets different cell clusters. It regulates the proliferation of T lymphocytes and it stimulates B cells in producing auto-antibodies. IL-12 plays a crucial role also in microbial response, by targeting NK cells. This cytokine is linked to the IL-23/Th17 axis. APCs release IL-23 and IL-17. IL-23 inhibitis IL-2 production and is fundamental for Th differentiation into Th17. These lymphocytes release IL-17, which target endothelial cells, macrophages, fibroblasts, and keratinocytes provoking tissue inflammation. (A color version of this figure is available in the online journal.)
IL-12: interleukin-12; IL-23: interleukin-23; IL-17: interleukin 17; IL-2: interleukin 2; NK: natural killer; APC: antigen presenting cell; Th1: T helper 1; Treg: T regulatory cell; Th17: T Helper 17; IL-12R: IL-12 Receptor; IL-23R: IL-23 receptor.

parasites.[14,15,25] IL-12 is rapidly secreted by dendritic cells (DCs) stimulated by toll like receptor (TLR) ligands, such as lipopolysaccharides (LPS), oligodeoxynucleotides (CpG), and polyinosinic-polycytidylic acid.[26] Macrophages can also produce IL-12 after being stimulated by microbial and bacterial products, or even by T cells through CD40-CD40L interactions.[27,28] Once IL-12 has been released, it mediates the differentiation of Th cells into Th1 cells, which are mainly responsible for antimicrobial responses through the production of IFN-γ.[14]

The role of IL-12 and IFN-γ in sustaining Th1 responses has further been investigated in mice, both in vitro and in vivo.[29,30] The p40-deficient mice were found to be more suppressed than p35-deficient mice in terms of their ability of resisting to mycobacterial infections.[29,30]

IL-12 also induces various cytotoxicity pathways and the expression of cytotoxic mediators[14] by amplifying the production of IFN-γ.[14,18,31]

Notably, IL-12 can activate natural killer (NK) cells, generate lymphokine-activated killer (LAK) cells, and it is involved in the generation of cytotoxic T lymphocytes.[14]

IFN-γ induced by IL-12 is essential for the development of different autoimmune diseases, such as experimental autoimmune uveitis (EAU) and experimental autoimmune encephalomyelitis (EAE).[32,33]

Only few studies evaluated IL-12 function on B-cell response,[15] likely due to the difficulty in blocking IL-12 responsiveness in B cells without blocking T cells.[15] There are some evidence that IL-12 can directly bind B cells, having either stimulatory or inhibitory effect. The stimulatory effect leads to IL-12-dependent differentiation of B cells into plasma cells secreting high levels of immunoglobulin M (IgM); the inhibitory effect induces loss of peritoneal B cells.[34] Finally, as reported by Trinchieri et al.,[14] hematopoietic progenitors are also targets of IL-12, in synergy with other colony-stimulating factors (CSF).

IL-12 in SLE

SLE genetic risk tends to be associated with IL-12/IL-12R pathway (IL12A, IL12B, IL12RB2, TYK2, STAT4).[35,36] A complex polymorphism in the promoter region of the IL-12B (IL12Bpro), resulting from four base-paired micro-insertion combined with an AA/GC transition (rs17860508), was found to be associated with SLE development in Bulgarian as well as Polish population.[37,38]

Higher levels of IL-12 were observed in SLE patients compared to controls[32,39] and p40 subunit serum levels were found to be positively correlated with SLE Disease Activity Index (SLEDAI) and negatively with C3 serum levels.[40] Interestingly, this elevation of IL-12 is not paralleled by a consistent increase of Th1-cytokines including IFNγ, whose serum levels are rather lowered,[39] suggesting a down-regulation of the Th1 phenotype in favor of a Th17 phenotype[41] (discussed below).

A dysregulation of IL-12 subunit expression was reported in SLE patients.[42,43]

IL-12p35mRNA expression in peripheral blood mononuclear cells was found to be significantly lower in SLE patients, either untreated or treated, than in healthy controls[42]; however, they were found to be higher in active SLE patients compared to inactive ones.[42] Interestingly, corticosteroids or corticosteroids plus immunosuppressants significantly suppressed IL-12p40 expression in SLE patients.[42,44]

T-follicular helper (Tfh) cells are critical in the development and progression of SLE and a recent study[43] suggested that IL-12-mediated co-activation of STAT1 and STAT4 altered histone modification, resulting in differentiation of T-follicular helper-Th1-like (Tfh-Th1) cells. This could be one of the underlying mechanisms responsible for the expansion of Tfh-Th1-like cells and potentially targeted by specific treatment.

IL-23/Th17 axis

The IL-23/Th17 axis is emerging as a critical regulatory system that bridges the innate and adaptive arms of the immune system and plays a critical role in the development of autoimmune inflammatory diseases.

IL-23

IL-23: Overall characteristics and structure. IL-23 is produced by macrophages, DCs, keratinocytes, and other antigen-presenting cells as well as T and NK lymphocytes, and it is mainly involved in the expansion of Th1-Th17 cells.[18,45]

Likewise IL-12, IL-23 consists of a heterodimeric structure, comprising p19 and p40 subunits. The p40 chain is shared with IL-12,[15,18,45] whereas IL-23p19 subunit is specific of IL-23.

Once IL-23 is secreted, it binds to IL-23 receptor which consists of two different receptor chains[45]: IL-12β1R and one receptor chain specific of IL-23, named IL-23 receptor (IL-23R). The first subunit is a glycosylated type I membrane protein of 70.5 kDa (in mice 79.7 kDa), which includes five extracellular domains, a single transmembrane domain and a cytoplasmic domain.[45] Since IL-12β1R is an essential component of both IL-12R and IL-23R, its deficiency will affect both IL-12 and IL-23-dependent innate and adaptive immune response. By contrast, IL-23 does not bind IL-12β2R (that is the second specific chain of IL-12R), suggesting that an additional IL-23 receptor chain is required.[46]

The second subunit, IL-23R, is a glycosylated type I membrane protein of 69 kDa (in mice 70.7 kDa) with three extracellular domains, a 37-aminoacid long-stalk region, a single transmembrane domain and a cytoplasmic domain.[45]

