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IL-23/IL-17 Axis in Inflammatory Rheumatic Diseases

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Abstract

In inflammatory rheumatic disorders, the immune system attacks and damages the connective tissues and invariably internal organs. During the past decade, remarkable advances having been made towards our understanding on the cellular and molecular mechanisms involved in rheumatic diseases. The discovery of IL-23/IL-17 axis and the delineation of its important role in the inflammation led to the introduction of many needed new therapeutic tools. We will present an overview of the rationale for targeting therapeutically the IL-23/IL-17 axis in rheumatic diseases and the clinical benefit which has been realized so far. Finally, we will discuss the complex interrelationship between IL-23 and IL-17 and the possible uncoupling in certain disease settings.

Keywords

Inflammatory rheumatic disorders; IL-23/IL-17 axis; Biologics

Introduction

Inflammatory rheumatic disorders are a group of diseases with variable phenotypic presentation [1–5]. However, the presence of either systemic inflammation or organ-specific inflammation is a common feature of these diseases [6, 7]. During the past decade, the identification of the proinflammatory function of interleukin-17 (IL-17) [8–10] and the discovery of a novel subset of T helper cells termed Th17 cells [11, 12] which drive inflammation by producing IL-17, the signature cytokine, have led to important insights into chronic inflammation. Interleukin-23 (IL-23), a heterodimeric cytokine comprising two subunits (p19 and p40), controls the production of pro-inflammatory cytokines including IL-17, IL-22, and GM-CSF by promoting the development and expansion of pathogenic Th17 cells [13]. This relationship between IL-23 and Th17s has led to the concept of the IL-23–IL-17 axis as a pivotal pathway driving various autoimmune processes [13–15]

Rheumatic diseases are the most common cause of disability and over 50 million Americans are living with some form of rheumatic diseases [16–18].Until late twentieth century, the main drugs available for the treatment of rheumatic diseases were limited to the use of classical disease-modifying antirheumatic drugs (DMARDs) which were developed without full understanding of involved cellular or molecular mechanisms [19, 20]. The introduction

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of biologic therapeutics at the end of the twentieth century has contributed significantly to the improvement in the management of these diseases [21]. However, considering the fact that no matter which novel biologics, there are always a significant proportion of patients who fail to respond; the effort to further understand the involved mechanisms and the identification of new targets should not abate.

Genetic and experimental data support the concept that the activation of IL-23/IL-17 axis contributes to the development of a series of inflammatory rheumatic diseases, including psoriasis, psoriatic arthritis (PsA), ankylosing spondylitis (AS), rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) [22–25]. Since IL-17 production is considered to be under the control of IL-23, it was expected that blockade of either IL-17 or IL-23 should have the same clinical effect [13, 14]. The encouraging clinical results in the treatment of psoriasis and PsA reinforce the blockade of this pathogenic axis [26–30]. However, the negative results in trials of patients with rheumatoid arthritis prompt the question whether synergistic blockade of IL-23/IL-17 axis with other biologics could lead to better therapeutic outcomes [31, 32]. Such a consideration will be discussed herein. Furthermore, the clinical trials in AS indicate that the interaction between IL-23 and IL-17 is more complicated than what we had speculated since blockade of IL-17 but not of IL-23 showed greater therapeutic efficacy in the treatment of patients with AS [33–37]. Therefore, further research is warranted to clarify the common and unique roles for IL-23 and IL-17 in the pathogenesis of inflammatory rheumatic diseases.

The IL-23/IL-17 Axis in Pathogenesis of Rheumatic Diseases

IL-23 is a heterodimeric cytokine composed of p19 and p40 two subunits and principally produced by dendritic cells (DCs) and macrophages [13, 38–40]. Comparative studies analyzing the susceptibility of mice with deficiency of either IL-12p40, IL-12p35, or IL-23p19 to autoimmunity revealed the crucial roles of IL-23 but not IL-12 in the development of EAE and CIA [41, 42]. Overexpression of IL-23 in mice through transgene or hydrodynamic delivery induces multiple organ inflammation [43–45], a fact which suggests the primary role of IL-23 in driving inflammation in autoimmunity [13, 14, 38].

