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REVIEW

The role of IL-23 receptor signaling in inflammation-mediated erosive autoimmune arthritis and bone remodeling

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The IL-23/Th17 axis has been implicated in the development of autoimmune diseases, such as rheumatoid arthritis (RA) and psoriatic arthritis (PsA). RA and PsA are heterogeneous diseases with substantial burden on patients. Increasing evidence suggests that the IL-23 signaling pathway may be involved in the development of autoimmunity and erosive joint damage. IL-23 can act either directly or indirectly on bone forming osteoblasts as well as on bone resorbing osteoclasts. As IL-23 regulates the activity of cells of the bone, it is conceivable that in addition to inflammation-mediated joint erosion, IL-23 may play a role in physiological bone remodeling. In this review, we focus on the role of IL-23 in autoimmune arthritis in patients and murine models, and provide an overview of IL-23 producing and responding cells in autoimmune arthritic joints. In addition, we discuss the role of IL-23 on bone forming osteoblasts and bone resorbing osteoclasts regarding inflammation-mediated joint damage and bone remodeling. At last, we briefly discuss the clinical implications of targeting this pathway for joint damage and systemic bone loss in autoimmune arthritis.

Keywords: Auto-immune arthritis · IL-23 · Joint damage · Osteoblasts · Osteoclasts

Introduction

Interleukin-23 (IL-23), a member of the IL-12 cytokine family, is a heterodimeric cytokine, which consists of an IL-12p40 subunit, shared with IL-12, and an IL-23 specific p19 subunit [1]. The receptor for IL-23 consists of IL-23Rα in complex with IL-12Rβ1, which also serves as a subunit for the IL-12 receptor [2]. Although structurally similar to IL-12, IL-23 has the unique ability of amplifying and stabilizing the proliferation of IL-17 secreting T helper-17 (Th17) cells [3]. In fact, exposure of Th17 cells to IL-23 drives their pathogenic phenotype [4, 5]. These pathogenic Th17 cells are characterized by their master regulator RORγt and production of pro-inflammatory cytokines such as IL-17A, IL-17F, IL-22, GM-CSF and are able to promote their lineage commitment through autocrine IL-21 production [6, 7]. Furthermore, these cells express the chemokine receptor CCR6, which enables them to migrate toward sites of inflammation in response to the chemokine CCL20 [8, 9].

In recent years, it has become clear that the IL-23/Th17 pathway plays a crucial role in many inflammatory autoimmune diseases including psoriasis, psoriatic arthritis (PsA), rheumatoid arthritis (RA) and systemic lupus erythematosus [10–12]. Both RA and PsA are disorders with distinct clinical phenotypes,

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Table 1. An overview of studies on IL-23R polymorphisms in RA

IL-23R SNP	Association with RA	Study population	Number of patients	Number of controls	Study reference
rs1004819	No	Spanish	322	342	Orozco et al. [26]
	No	Korean	1204	979	Park et al. [19]
	No	New Zealand	855	557	Hollis-Moffatt et al. [27]
rs7517847	No	Spanish	322	342	Orozco et al. [26]
	No	Korean	1204	979	Park et al. [19]
	No	New Zealand	855	557	Hollis-Moffatt et al. [27]
rs10489629	No	Spanish	322	342	Orozco et al. [26]
	No	Korean	1204	979	Park et al. [19]
	No	New Zealand	855	557	Hollis-Moffatt et al. [27]
	No	Algerian	343	323	Louahchi et al. [20]
rs11209026	No	Spanish	322	342	Orozco et al. [26]
	No	New Zealand	855	557	Hollis-Moffatt et al. [27]
	No	North American	1136	1797	Chang et al. [21]
	No	Dutch	596	705	Chang et al. [21]
	Yes	Egyptian	120	120	Hamdy et al. [22]
	No	Polish	89	125	Bogunia-Kubik et al. [25]
	No	Algerian	343	323	Louahchi et al. [20]
rs1343151	No	Spanish	322	342	Orozco et al. [26]
	No	Korean	1204	979	Park et al. [19]
	No	New Zealand	855	557	Hollis-Moffatt et al. [27]
	No	Algerian	343	323	Louahchi et al. [20]
rs10889677	No	Spanish	322	342	Orozco et al. [26]
	Yes	Hungarian	412	220	Faragó et al. [23]
	Yes	Brazilian	127	134	Da Silva et al. [24]
	No	Egyptian	120	120	Hamdy et al. [22]
rs11209032	No	Spanish	322	342	Orozco et al. [26]
	No	Korean	1204	979	Park et al. [19]
rs1495965	No	Spanish	322	342	Orozco et al. [26]
	No	Korean	1204	979	Park et al. [19]
rs2201841	No	Korean	1204	979	Park et al. [19]
	No	New Zealand	855	557	Hollis-Moffatt et al. [27]
	Yes	Hungarian	412	220	Faragó et al. [23]
	No	Egyptian	120	120	Hamdy et al. [22]
rs7530511	No	North American	1136	1797	Chang et al. [21]
	No	Dutch	596	705	Chang et al. [21]
rs1884444	No	Hungarian	412	220	Faragó et al. [23]

Meta-analyses are not included.

resulting from complex interactions between genetic and environmental factors such as smoking or infections. Although there are some similarities between RA and PsA including the occurrence of erosive joint inflammation and systemic bone loss, there are also important differences [13]. For instance, PsA displays features of spondyloarthropathy such as new bone formation and enthesitis, while RA does not. Furthermore, both diseases affect different anatomical joints and in addition to the joint, PsA targets the skin, eyes and the spine [13].