As for IL-12, IL-23 signaling depends on the activation of TYK2 (via IL-12β1R) and JAK2 (via IL-23R), which predominantly phosphorylate STAT3 and to a lesser extent STAT1, STAT4, and STAT5.[45]

IL-23 functions in immune response. Concerning T-cell response, while IL-12 promotes differentiation of naive CD4+ T cells into IFNγ-producing Th1 cells, IL-23 does not directly promote Th cell differentiation, owing to the absence of IL-23R in human and mouse naïve T cells.[15]

IL-23 leads naïve CD4+ T cells to differentiate into Th17 cells,[46] which have intimately been associated with the development of autoimmune diseases.[6]

In addition, IL-23 has recently emerged as a key player in chronic inflammation,[15] as shown by studies carried out in a murine model of multiple sclerosis (MS).[5,47] Indeed, IL-23-deficient (p19–/–) mice were resistant to central nervous system inflammation, and they were able to develop Th1 cell response, but not Th17 cell response.[48] IL-23 is also essential in developing collagen-induced arthritis (CIA), a rodent model of rheumatoid arthritis (RA).[6] Interestingly, IL-23 gene-targeted mice (p35–/– or p19–/–) did not develop clinical signs of disease and were completely resistant to the development of joint and bone damage.[6] Conversely, IL-12 appeared to protect animals from developing CIA.[6]

IL-23 and IL-12 act as complementary cytokines in the protection against infectious agents. As reported above, IL-12 is essential in the response to intracellular pathogens; by contrast, the role of IL-23 in immune response against these pathogens is less clear.[15] It has to be noted that IL-23 production in response to microbial infections is less dependent from IFN-γ than that of IL-12.[15] Indeed, IFN-γ only slightly enhances IL-23 expression in type 1 macrophages and IFNγ is not required by DCs in order to produce IL-23 in response to microbial stimulation.[28]

Increased serum levels of IL-23 were observed in systemic sclerosis, RA, SLE, primary antiphospholipid syndrome, spondyloarthropathies, and inflammatory bowel diseases.[49]

IL-23 in SLE. IL-23 has recently emerged as a key cytokine in the pathogenesis of SLE.[41]

Some authors found that mRNA levels of p19, p40, and p35 were significantly higher in active SLE patients than in patients with inactive SLE.[41]

IL-23 has been investigated in LN, either in humans or mice. A number of studies reported high IL-23 serum levels in SLE patients with LN[50,51] and an expansion of T cells, expressing both high IL-23 and IL-17 receptors in lupus-prone mice.[52]

Zhang et al.[52] found that lupus-prone B6/lpr-derived lymphnode cells expressed IL-23R mRNA. Treating these cells with IL-23, they observed a manifold increase in the expression of IL-23R and IL-17A with a significant correlation with IL-17A mRNA levels.[52] The transfer of IL-23-treated lymphocytes in Rag-1−/− mice led to a significant increase in proteinuria and to the appearance of white blood cells in the urine sediment. By contrast, mice transplanted with B6-derived lymphocytes untreated with IL-23 did not show significant proteinuria or leukocyturia.[52] IL-23R deficiency has been found to prevent the development of LN in mice.[12]

Several studies investigated the role of IL-23 in the pathogenesis of SLE and its relationship with disease activity.[48–50,52]

Concerning LN, glomerular IL-23 expression was found to be positively correlated with renal SLEDAI and histologic activity index.[47] The relationship between IL-23 and LN is also supported by the observation that patients with LN who were British Isles Lupus Assessment Group (BILAG)-non-responders had high IL-23 serum levels at baseline.[54] Apart from LN, high IL-23 serum levels were shown to be associated with other SLE manifestations in humans, including cutaneous involvement and serositis.[53]

Interestingly, high IL-23 serum levels were also associated with obesity and atherosclerotic plaques.[49,50,53] A significant correlation between IL-23 serum levels and antiphospholipid antibodies (aPL) was observed.[49]

IL-23 serum levels were found to be correlated with IFN-λ1 and associated with anti-nucleosome antibodies, lymphopenia, and absence of musculoskeletal damage.[48] Moreover, patients with high levels of IL-23, IFN-λ1, and IL-17A had more disease damage, especially in renal domain.[48] IL-23 mRNA serum levels were found to be elevated in Asian SLE patients with renal disease.[55]

Dai et al.[56] observed that when IL-23 is added to T cells from SLE patients in vitro, it induces the production of IL-17, while concomitantly limiting that of the regulatory cytokine IL-2, thus resulting in an expansion of T follicular helper and double negative (DN) T cells and worsened inflammation. The same authors generated IL-23 receptor-deficient MRL/lpr mice which displayed attenuated LN with a striking decrease in the accumulation of DN T cells in the kidneys and secondary lymphoid organs. Moreover, T cells from IL-23R−/−MRL/*lpr* mice produced increased amounts of IL-2 and reduced amounts of IL-17 compared with T cells from wild-type animals.[56]

Th17

Th17: Overall characteristics. Th17 lymphocytes are an important, new subset of Th cells which play a major role in autoimmunity. They derive from naïve CD4+ T cells and are characterized by the expression of the transcription factor named "related orphan receptor gamma" (RORγT).[57,58] Once stimulated by different cytokines including IL-23,[4] Th17 secrete cytokines, i.e. IL-17 family members as well as IL-21, IL-22, tumor necrosis factor (TNF)-α, and IL-6.[57]

Th17 in immune response. The interaction between IL-23/Th17 and Th1 cells has recently been shown to be involved in renal injury.[59] Odobasic et al.[8] found that mice deficient in IL-17A or IL-23 were protected in the early stage of anti-glomerular basement membrane (GBM) nephritis, whereas IL-12-knockout mice lacking Th1 response were protected in the later stages. Hence, Th17 response seems to be an early effector of the disease, whereas Th1 immune response acts as a late effector at least in models of crescent glomerulonephritis.[8] Renal $\gamma\delta$ T cells were shown to be the primary source of IL-17 production in the early stage of nephrotic syndrome due to immune-mediated glomerular diseases.[60] In a following step, CD4+ Th17 cells infiltrate the kidney and secrete IL-17, and thereafter Th17 cell response declines and Th1 immune response increases.[60]