The interleukin-17 (IL-17) family consists of six members, IL-17A through IL17F [9]. IL-17A, the founding member of this family, exists as either homodimers or heterodimers paired with IL-17F and is mainly produced by T helper 17 (Th17) cells [11, 12, 46], a distinct T cell subset [47]. IL-17 has been implicated in the immunopathology of many autoimmune or chronic inflammatory diseases, by acting on many cell types of non-hematopoietic origin, including fibroblasts, epithelial cells, and synoviocytes [48, 49], which lead to the secretion of a range of pro-inflammatory cytokines (including IL-6, TNFα, and IL-1) and T cell- and neutrophil-attracting chemokines including CCL2, CCL7, CXCL1, and CXCL2 [9, 15, 50, 51]. Additionally, IL-17 works in concert with other pro-inflammatory molecules, particularly TNFα, which in turn amplifies the inflammatory signaling in inflammatory environments [15, 52, 53]. Moreover, IL-17 promotes antibody production during inflammation by acting on IL-17 receptor expressing follicular dendritic cells, T cells and B cells [54–56]. As IL-23 is known to be important in sustaining IL-17 production from Th17 cells [57] and disturbing the Th17/Treg balance [58, 59], the evidence generated in

animal models positioned IL-23/IL-17 axis as a pinnacle therapeutic target for rheumatic diseases characterized by chronic inflammation [13].

Genetic studies in human subjects have linked IL-23 receptor (IL-23R) polymorphisms with susceptibility to autoimmune diseases such as psoriasis, PsA, AS, and multiple sclerosis [22, 24, 25, 60, 61]. Later, more variants in genes encoding critical molecules involved in the IL-23/IL-17 pathway, such as IL-12B, CCR6, STAT3, and TYK2, were identified [24, 62–64]. The functional impact of some variants has been verified using genetically engineered cells or mice carrying orthologous amino acid substitutions [65–67]. Moreover, the presence of IL-17 and IL-23 in the circulation or locally inflamed tissues has been documented in patients with various inflammatory rheumatoid diseases and elevated levels correlate positively with disease severity, a fact that further supports a pathogenic role for the IL23/IL-17 axis in patients with inflammatory rheumatoid diseases [13, 37, 49, 59, 68].

Biologics Targeting IL23/IL-17 Axis

Although experimental data from animal models of chronic inflammatory diseases including uveitis, lupus, multiple sclerosis, collagen-induced arthritis, and AS have provided insights, the clinical data generated from trials in humans for this therapeutic concept are still limited. Currently, a series of antibody-based drugs targeting IL-23/IL-17 axis have been developed including those blocking IL-17A (Ixekizumab, Secukinumab, and Netakimab), the IL-17 receptor A subunit (brodalumab and KHK4827), IL-23p19 (Guselkumab, Risankizumab, Tildrakizumab, Mirikizumab, and Brazi-kumab), or IL-23p40 (Ustekinumab) [37, 69, 70] (Fig. 1). Despite the success of these biologics targeting individual cytokines or cytokine receptors (Table 1), bispecific antibodies targeting two cytokines with nonoverlapping proinflammatory roles present an attractive opportunity. COVA 322 and ABT-122, two bispecific antibodies targeting both TNF-α and IL-17A, are currently being tested in clinical studies in patients with rheumatoid arthritis and the results appear encouraging [71, 72] (Fig. 1). Besides the synergism with TNF-α, IL-17A effects could also be potentiated by IL-17F, which displays 50% sequence homology and signals through the same receptor [73]. Related trials with different antibodies synergistically targeting two isoforms of IL-17 (Bimekizumab, ALX-0761 and NI-1401) (Fig. 1) are ongoing [73–75].

Understanding of the IL-23/IL-17 axis-mediated signal cascades advances the search for additional targets for inflammatory rheumatic diseases. Although this axis shares many signaling molecules with other inflammatory pathways like IL-1R and TLR-mediated pathways, there are also distinct molecules which are specific and could represent novel treatment targets [13, 76, 77]. Similarly, deciphering the epigenetics and transcriptional requirements of Th17 cell development also will help identify novel therapeutic candidates [78, 79]. Indeed, small molecules which directly disrupt IL-23 signaling and modulate Th17 linage stability by targeting JAK2 and TYK2-dependent STAT3 activation, displayed impressive efficacy in preclinical disease models [80–83] (Fig. 1). Moreover, functional suppression by targeting downstream signaling molecules (JAK1 and JAK3) of proinflammatory cytokines produced by Th17 (IL-22, IL-21, and GM-CSF) also affords tremendous therapeutical values [81, 82]. Although until now, only limited numbers of JAK inhibitors have been approved for the treatment of rheumatic diseases [84–87] (Table 1), it is

just a matter of time that these new therapeutic reagents will be shown to improve the life quality of patients with various autoimmune diseases, including AS, lupus, psoriasis, and other skin diseases such as atopic dermatitis.

Clinical Trial Data

Psoriasis and Psoriatic Arthritis

Psoriasis is a complex inflammatory skin disease typified by the presence of large, erythematous, scaly plaques [18, 88, 89]. Histology examination frequently reveals the presence of T lymphocyte infiltrates under the cutaneous lesions [90]. Around 30% of patients with psoriasis develop PsA, characterized by inflammation-mediated progressive damage of the peripheral joints, spine, and the entheses [91–95]. Common DMARDs including methotrexate, leflunomide, sulfasalazine, and the more recently included anti-TNF-α biologic agents have significantly slowed down the disease progression and relieved the symptoms [96–99]. However, a considerable proportion of patients do not adequately respond to currently approved therapies; therefore, there is need for the development of novel therapies [96, 100].

Genetic, mechanistic, and clinical data support the concept that activation of IL-23–IL-17 axis contributes to the development of psoriasis and PsA [91, 101–105]. First, genome-wide association studies revealed the association of single-nucleotide polymorphisms (SNPs) mapping to *Il12b*, *Il23a*, *Il17a*, and *Il17ra* genes with susceptibility to psoriasis and PsA [60, 106, 107]. A current pathogenic model of psoriasis depicted that the inflammation started with the activation of IL-23-producing dermal dendritic cells [108–110], which in turn activates Th17 cells which release key cytokines including IL-17 and TNF-a [111]. These cytokines act on epidermal keratinocytes and lead to observed tissue lesions [112–116]. Of note, overexpression of IL-17 in mice leads to epidermal hyperplasia and bone destruction which are often observed in humans with psoriasis and PsA [113]. The occurrence of both psoriasis and PsA and the presence of Th17 cells in psoriatic synovium [68, 91, 117] lead to the hypothesis for similar immune responses in synovial tissues although it remains unknown whether there were specific autoantigens shared between the joint and the skin. Furthermore, the assessment of the expression of IL-23, IL-17, and their related receptors in psoriatic skin lesions and inflamed synovium did confirm significantly increased expression of these molecules and their positive correlation with disease severity, which strongly suggests the pivotal role of IL-23/IL-17 axis [91, 103].

The above findings have led to a substantial increase of testing novel IL-17 and IL-23 antagonists in people with psoriasis and PsA. Recently, different highly effective therapies that disrupt interleukin-17 (Secukinumab, Ixekizumab, and Brodalumab) and interleukin-23 (Ustekinumab and Guselkumab) signaling has been approved by FDA for both psoriasis and PsA management [26, 91, 118–124]. Another two agents targeting IL-23 (Risankizumab and Tildrakizumab) have been approved for psoriasis while the clinical trials for PsA are still ongoing [125]. These new biologic therapies have proven to be highly effective and result in significant improvements in approximately 70–90% psoriasis or PsA patients with excellent safety profiles [91, 126]. The unprecedented success of these antagonists validated the essential role of this inflammatory axis in driving chronic inflammation. The reported

common adverse events include headache, upper respiratory tract infection, nasopharyngitis, arthralgias, and infections; however, the safety profiles are still comparable with more classical biologics like etanercept [91, 124, 127]. It should be noted that unlike anti-TNFα reagents which deliver comparable rates of amelioration on both skin and joint pathology, the selective blockade of IL-23/IL-17 axis is more effective in treating psoriatic skin over psoriatic joints. These differential responses bespeak to the complexity of involved processes in the development of psoriatic diseases [91].

The JAK/STAT pathway is well linked to the IL-23/−17 axis [13, 128], for example, IL-23 acts through JAK2-TYK2/STAT3-STAT4 pathway and IL-22 [13, 38, 129], an important cytokine produced by Th17 cells, acts through the JAK1/TYK2/STAT1-STAT3 pathway [129]. The first generation of JAK inhibitors includes Tofacitinib, Baricitinib, Ruxolitinib, and Oclacitinib [128]. Although most of them have demonstrated efficacy in the treatment of plaque psoriasis, the long-term safety data require further evaluation considering their limited selectivity [130, 131]. Until now, the risk for serious adverse events appears comparable with that of approved biologic agents [130, 131]. Following the approval of Tofacitinib, the most extensively studied JAK inhibitor, for the treatment of patients with active psoriatic arthritis [132, 133], the development of the second generation of JAK inhibitors with improved selectivity including Peficitinib, Filgotinib, Upadacitinib, and Lestaurtinib has been undertaken seeking better efficacy and safety [81, 134]. In addition, a selective inhibitor of TYK2 (BMS-98616) also showed positive results in a phase II study of people with psoriasis [135].