In contrast to Th1 and Th2 cells which are considered stable lineages, Th17 cells exhibit high degree of plasticity.[61] This concept deals with the possibility that CD4+ IL-17 producing T cells can potentially acquire features of Th1 or, alternatively, T regulatory (reg) cells.[61] Indeed, a small proportion of human peripheral Treg cells produce IL-17 in healthy people.[62]

Whether Th17-like Treg cells are a transient stage in the differentiation of Treg into Th17 cells remains to be determined,[62] although this conversion has been described in several experimental models both in CIA and in mouse models of psoriasis.[62]

Due to their opposite effects on the immune response, Th17/Treg balance is critical in maintaining immune homeostasis, and if Treg cells are defective, they can be converted into Th17 cells leading to inflammatory diseases.[63,64]

However, other studies showed that Th17 plasticity is typical of Th17 cells in central nervous system and intestine,[65,66] but it does not seem to occur in kidney, where a unique microenvironment enables Th17 cells to maintain their phenotype.[60]

In addition, Th17 cells are involved in several functions including protection against extracellular bacteria, viruses, and fungi via the production of IL-17.[67]

Th17 cells play a crucial role in the IL-23/Th17 axis, which has been recently shown to be involved in the pathogenesis of asthma, psoriasis, inflammatory bowel disease,

and some autoimmune diseases including MS, RA and SLE.[15,68]

Th17 in SLE. An increase in Th17 cells and IL-23 serum levels was detected in SLE patients compared with healthy controls.[53] Chen et al.[50] found that the frequency of circulating Th17 cells as well as IL-17 and IL-23 serum levels was higher in patients with LN compared with controls. In the same study, circulating Th17 frequency was found to be correlated with SLE activity, in particular with SLEDAI, renal SLEDAI, and histological activity index,[50] consistently with previous findings.[39]

The potent proinflammatory activities of Th17 cells can contribute to several pathological pathways of SLE, such as the induction of vascular inflammation, recruitment of leukocytes, activation of B cells, and autoAbs production.[68,69] Notably, hydroxychloroquine was shown to inhibit the differentiation of Th17 cells which could potentially explain the beneficial effects of this drug in SLE treatment,[70] while Th17 may be involved in resistance to glucocorticoid treatment in SLE through secretion of proinflammatory cytokines.[71]

Regarding experimental models, Th17 cells were also shown to be increased in MRL/lpr mice.[72] In a pristane-induced mouse model of SLE bearing a specific deletion of STAT3-dependent Tregs, Kluger et al. found an overshooting Th17 response associated with a worsening of LN at four and nine months after pristane injection.[67] Tregs deficiency was also found to be associated with pulmonary vasculitis and a significant higher mortality. Hence, STAT3 Treg has been speculated to be the novel anti-inflammatory mediators in SLE.[67]

IL-17

IL-17: Overall characteristics and structure

IL-17 is a family of cytokines, produced by Th17 lineage, which includes IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25), and IL-17F.[73]

IL-17A is the most studied,[63] while the contribution of the other Th17 cell-derived cytokines has to be fully elucidated yet, especially regarding IL-17B, C and D.[61,63] IL-25 has the lowest homology and is involved in Th2 cell responses against parasites and allergy.[63] IL-25 regulates IL-17 function, which may occur via a competition at the receptor level.[63]

Homodimers and heterodimers of IL-17 cytokines signal via a dimeric IL-17Rs, which consist of five identified subunits (IL-17A to E).[63] The precise binding affinity and downstream signal of the various IL-17Rs have not been elucidated yet. However, the blockade of different IL-17 cytokines or their receptors can quantitatively and qualitatively yield different biologic effects.[74]

IL-17A, IL-17F bind the same receptor complex composed of IL-17RA and IL-17RC subunits.[63] IL-17RA is also one of the receptor subunits of IL-25, which includes IL-17RA and IL-17RB.[63] This is important when targeting IL-17RA, which blocks the proinflammatory pathways mediated by IL-17A, IL-17F but also the anti-inflammatory response mediated by IL-25.[64]

IL-17 in immune response

IL-17 has been shown to be involved in various inflammatory processes, and it has a pivotal role in the initiation and development of autoimmunity.[57] IL-17 deficiency leads to a lower control of infections, but its overproduction can lead to several chronic inflammatory and autoimmune diseases.[63]

IL-17 induces the production of inflammatory cytokines (namely TNF, IL-1β, and IL-6), different CSF, i.e. granulocyte (G)-CSF and granulocyte-macrophage (GM)-CSF, and chemokines (CXCL-8 and CXCL-2).[75] One of the main functions of IL-17 family cytokines is the induction of metalloproteinases (MMP) leading to tissues degradation.[16] Besides, IL-17 stimulates different cellular populations including fibroblasts, endothelial and epithelial cells, keratinocytes, and macrophages to produce several cytokines, including TNFα, which activate and attract neutrophils into the site of inflammation.[32]

IL-17 is a driving cytokine in the rheumatoid synovitis, psoriasis, and uveitis as well as in the dysregulation of immune system, leading to MS and other autoimmune diseases.[48,54] Mice genetically deficient for IL-17A were found to be less susceptible to the development of CIA or EAE.[76]

IL-17 seems to be involved in autoimmune glomerulonephritis.[77,78] It has been suggested that IL-17R-knockout mice were protected from crescent formation but not from glomerular necrosis or renal interstitial injury.[77,78] The role of other IL-17 cytokine family members and their receptors in inflammatory nephropathies remains unclear.[61]

IL-17 in SLE

IL-17 has been speculated to be essential in the development of LN. Indeed, pioneering works in 2009 demonstrated the presence of IL-17 producing T cells in Fas/lpr mice, a model of spontaneous lupus with renal involvement, previously thought to be mediated by IFN-γ-producing T cells.[51,52]

IL-17 was in fact shown to exert detrimental effects on intrinsic renal cells in either mice models of diverse autoimmune-nephropathies and humans, namely endothelial cells, tubular epithelial cells, mesangial cells, and fibroblasts where it can enhance the production of neutrophil-attracting chemokines and induce direct apoptosis of podocytes in mice.[79] Interestingly, CD3+ T cells, which are double negative for CD4 and CD8 expression, were found to be the main source of IL-17 in MRL/lpr mice.[52] The same authors showed an expansion of T cells expressing both high IL-17 and IL-23R,[52] and they found that lymphocytes isolated from MRL/lpr mice progressively expressed higher levels of IL-17R and IL-23R mRNA as their disease became more severe.[52]

In pristane mouse model, the induction of SLE did not occur in IL-17-deficient mice which were protected from developing auto-Abs and LN, compared to control mice.[80,81] In addition, the up-regulation of Th17 response due to impaired Treg cell function led to a worsening of

LN.[80,81] Consistently, treatment of a systemic model of SLE, i.e. MRL/lpr lupus mice with anti-IL-23 mAbs ameliorated LN[82] and was associated with a decrease in IL-17 serum levels without any significant change in Th1 activity. Taken together, these findings suggest that signaling of IL-17A worsens LN and may further emphasize that IL-17-producing T cells play a pivotal role in LN.[82]

On the other hand, Schmidt et al.[83] showed that anti-IL-17 treatment did not affect the course of LN in NZB/NZW mice, whereas anti-IFN-γ treatment attenuated the severity of disease, suggesting a predominance of Th1 immune response in these lupus mouse models. Thus, a different genetic background might account for these discrepancies, suggesting Th17 and Th1 cell responses might contribute to LN by distinct pathways.[61] These differences could also explain the divergent response to the treatment of these mice when treated with Th17- or Th1-targeted therapies.[61]

Concerning humans, serum levels of IL-17 were shown to be higher in SLE patients compared to controls,[39,54] and an increased IL-17 expression was documented in inflammatory infiltrates in renal tissue of patients with active LN.[54] High IL-17 serum levels were shown to be a marker of adverse histopathological outcome after immunosuppressive therapy in LN, indicating that IL-17 production could be associated with a severe or therapy-resistant disease phenotype.[16] In renal biopsies of LN, IL-17A, and IL-23 expression was demonstrated in DN, CD4, and CD8 T cells[84]; in addition, glomerular IL-17A and IL-23 were found to be positively correlated with renal SLEDAI and histological activity index,[50] while a negative correlation of IL-17 with chronicity index was reported,[85] suggesting IL-17 may act at early stages of inflammation in LN.

Finally, Abdel Galil et al.[86] observed a positive correlation between IL-17 serum levels and proteinuria or anti-double strand DNA antibodies (anti-dsDNA ab) in patients with LN, suggesting a potential pathogenetic link between the IL-23/Th17 axis and SLE activity.[61]

New therapeutic strategies in SLE

Increasing knowledge in the IL-12 and IL-23/Th17 axis in inflammatory autoimmune diseases has led to develop novel therapeutic strategies targeted to such molecules.[74]

There are different strategies to block IL-17 including monoclonal antibodies directed against IL-17, IL-17R, IL-12/23p40, and IL-23p19.[74]

Ustekinumab (Stelara®; Janssen Biotech, Inc., Horsham, PA), is a fully human IgG1κ mAb directed against the shared p40 subunit of IL-12 and IL-23.[74,87] By linking this subunit, it precludes the binding to IL-12Rβ1 cell surface receptor, thereby hindering the activity of both cytokines.[88]

Ustekinumab has been recently approved by the U.S. Food and Drug Administration and the European Medicines Agency for different autoimmune diseases, including psoriasis, psoriatic arthritis,[89] and Chron's disease.[87,88] It is currently under evaluation in SLE since a decrease in disease activity was observed in animal models lacking the shared IL-12/23 p40 subunit, suggesting this could be a potential target also in humans.[54]

Phase III and other clinical trials confirmed the efficacy of this novel mAb in treating moderate to severe plaque psoriasis,[89–91] where ustekinumab was even superior to anti-TNFα agents. A meta-analysis showed that the likelihood expressed as risk ratio (RR) for achieving psoriasis area and severity index improvement by 75% (PASI75) at week 12 was 18.28 (95% CI 12.76–26.17 $p < 0.001$) for ustekinumab 45 mg compared to placebo and 20.21 (95% CI 13.85–29.49 $p < 0.001$) for ustekinumab 90 mg compared to placebo.[92]

Ustekinumab is under investigation in SLE patients and very promising data were recently disclosed. In a phase II RCT carried out in active SLE patients,[93] ustekinumab was found to be superior to placebo in terms of SLE Responder Index-4 (SRI-4) response after 24 weeks (60% vs. 31%, $p = 0.0046$). Ustekinumab resulted to be particularly effective in patients with skin and joint manifestations. In addition, a significant increase in C3 and a decrease in anti-dsDNA ab levels were found after treatment suggesting that ustekinumab could have an immunomodulatory effect in SLE.

Very few data on the use of IL-17 inhibitors in SLE are available. A case of a 62-year-old female who presented with psoriasis vulgaris and refractory LN treated with the anti-IL-17A mAb secukinumab was reported.[94] The patient was resistant to conventional treatment, and flow cytometry confirmed the proliferation of activated Th17 cells in peripheral blood, and examination of a renal biopsy tissue sample confirmed the infiltration of numerous IL-17-positive lymphocytes into the renal interstitium. After starting secukinumab, the clinical and biological features were improved.

Summary and conclusion

A wide variety of cytokines are involved in SLE pathogenesis. Recently, the IL-23/Th-17 axis has been identified as a key mediator of inflammation in SLE, especially in LN, as suggested by data derived from mouse models and humans. Beside this axis, it has become clear that the interaction between Th1 and Th17 cell lineages is much more interlined and complex than it was initially thought.

Ustekinumab, which target the p40 subunit of IL-12 and IL-23, might be a potential strategy for active SLE. Despite these promising findings, further studies are needed in order to define the efficacy of treatments aimed at blocking IL-12, IL-23, and IL-17 in SLE.