Recent emerging data suggest that the simultaneous inhibition of two inflammatory cytokines with nonoverlapping functions may provide better efficacy [136]. Specifically, TNF-α and IL-17A, two mediators in the psoriatic pathogenic process, act synergistically on keratinocytes for the induction of key genes involved in inflammation and pathogenesis [15]. Along this line, a few bispecific agents have been designed and clinical trials are ongoing although the safety profile remains a concern particularly the risk of increased rates of infections [137].

Rheumatoid Arthritis

In 1999, Miossec and co-workers demonstrated the presence of IL-17A in synovial tissues from patients with rheumatoid arthritis which first indicated the potential inflammatory role of IL-17A in rheumatoid arthritis [15, 138, 139]. This concept was rapidly supported by numerous studies using various murine models [140]. Subsequently, mice lacking IL-23p19 but not IL-12p35 were shown to be resistant to collagen-induced arthritis due to the absence of IL-17-producing CD4 T cells [42]. After the establishment of Th17 lineage in 2005 [11, 12], several studies documented the increased presence of IL-23, IL-17, Th17 cells, and other IL-23R-expressing cells in the circulation or inflamed joints of people with RA patients which correlated positively with disease activity or joint damage [13, 141–143]. In addition, data from different groups affirmed that IL-17A enhanced osteoclastogenesis and angiogenesis by acting locally on synoviocytes and osteoblasts which lead to synovitis and joint destruction [48]. Of note, IL-23/IL-17 axis has also been reported essential in the control of antibody glycosylation profiles which determine autoantibody activities [144]

(Fig. 2). Together, all evidence has emphasized that IL-23/IL-17 axis should be considered for the development of targeted therapies to treat people with RA [145, 146].

Several clinical trials which aimed to evaluate the therapeutic values of blocking IL-23 or IL-17 in RA have now been completed [140]. However, only poor or moderate efficacy was observed. For example, clinical trials with Secukinumab in biological-naive RA patients or patients with inadequate response to methotrexate or anti-TNFð showed that while there was clinical efficacy of IL-17A blockade, the effect, as judged by ACR20 response, was relatively modest [140]. Studies have also investigated IL-17RA blockade using Brodalumab, and similarly, the trial did not meet the set efficacy endpoints [147]. Consistently, treatment with Ustekinumab or Guselkumab did not significantly reduce the signs and symptoms in patients with RA as well [31].

These results bring out the question why blockade of IL-23/IL-17 axis did not deliver therapeutic value in RA. There are different possibilities. First, RA is a heterogeneous disease and IL-23/IL-17 axis may not be the dominant player for every patient, which is supported by the observation that not all patients display high IL-17A levels or Th17 cell frequencies [148]. It has been shown that IL-17A expression in the joint correlates with serum CRP levels, and interestingly, one Secukinumab trial reported better responses in patients with elevated CRP levels. It would be intriguing to identify the patient subgroups which may respond better to IL-17 or IL-23 blocking biologics. Of note, IL-23 is not required for early Th17 development although it is strictly necessary for late stage IL-17A production [57]. Beside IL-17A, Th17s produce a variety of other inflammatory factors including IL-17F, IL-21, IL-22, and GM-CSF [14, 149, 150], which provide additional explanation for the poor efficacy of current therapies targeting IL-23 or IL-17 alone in RA [151]. Notably, a recent phase II study with Bimekizumab (dual blockade of IL-17A and IL-17F) in RA patients with an inadequate response to anti-TNF showed great therapeutic efficacy [152]. In addition, the synergistic effects of IL-17 with other inflammatory cytokines need attention, for example, IL-17A potentiates the effects of TNFα [9, 15, 153]. More recently, simultaneous blockade of IL-17A and TNF is under investigation using ABT-122, a bispecific antibody which targets both TNF and IL-17A [154].

In contrast to antibody-based therapies, indirect blocking of cytokine production by targeting JAKs offers additional approaches for the management of patients with RA [155]. There are three JAK inhibitors currently approved for the treatment of people with active RA (Tofacitinib, Baricitinib, and Upadacitinib) after demonstrating great efficacy in extensive clinical trials [85]. All agents efficiently inhibit structural damage progression [156]. In clinical practice, JAK inhibitors are increasingly being used after classical DMARD failure [85, 156, 157].