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REFERENCES

1. Gatto M, Zen M, Ghirardello A, Bettio S, Bassi N, Iaccarino L, Punzi L, Doria A. Emerging and critical issues in the pathogenesis of lupus. *Autoimmun Rev* 2013;**12**:523–36
2. Herrmann M, Voll RE, Zoller OM, Hagenhofer M, Ponner BB, Kalden JR. Impaired phagocytosis of apoptotic cell material by monocyte-derived macrophages from patients with systemic lupus erythematosus. *Arthritis Rheum* 1998;**41**:1241–50
3. Ramani K, Biswas PS. Interleukin 17 signaling drives Type I interferon induced proliferative crescentic glomerulonephritis in lupus-prone mice. *Clin Immunol* 2016;**162**:31–6
4. La Paglia GMC, Leone MC, Lepri G, Vagelli R, Valentini E, Alunno A, Tani C. One year in review 2017: systemic lupus erythematosus. *Clin Exp Rheumatol* 2017;**35**:551–61
5. Becher B, Durell BG, Noelle RJ. Experimental autoimmune encephalitis and inflammation in the absence of interleukin-12. *J Clin Invest* 2002;**110**:4939–7
6. Murphy CA, Langrish CL, Chen Y, Blumenschein W, McClanahan T, Kastelein RA, Sedgwick JD, Cua DJ. Divergent pro- and antiinflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation. *J Exp Med* 2003;**198**:1951–7
7. Luger D, Silver PB, Tang J, Cua D, Chen Z, Iwakura Y, Bowman EP, Sgambellone NM, Chan CC, Caspi RR. Either a Th17 or a Th1 effector response can drive autoimmunity: conditions of disease induction affect dominant effector category. *J Exp Med* 2008;**205**:799–810
8. Odobasic D, Gan PY, Summers SA, Semple TJ, Muljadi RC, Iwakura Y, Kitching AR, Holdsworth SR. Interleukin-17 A promotes early but attenuates established disease inc crescentic glomerulonephritis in mice. *Am J Pathol* 2011;**179**:1188–98
9. Lieberman LA, Cardillo F, Owyang AM, Rennick DM, Cua DJ, Kastelein RA, Hunter CA. IL-23 provides a limited mechanism of resistance to acute toxoplasmosi in the absence of IL-12. *J Immunol* 2004;**173**:1887–93
10. Riedel JH, Paust HJ, Krohn S, Turner JE, Kluger MA, Steinmetz OM, Krebs CF, Stahl RA, Panzer U. IL-17F promotes tissue injury in autoimmune kidney diseases. *J Am Soc Nephrol* 2016;**27**:3666–77
11. Krohn S, Nies JF, Kapffer S, Schmidt T, Riedel JH, Kaffke A, Peters A, Borchers A, Steinmetz OM, Krebs CF, Turner JE, Brix SR, Paust HJ, Stahl RAK, Panzer U. IL-17C/IL-17 receptor E signaling in CD^{4+} T cells promotes $_{TH}17$ cell-driven glomerular inflammation. *JASN* 2018;**29**:1210–22
12. Kyttaris VC, Zhang Z, Kuchroo VK, Oukka M, Tsokos GC. Cutting edge: IL-23 receptor deficiency prevents the development of lupus nephritis in C57BL/6-lpr/lpr mice. *J Immunol* 2010;**184**:4605–9
13. Pisitkun P, Ha HL, Wang H, Claudio E, Tivy CC, Zhou H, Mayadas TN, Illei GG, Siebenlist U. Interleukin-17 cytokines are critical in development of fatal lupus glomerulonephritis. *Immunity* 2012;**37**:1104–15
14. Trinchieri G. Interleukin-12 and the regulation of innate resistance and adaptive immunity. *Nat Rev Immunol* 2003;**3**:133–46
15. Langrish CL, McKenzie BS, Wilson NJ, de Waal Malefyt R, Kastelein RA, Cua DJ. IL-12 and IL-23: master regulators of innate and adaptive immunity. *Immunol Rev* 2004;**202**:96–105
16. Wolfe SF, Temple PA, Kobayashi M, Young D, Dicig M, Lowe L, Dzialo R, Fitz L, Ferenz C, Hewick RM. Cloning of cDNA for natural killer cell stimulatory factor, a heterodimeric cytokine with multiple biologic effects on T and natural killer cells. *J Immunol* 1991;**146**:3074–81
17. Trinchieri G, Wysocka M, D'Andrea A, Rengaraju M, Aste-Amezaga M, Kubin M, Valiante NM, Chehimi J. Natural killer cell stimulatory factor (NKSF) or interleukin-12 is a key regulator of immune response and inflammation. *Prog Growth Factor Res* 1992;**4**:355–68
18. Teng MW, Bowman EP, McElwee JJ, Smyth MJ, Casanova JL, Cooper AM, Cua DJ. IL-12 and IL-23 cytokines: from discovery to targeted therapies for immune-mediated inflammatory diseases. *Nat Med* 2015;**21**:179–229
19. Heinzel FP, Hujer AM, Ahmed FN, Rerko RM. In vivo production and function of IL-12 p40 homodimers. *J Immunol* 1997;**158**:4381–8
20. Carra G, Gerosa F, Trinchieri G. Biosynthesis and postranslational regulation of human IL-12. *J Immunol* 2000;**164**:4752–61
21. Gillessen S, Carvajal D, Ling P, Podlaski FJ, Stremlo DL, Familletti PC, Gubler U, Presky DH, Stern AS, Gately MK. Mouse interleukin-12 (IL-12) p40 homodimer: a potent IL-12 antagonist. *Eur J Immunol* 1995;**25**:200–6
22. Manetti R, Parronchi P, Giudizi MG, Piccinni MP, Maggi E, Trinchieri G, Romagnani S. Natural killer cell stimulatory factor (interleukin 12 [IL-12]) induces T helper type 1 (Th1)-specific immune responses and inhibits the development of IL-4-producing Th cells. *J Exp Med* 1993;**177**:1199–204
23. Noble A, Thomas MJ, Kemeny DM. Early Th1/Th2 cell polarization in the absence of IL-4 and IL-12: T-cell receptor signaling regulates the response cyokines in CD4 and CD8 T cells. *Eur J Immunol* 2001;**31**:2227–35
24. Nembrini C, Abel B, Kopf M, Marsland BJ. Strong TCR signaling, TLR ligands, and cytokine redundancies ensure robust development of type 1 effector T cells. *J Immunol* 2006;**176**:7180–8
25. Fieschi C, Bosticardo M, de Beaucoudrey L, Boisson-Dupuis S, Feinberg J, Santos OF, Bustamante J, Levy J, Candotti F, Casaova JL. A novel form of complete IL-12/IL-23 receptor beta1 deficiency with cell surface-expressed nonfunctional receptors. *Blood* 2004;**104**:2095–101
26. Hochrein H, Shortman K, Vremec D, Scott B, Hertzog P, O'Keeffe M. Differntial production of IL-12, IFN-alpha, and IFN-gamma by mouse dendiritic cell subsets. *J Immunol* 2001;**166**:5448–55
27. Shu U, Kiniwa M, Wu CY, Maliszewski C, Vezzio N, Hakimi J, Gately M, Delespesse G. Activated T cells induce iterleukin-12 production by monocytes via CD40-CD40 ligand interaction. *Eur J Immunol* 1995;**25**:1125–8
28. Verreck FA, de Boer T, Langenberg DM, Hoeve MA, Kramer M, Vaisberg E, Kastelein R, Kolk A, de Waal-Malefvt R, Ottenhoff TH. Human IL-23-producing type 1 macrophages promote but IL-10 producing type 2 macrophages subvert immunity to (myco)bacteria. *Proc Natl Acad Sci USA* 2004;**101**:4560–5
29. Li K, Chan SY, Ferrante J, Magram J, Eichwald EJ, Bishop DK. Alloantigen-reactive Th1 development in IL-12 deficient mice. *J Immunol* 1998;**160**:1132–8
30. Cooper AM, Kipnis A, Turner J, Magram J, Ferrante J, Orme IM. Mice lacking bioactive IL-12 can generate protective, antigen specific cellular responses to mycobacterial infection only if the IL 12 p40 subunit is present. *J Immunol* 2002;**168**:1322–7
31. Ohteki T, Fukao T, Suzue K, Maki C, Ito M, Nakamura M, Koyasu S. Interleukin 12-dependent interferon gamma production by CD8alpha+ lymphoid dendritic cells. *J Exp Med* 1999;**189**:1981–6
32. Damsker JM, Hansen AM, Caspi RR. Th1 and Th17 cells: adversaries and collaborators. *Ann N Y Acad Sci* 2010;**1183**:211–21
33. Pettinelli CB, McFarlin DE. Adoptive transfer of experimental allergic encephalomyelitis in SJL/J mice after in vitro activation of lymph node cells by myelin basic protein: requirement for Lyt 1+ 2- T lymphocytes. J. *J Immunol* 1981;**127**:1420–3
34. Jelinek DF, Braaten JK. Role of IL-12 in human B lymphocyte proliferation and differentiation. *J Immunol 1995* 1995;**154**:1606–13 [Mismatch]
35. Remmers EF, Plenge RM, Lee AT, Graham RR, Hom G, Behrens TW, de Bakker PI, Le JM, Lee HS, Batliwalla F, Li W, Masters SL, Booty MG, Carulli JP, Padyukov L, Alfredsson L, Klareskog L, Chen WV, Amos CI, Criswell LA, Seldin MF, Kastner DL, Gregersen PK. STAT4 and the risk of rheumatoid arthritis and systemic lupus erythematosus. *N Engl J Med* 2007;**357**:977–86 [Mismatch]
36. Liu CC, Kao AH, Manzi S, Ahearn JM. Biomarkers in systemic lupus erythematosus: challenges and prospects for the future. *Ther Adv Musculoskelet Dis* 2013;**5**:210–33
37. Miteva LD, Manolova IM, Ivanova MG, Rashkov RK, Stoilov RM, Gulubova MV, Stanilova SA. Functional genetic polymorphisms in interleukin-12B gene in association with systemic lupus erythematosus. *Rheumatol Int* 2012;**32**:539[Mismatch]