Axial Spondyloarthritis

Axial spondyloarthritis (AS) is a chronic inflammatory disease that affects primarily the spine and the sacroiliac joints [5, 158]. Genetic and epigenetic fine mapping studies have provided evidence for a close relationship between AS and PsA. For example, an association with the IL23R locus exists in PsA and AS [22]. In addition, the integrated genomics

approach further explored the involvement of genes of the IL-23/IL-17 axis in the pathogenesis of AS [22, 24, 63].

In addition to the genetic evidence, experimental data have also linked the IL-23/IL-17 axis to AS [159]. First, intracellular misfolded HLA-B27, a molecule strongly associated with AS, stimulates the IL-23–IL-17 pathway in vitro [160]. Second, overexpression of IL-23 in mice induces enthesitis and peripheral arthritis which resembles human AS [44]. In this model, IL-23 responding T cells reside in entheseal sites, produce IL-17, and initiate local tissue damage [161]. Moreover, the effects of these two cytokines on osteoclasts and on bone resorption suggest that they might have a catabolic effect on the bone [45, 113, 159, 162]. Of note, in contrast to IL-17, IL-23 did not have any effect on the proliferation and differentiation of osteoblasts, which may explain the discrepancy between individual IL-17 and IL-23 blockade in AS trials [159].

Antibodies targeting IL-17 including Secukinumab, Ixekizumab, Bimekizumab, and Netakimab did show superiority in improving AS over placebo in clinical trials [35, 36, 163, 164]. Surprisingly, in contrast to the positive results of IL-17 inhibitors, the clinical trial results of two IL-23 blocking antibodies Ustekinumab and Risankizumab were clearly negative [34, 165]. Although it cannot be completely excluded that higher doses of Ustekinumab or Risankizumab may be more efficient in reaching the inflamed tissues and provide therapeutical values, the data from psoriasis and PsA clinical trials with different doses did not support this speculation [37]. The data achieved from other inflammatory rheumatic diseases shows a tight connection between IL-23 and IL-17 [13, 38] and the results of either IL-17 or IL-23 inhibition are somewhat similar [14, 68, 91]. Therefore, it is surprising to see the discrepancy of IL-17 and IL-23 blockade in AS clinical trials. A number of considerations have been verbalized to explain this divergence. First, there is a variety of immune cells other than Th17s which can produce IL-17, and especially IL-17F independent of IL-23 [166, 167]. Second, there are many types of cells including B cells and epithelial cells, which can respond to IL-23 without producing IL-17 [144, 168]. Last but not least, the temporal difference between IL-17-mediated and IL-23-mediated process may lead to the observed discrepancy, for example, IL-23 may contribute more to disease initiation but not to progression in patients with AS [159]. However, further studies are needed to explore the details of the underlining molecular and cellular mechanisms.

Notably, two JAK inhibitors, Tofacitinib (JAK1 and JAK3) and Filgotinib (a selective inhibitor for JAK1), significantly reduced the signs and symptoms in clinical trials in AS although the exact mechanisms whereby they regulate AS needs to be further explored [169, 170].

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a clinically heterogeneous autoimmune disease characterized by a loss of self-tolerance with the development of autoantibodies against a multitude of self-antigens [1, 171]. There is sufficient evidence that IL-23 and IL-17 are involved in the pathogenesis of SLE [59, 70, 172–174]. Increased frequency of IL-17-producing CD4 T cells and double negative (DN) TCRδβ^{-}CD4^{-}CD8^{-} T cells were observed in peripheral blood of SLE patients and these cells infiltrated inflamed tissues including the

skin and the kidney [59, 175, 176]. Accordingly, the circulating IL-23 and IL-17 levels are elevated in SLE patients and correlate positively with disease severity [59, 70, 177–180].

Data from animal models have provided insights on the cellular and molecular mechanisms which underlie SLE development. *Il23* deficiency in lupus-prone mice significantly ameliorates disease followed by a dramatic reduction of IL-17-producing T cells including Th17s and DN T cells [181, 182]. Consistently, IL-23 overexpression in vivo exaggerates disease progression by promoting expansion of Th17s and DN T cells [183] (Fig. 2). However, the results from IL-17 signaling deficiency in different murine lupus models are paradoxical. In BXD2 mice, IL-23-dependent Th17 cells promote autoantibody production by producing IL-17 which in turn regulates B cell migration inside germinal center area for more rounds of somatic hypermutation [55, 184] (Fig. 2). This concept was subsequently validated by in vivo adoptive transfer of Th17 cells [54]. However, *Il17a* deficiency in MRL.*lpr* mice has minimal effects on the course of nephritis [185]. The distinct cellular and molecular mechanisms for disease progression in different murine models may explain the reported discrepancy [186]. Together, the experimental evidence leads to the speculation that IL-23 and IL-17 producing T cells somewhat orchestrate the dysregulated immune responses in lupus.

In theory, all antibodies targeting IL-23/IL-17 axis which have been approved for the management of other inflammatory rheumatic diseases could be tested in patients with SLE. It is disappointing that the phase 3 clinical trial of Ustekinumab in SLE was discontinued due to lack of expected efficacy following planned futility analysis although the phase 2 results were promising [187]. In addition, Barcitinib, an inhibitor for both JAK1 and JAK2, improved significantly the symptoms in patients with active SLE in a phase 2 trial [188, 189] while the phase 3 trial is ongoing.

Currently, SLE treatment faces big challenges since the results of most trials have been disappointing [190]. Considering the high clinical heterogeneity of SLE [191–193], it becomes self-evident that there is need to administer biologics targeting processes which are responsible for the expression of the disease in defined subsets of patients. The need for personalized treatment in patients with SLE cannot be overemphasized. Along this line, three different trials will be conducted in people with discoid lupus erythematosus (Secukinumab, NCT03866317) and patients with active lupus nephritis (Secukinumab, NCT04181762; Guselkumab, NCT04376827) (Table 2).

Conclusion

After the establishment of pathogenic role of IL-23/IL-17 axis in different autoimmune and inflammatory diseases [9, 38], diligent work by many groups of researchers, clinicians, and industry colleagues has opened a new era for treatment opportunities for people who suffer from inflammatory rheumatic diseases. Although encouraging clinical results emerge, the overall outcome remains complex [14, 37]. The agents targeting IL-23/IL-17 generally work impressively well in psoriasis and even surpass the effect of anti-TNF therapy but they display only moderate therapeutic efficacy for people with PsA [68, 91]. Moreover, most of these IL-23/IL17 directed biologics have delivered negative results in the management of

RA despite the fact that strong experimental evidence had demonstrated the involvement of this axis in the pathogenesis of RA [15, 48, 50, 140]. Last but not least, even though IL-17 inhibitors have been proven quite effective, IL-23 blocking agents have not shown therapeutic value in the treatment of patients with AS [37]. Despite the advances made in the above discussed diseases, little is known about the role of this axis in other rheumatic diseases including Sjogren's syndrome, vasculitis, and gout.

Given the evidence that IL-23 and IL-17 have complex roles in the development of inflammation in diverse patients with rheumatic diseases [13], the discrepancy of therapeutic values by targeting IL-23/IL-17 axis in different rheumatic diseases [49, 140, 159], the inconsistent clinical outcomes by targeting IL-17 vs targeting IL-23 in the same disease setting, and the diverse response to IL-23/IL-17 axis targeted therapies in patients with the same rheumatic disease (responders vs non-responders) [15, 37, 49, 50], research should be directed towards the identification of subsets of patients with any of these diseases who have better chance of responding to a targeted therapy. The sharing of genetic susceptibility and cellular/molecular pathogenic processes by various rheumatic diseases demands an advanced reclassification of diseases apart from the established clinical nosology. It is obvious that the cellular and molecular processes that we have identified as contributors of the expression of rheumatic diseases are interconnected logically and represent in some ways a "house of cards" whereby removal of any of them results in clinical benefits in certain patients. The efforts to develop biologics to tackle two molecules using a hybrid biologic [194] or administer two biologics simultaneously may represent a promising path to take. Exciting prospects are offered but the use of small molecule inhibitors of intracellular kinases essential for the signal transduction downstream of the engagement of cytokines with their cognate receptors. The opportunity to use these drugs orally represents great advantage to physicians and patients alike. Yet, a simple inspection of any of the diagrams which depict various cytokine-kinase signal cascades reveals the fact that many of them are used interchangeably [195–197]. This is confounded further by the fact that small drug inhibitors are almost never specific. Also, the same kinases are present and are of functional importance in non-immune cells and therefore the short- and long-term side effects should be considered and hopefully can be lessened by carefully titrating the administered dose.