38. Paradowska-Gorycka A, Sowinska A, Stypinska B, Grobelna MK, Walczyk M, Olesinska M, Piotrowski P, Jagodzinski PP. Genetic variants in IL-12B and IL-27 in the Polish patients with systemic lupus erythematosus. *Scand J Immunol* 2016;**8**:49–60
39. Talaat RM, Mohamed SF, Bassyouni IH, Raouf AA. Th1/Th2/Th17/Treg cytokine imbalance in systemic lupus erythematosus (SLE) patients: correlation with disease activity. *Cytokine* 2015;**72**:146–53
40. Lauwerys BR, Van Snick J, Houssiau FA. Serum IL-12 in systemic lupus erythematosus: absence of p70 heterodimers but presence of p40 monomers correlating with disease activity. *Lupus* 2002;**11**:384–7
41. Suárez-Fueyo A, Bradley SJ, Tsokos GC. T cells in systemic lupus erythematosus. *Curr Opin Immunol* 2016;**43**:32–8
42. Huang X, Hua J, Shen N, Chen S. Dysregulated expression of interleukin-23 and interleukin-12 subunits in systemic lupus erythematosus patients. *Mod Rheumatol* 2007;**17**:220
43. Ma X, Nakayamada S, Kubo S, Sakata K, Yamagata K, Miyazaki Y, Kitanaga Y, Zhang M, Tanaka Y. Expansion of T follicular helper-T helper 1 like cells through epigenetic regulation by signal transducer and activator of transcription factors. *Ann Rheum Dis* 2018;**77**:1354–61
44. Qiu F, Song L, Yang N, Li X. Glucocorticoid downregulates expression of IL-12 family cytokines in systemic lupus erythematosus patients. *Lupus* 2013;**22**:1011–6
45. Floss DM, Schröder J, Franke M, Scheller J. Insight into IL-23 biology: from structure to function. *Cytokine Growth Factor Rev* 2015;**26**:569–78
46. Vogel LA, Lester TL, Van Cleave VH, Metzger DW. Inhibition of murine B1 lymphocytes by interleukin-12. *Eur J Immunol* 1996;**26**:219–23
47. Cua DJ, Sherlock J, Chen Y, Murphy CA, Joyce B, Seymour B, Lucian L, To W, Kwan S, Churakova T, Zurawski S, Wiekowki M, Lira SA, Gorman D, Kastelein RA, Sedwick JD. Interleukin-23 rather than interleukin-12 is the critical cytokine for autoimmune inflammation of the brain. *Nature* 2003;**421**:744–8
48. Oke V, Brauner S, Larsson A, Gustafsson J, Zickert A, Gunnarsson I, Svenugsson E. IFN-λ1 with Th17 axis cytokines and IFN-α define different subsets in systemic lupus erythematosus (SLE). *Arthritis Res Ther* 2017;**19**:139
49. Fischer K, Przepiera-Będzak H, Sawicki M, Walecka A, Brzosko I, Brzosko M. Serum interleukin-23 in Polish patients with systemic lupus erythematosus: association with lupus nephritis, obesity, and peripheral vascular disease. *Mediators Inflamm* 2017;**2017**:9401432
50. Chen DY, Chen YM, Wen MC, Hsieh TY, Hung WT, Lan JL. The potential role of Th17 cells and Th17-related cytokines in the pathogenesis of lupus nephritis. *Lupus* 2012;**21**:1385–96
51. Steinmetz OM, Turner JE, Paust HJ, Lindner M, Peters A, Heiss K, Velden J, Hopfer H, Fehr S, Krieger T, Meyer-Schwesinger C, Meyer TN, Helmchen U, Mittrücker HW, Stahl RA, Panzer U. CXCR3 mediates renal Th1 and Th17 immune response in murine lupus nephritis. *J Immunol* 2009;**183**:4693–704
52. Zhang Z, Kyttaris VC, Tsokos GC. The role of IL-23/IL-17 axis in lupus nephritis. *J Immunol* 2009;**183**:3160–9
53. Wong CK, Lit LC, Tam LS, Li EK, Wong PT, Lam CW. Hyperproduction of IL-23 and IL-17 in patients with systemic lupus erythematosus: implications for Th17-mediated inflammation in auto-immunity. *Clin Immunol* 2008;**127**:385–93
54. Zickert A, Amoudruz P, Sundström Y, Rönnelid J, Malmström V, Gunnarsson I. IL-17 and IL-23 in lupus nephritis-association to histopathology and response to treatment. *BMC Immunol* 2015;**16**:7
55. Du J, Li Z, Shi J, Bi L. Associations between serum interleukin-23 levels and clinical characteristics in patients with systemic lupus erythematosus. *J Int Med Res* 2014;**42**:1123–30
56. Dai H, He F, Tsokos GC, Kyttaris VC. IL-23 limits the production of IL-2 and promotes autoimmunity in lupus. *J Immunol* 2017;**199**:903–10
57. Qu N, Xu M, Mizoguchi I, Furusawa J, Kaneko K, Watanabe K, Mizuguchi J, Itoh M, Kawakami Y, Yoshimoto T. Pivotal roles of T-helper 17-related cytokines, IL-17, IL-22, and IL-23, in inflammatory diseases. *Clin Dev Immunol* 2013;**2013**:968549
58. Kleczynska W, Jakiela B, Plutecka H, Milewski M, Sanak M, Musial J. Imbalance between Th17 and regulatory T-cells in systemic lupus erythematosus. *Folia Histochem Cytobiol* 2011;**49**:646–53