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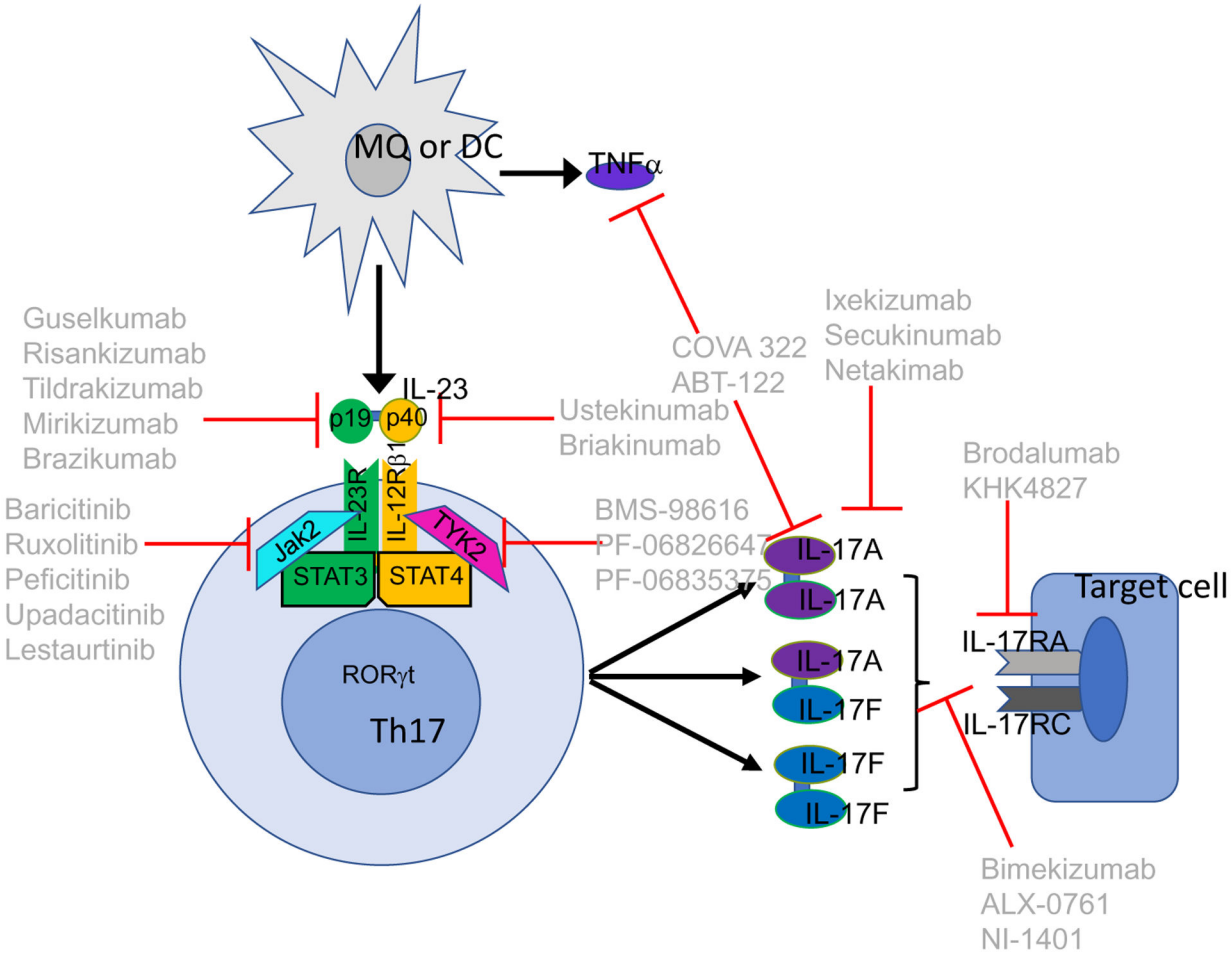

Fig. 1.

Biologics targeting IL-23/IL-17 axis in rheumatic diseases. Specific blocking antibodies and small molecules targeting IL-23/IL-17 axis which are currently used in clinical practice or still under development are depicted (MQ: macrophages; DC: dendritic cells)