59. Paust HJ, Turner JE, Riedel JH, Disteldorf E, Peters A, Schmidt T, Krebs C, Velden J, Mittrücker HW, Steinmetz OM, Stahl RA, Panzer U. Chemokines play a critical role in the cross-regulation of Th1 and Th17 immune responses in murine crescentic glomerulonephritis. *Kidney Int* 2012;**82**:72–83
60. Krebs CF, Schmidt T, Riedel JH, Panzer U. T helper type 17 cells in immune-mediated glomerular disease. *Nat Rev Nephro* 2017;**13**:647–59
61. Guéry L, Hugues S. Th17 cell plasticity and functions in cancer immunity. *Biomed Res Int* 2015;**2015**:314620
62. Dominguez-Villar M, Hafler DA. Regulatory T cells in autoimmune disease. *Nat Immunol* 2018;**19**:665–73
63. Beringer A, Noack M, Miossec P. IL-17 in chronic inflammation: from discovery to targeting. *Trends Mol Med* 2016;**22**:230–41
64. Dolff S, Bijl M, Huitema MG, Limburg PC, Kallenberg CG, Abdulahad WH. Disturbed Th1, Th2, TH17 and Treg balance in patients with systemic lupus erythematosus. *Clin Immunol* 2011;**141**:197–204
65. Gagliani N, Amezcua Vesely MC, Iseppon A, Brockmann L, Xu H, Palm NW, de Zoete MR, Licona-Limón P, Paiva RS, Ching T, Weaver C, Zi X, Pan X, Fan R, Garmire LX, Cotton MJ, Drier Y, Bernstein B, Geginat J, Stockinger B, Esplugues E, Huber S, Flavell RA. Th17 cells transdifferentiate into regulatory T cells during resolution of inflammation. *Nature* 2015;**523**:221–5
66. Pelczar P, Witkowski M, Perez LG, Kempski J, Hammel AG, Brockmann L, Kleinschmidt D, Wende S, Haueis C, Bedke T, Witkowski M, Krasemann S, Steurer S, Booth CJ, Busch P, König A, Rauch U, Benten D, Izbicki JR, Rösch T, Lohse AW, Strowig T, Gagliani N, Flavell RA, Huber S. A pathogenic role for T cell-derived IL-22BP in inflammatory bowel disease. *Science* 2016;**354**:358–62
67. Kluger MA, Melderis S, Nosko A, Goerke B, Luig M, Meyer MC, Turner JE, MeyerSchwesinger C, Wegscheid C, Tiegs G, Stahl RA, Panzer U, Steinmetz OM. Treg17 cells are programmed by Stat3 to suppress Th17 responses in systemic lupus. *Kidney Int* 2016;**89**:158–66
68. Yang J, Yang X, Zou H, Li M. Oxidative stress and Treg and Th17 dysfunction in systemic lupus erythematosus. *Oxid Med Cell Longev* 2016;**2016**:2526174
69. Li D, Guo B, Wu H, Tan L, Chang C, Lu Q. Interleukin-17 in systemic lupus erythematosus: a comprehensive review. *Autoimmunity* 2015;**48**:353–61
70. Yang J, Yang X, Yang J, Li M. Hydroxychloroquine inhibits the differentiation of Th17 cells in systemic lupus erythematosus. *J Rheumatol* 2018;**45**:818–26
71. Gao H, Wang Q, Yu X, Liu J, Bai S, Feng J, Wu B. Molecular mechanisms of glucocorticoid resistance in systemic lupus erythematosus: a review. *Life Sci* 2018;**209**:383–7
72. Koga T, Ichinose K, Tsokos GC. T cells and IL-17 in lupus nephritis. *Clin Immunol* 2017;**185**:95–9
73. Moseley TA, Haudenschild DR, Rose L, Reddi AH. Interleukin-17 family and IL-17 receptors. *Cytokine Growth Factor Rev* 2003;**14**:155–74
74. Baker KF, Isaacs JD. Novel therapies for immune-mediated inflammatory diseases: what can we learn from their use in rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, psoriasis, Crohn's disease and ulcerative colitis? *Ann Rheum Dis* 2018;**77**:175–87
75. Gaffen SL, Jain R, Garg AV, Cua DJ. The IL-23-IL-17 immune axis: from mechanisms to therapeutic testing. *Nat Rev Immunol* 2014;**14**:585–600
76. Hofstetter HH, Ibrahim SM, Koczan D, Kruse N, Weishaupt A, Toyka KV, Gold R. Therapeutic efficacy of IL-17 neutralization in murine experimental autoimmune encephalomyelitis. *Cell Immunol* 2005;**237**:123–30
77. Ramani K, Pawaria S, Maers K, Huppler AR, Gaffen SL, Biswas PS. An essential role of interleukin-17 receptor signaling in the development of autoimmune glomerulonephritis. *J Leukoc Biol* 2014;**96**:463–72
78. Ghali JR, O'Sullivan KM, Eggenhuizen PJ, Holdsworth SR, Kitching AR. Interleukin-17RA promotes humoral responses and glomerular injury in experimental rapidly progressive glomerulonephritis. *Nephron* 2017;**135**:207–23
79. Ghali JR, Holdsworth SR, Kitching AR. Targeting IL-17 and IL-23 in immune mediated renal disease. *Curr Med Chem* 2015;**22**:4341–65
80. Summers SA, Odobasic D, Khouri MB, Steinmetz OM, Yang Y, Holdsworth SR, Kitching AR. Endogenous interleukin (IL)-17A

promotes pristane-induced systemic autoimmunity and lupus nephritis induced by pristane. *Clin Exp Immunol* 2014;**176**:341–50
81. Amarilyo G, Lourenço EV, Shi FD, La Cava A. IL-17 promotes murine lupus. *J Immunol* 2014;**193**:540–3
82. Kyttaris VC, Kampagianni O, Tsokos GC. Treatment with anti-interleukin 23 antibody ameliorates disease in lupus-prone mice. *Biomed Res Int* 2013;**2013**:861028
83. Schmidt T, Paust HJ, Krebs CF, Turner JE, Kaffke A, Bennstein SB, Koyro T, Peters A, Velden J, Hünemörder S, Haag F, Steinmetz OM, Mittrücker HW, Stahl RA, Panzer U. Function of the Th17/interleukin-17A immune response in murine lupus nephritis. *Arthritis Rheumatol* 2015;**67**:475–87
84. Crispín JC, Oukka M, Bayliss G, Cohen RA, Van Beek CA, Stillman IE, Kyttaris VC, Juang YT, Tsokos GC. Expanded double negative T cells in patients with systemic lupus erythematosus produce IL-17 and infiltrate the kidneys. *J Immunol* 2008;**181**:8761–6
85. Wang Y, Ito S, Chino Y, Goto D, Matsumoto I, Murata H, Tsutsumi A, Hayashi T, Uchida K, Usui J, Yamagata K, Sumida T. Laser microdissection-based analysis of cytokine balance in the kidneys of patients with lupus nephritis. *Clin Exp Immunol* 2010;**159**:1–10
86. Abdel Galil SM, Ezzeldin N, El-Boshy ME. The role of serum IL-17 and IL-6 as biomarkers of disease activity and predictors of remission in patients with lupus nephritis. *Cytokine* 2015;**76**:280–7
87. Johnnson HJ, McInnes IB. Interleukin-12 and interleukin-23 inhibition in psoriatic arthritis. *Clin Exp Rheumatol* 2015;**33**:S115–8
88. Katsanos KHBiological therapies in inflammatory bowel disease: beyond anti-TNF therapies. *Clin Immunol* 2018; https://doi.org/10.1016/j.clim.2018.03.004
89. Roberts J, O'Rielly DD, Rahman P. A review of ustekinumab in the treatment of psoriatic arthritis. *Immunotherapy* 2018;**10**:361–72
90. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, Li S, Dooley LT, Gordon KB, Phoenix 1, Study I. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008;**371**:1665–74
91. Griffiths CE, Strober BE, van de Kerkhof P, Ho V, Fidelus-Gort R, Yeilding N, Guzzo C, Xia Y, Zhou B, Li S, Dooley LT, Goldstein NH, Menter A, Accept SG. Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med* 2010;**362**:118–28
92. Papp KA, Griffiths CE, Gordon K, Lebwohl M, Szapary PO, Wasfi Y, Chan D, Hsu MC, Ho V, Ghislain PD, Strober B, Reich K. PHOENIX 1 Investigators; PHOENIX 2 Investigators; ACCEPT Investigators. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. *Br J Dermatol* 2013;**168**:844–54
93. van Vollenhoven RF, Hahn BH, Tsokos GC, Wagner CL, Lipsky P, Touma Z, Werth VP, Gordon RM, Zhou B, Hsu B, Chevrier M, Triebel M, Jordan JL, Rose S. Efficacy and safety of ustekinumab, an IL-12 and IL-23 inhibitor, in patients with active systemic lupus erythematosus: results of a multicentre, double-blind, phase 2, randomised, controlled study. *Lancet* 2018;13;**392**:1330-39.
94. Satoh Y, Nakano K, Yoshinari H, Nakayamada S, Iwata S, Kubo S, Miyagawa I, Yoshikawa M, Miyazaki Y, Saito K, Tanaka Y. A case of refractory lupus nephritis complicated by psoriasis vulgaris that was controlled with secukinumab. *Lupus* 2018;**27**:1202–6