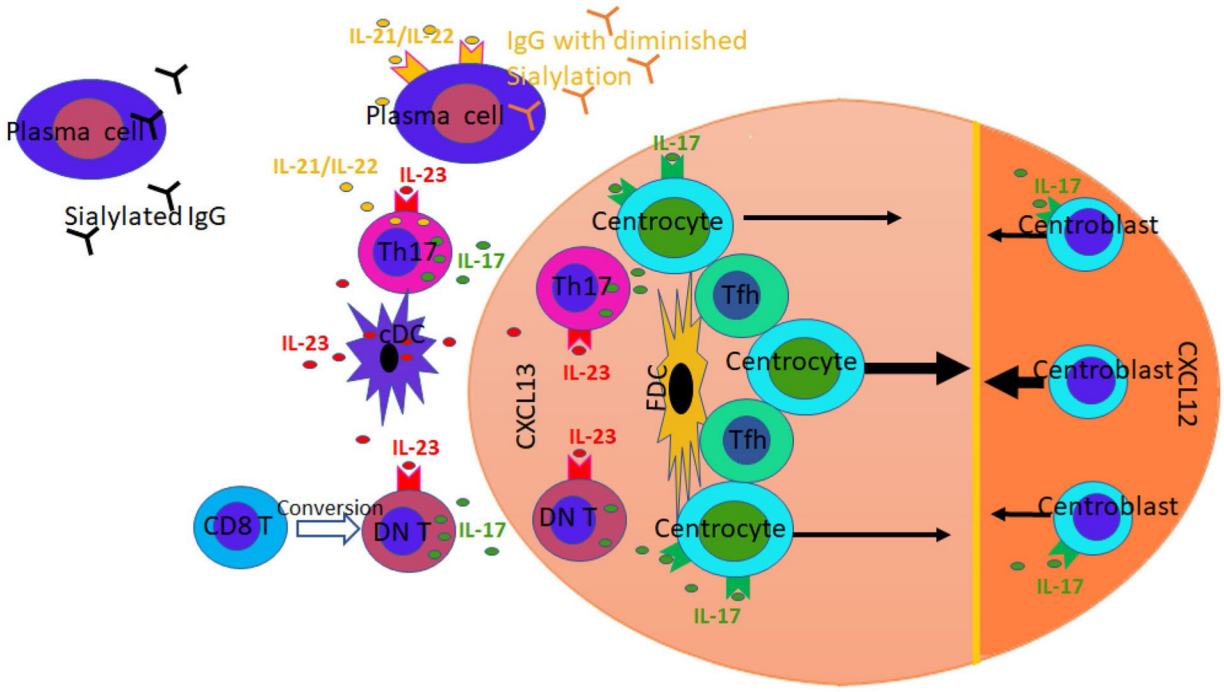

Fig. 2.

IL-23/IL-17 axis contributes to autoantibody-driven diseases. B cells migrate between the dark and light zones of the germinal centers (GCs), a process mediated by CXCL12/CXCR4 and CXCL13/CXCR5, to undergo somatic hypermutation, clonal expansion, and affinity-based selection. Exposure to IL-17 reduces their migration which results in more rounds of somatic hypermutation and the production of IgG with increased affinity. Plasma cells emigrating from GCs produce autoantibodies. IL-23-activated T_H17 cells suppress *St6gal1* expression in antibody-producing cells via IL-21 and IL-22, which results in changes in the glycosylation profile as well as increased inflammatory activity of IgG (cDC: classical dendritic cells; FDC: follicular dendritic cells)

Table 1

Biologics and small molecule drugs targeting the IL-23/IL-17 axis approved by FDA to treat patients with rheumatic diseases

Medication	Target	Indication
Secukinumab (Novartis)	IL-17A	Plaque psoriasis Psoriatic arthritis Ankvlosing spondylitis
lxekizumab (Lilly)	IL-17A	Plaque psoriasis Psoriatic arthritis Psoriatic arthritis
Brodalumab (AstraZeneca)	IL-17RA	Plaque psoriasis
Ustekinumab (Janssen)	IL-12 and IL-23	Plaque psoriasis Psoriatic arthritis
Guselkumab (Janssen)	IL-23	Plaque psoriasis Psoriatic arthritis
Risankizumab (AbbVie)	IL-23	Plaque psoriasis
Tildrakizumab (Sun Pharmaceuticals)	IL-23	Plaque psoriasis
Tofacitinib (Novartis)	JAK.l, JAK3 and a lesser degree JAK2	Psoriatic arthritis Rheumatoid arthritis
Baricitinib (Eli Lilly)	JAK1 and JAK2	Rheumatoid arthritis
Upadacitinib (AbbVie)	JAK1	Rheumatoid arthritis

Table 2

Biologics and small molecule drugs in clinical trials targeting the IL-23/IL-17 axis in SLE patients

Medication	Target	Indication	Phase	Trial identifier
Guselkumab	IL-23	Lupus nephritis	Phase 1/2	NCT04376827
Ustekinumab	IL-12 and IL-23	Systemic lupus erythematosus	Phase 3	NCT04060888
Secukinumab	IL-17A	Lupus nephritis	Phase 3	NCT04181762
		Discoid lupus erythematosus	Phase 2	NCT03866317
PF-06835375	TYK2	Systemic lupus erythematosus	Phase 1	NCT03334851
Baricitinib	JAK 1 and JAK2	Systemic lupus erythematosus	Phase 3	NCT03843125