Another difference is the occurrence of autoantibodies such as rheumatoid factor and anti-citrullinated protein antibodies (ACPAs), which are specific to RA, but not to PsA. Although the IL-23 signaling pathway is implicated in both RA and PsA, its involvement in the pathogenesis of these disorders may be diverse as demonstrated by clinical studies where targeting IL-23 has different outcomes [14, 15]. In PsA, treatment with anti-IL-23 antibodies have shown beneficial effects but not in RA so far. Another finding supporting this hypothesis, is the notion that polymorphisms in the IL-23 receptor (IL-23R) have been linked to susceptibility for psoriasis and PsA [16–18], but are still a matter of debate in RA (Table 1) [19–27].

In this review, we focus on the role of IL-23 in the development of autoimmune arthritis and give an outline of IL-23 producing and responding cells in arthritic joints. In addition, we review on the role of IL-23 on bone forming and bone resorbing cells in relation to erosive joint damage and bone remodeling. At last, we discuss the implications of targeting the IL-23 signaling pathway for joint damage and systemic bone loss.

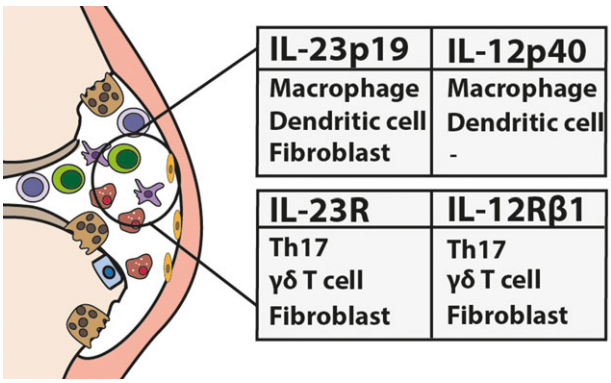

Figure 1. An overview of the reported immune cells in the RA or PsA joints which express IL-23 or IL-23R subunits. Both IL-23 subunits (p19 and p40) are expressed by macrophages and dendritic cells, while fibroblasts express only the p19-subunit of IL-23. Expression of both subunits for the IL-23R is found so far on synovial Th17 cells, γδ T cells, and fibroblasts.

IL-23 signaling pathway

The biologically active IL-23 is composed of IL-23p19 linked through a disulphide-bond to IL-12p40 and signals through the IL-23R in complex with IL-12Rβ1 [1, 2]. IL-23R associates constitutively with Janus Kinase 2 (JAK2) and IL-12Rβ1 interacts with Tyrosine kinase 2 (Tyk2) [2]. In a ligand dependent manner, IL-23R associates with STAT3, resulting in STAT3 phosphorylation and activation [2, 28]. Activated STAT3 homodimerizes and translocates into the nucleus and induces expression of the transcription factor RORγt which can activate transcription of downstream cytokines such as IL-17A, IL-17F, IL-22, Csf2 [29]. In addition to these pro-inflammatory cytokines, the chemokine receptor CCR6, often used as an identification marker for Th17 cells [8], and its ligand CCL20 are downstream of the IL-23 pathway [30]. Interestingly, the IL-23R is another downstream target of the IL-23 pathway, resulting in a positive feedback loop and further promoting the pathogenic activity of this pathway [31].

IL-23 producing and responding cells in autoimmune arthritic joints

Both RA and PsA are characterized by synovitis due to infiltration of immune cells including T cells, B cells, dendritic cells, monocytes, macrophages and hyper-proliferation of synovial fibroblasts. These cells interact via direct cell-cell contact and/or by secretion of inflammatory cytokines including IL-23 in the joint (Fig. 1). The IL-23p19 protein is abundantly present in RA synovial fibroblasts [32, 33]. However, these cells do not express functional IL-23. This was demonstrated by the finding that heterodimeric IL-23 protein is not detected in co-cultures of human Th17 cells with RA synovial fibroblasts and neutralizing IL-23 has no effect on IL-17 or IL-6 levels in these co-cultures [34]. On the other hand, dendritic cells are a source of IL-23 in the joint as RA synovial dendritic cells co-express both p19 and p40 subunits [33]. This is in line with another study which demonstrated that $CD1c^+$ myeloid dendritic cells (mDCs) were abundantly present in synovial fluid from RA patients and produce IL-23, IL-12, IL-33 and IL-1β in vitro [35]. Other producers of IL-23 are synovial macrophages as the expression of functional IL-23 by RA synovial macrophages is induced upon TLR2 stimulation in vitro [32, 36].

In addition to IL-23 producing cells, the presence of IL-23 responding cells in the joints of autoimmune arthritis patients is reported (Fig. 1). RA synovial fibroblasts express IL-23R as they respond to IL-23 by increasing their receptor activator of NF-κB ligand (RANKL) expression [37]. Furthermore, $CCR6^+$ Mucosal associated invariant T cells (MAIT cells) have been detected in the synovial fluid of RA patients [38]. However, it remains to be elucidated whether these cells express the IL-23R. In addition, $IL\text{-}23R^+$ Th17 cells are detected in PsA synovial fluid [39, 40] and $IFNy^+$, $IL\text{-}17^+$ γδ T cells are found enriched in the synovial fluid compared to peripheral blood [41].

Inflammation and ossification of the entheseal tissue (the region where tendon fibers or ligaments attach to the bone) is characteristic for PsA. In a mouse model of spondyloarthritis (SpA), IL-23 has been reported to be involved in the induction of entheseal inflammation through its actions on enthesis-resident $IL\text{-}23R^+CD3^+CD4^-CD8^-$ lymphocytes [42]. These cells are possibly tissue-resident $IL\text{-}23R^+$ γδ T cells and have been shown to accumulate at inflammatory sites and to be the main IL-17-producing cells in the enthesis of mice [43].

IL-23: a major player in early autoimmune arthritis

Serum levels of IL-23 are increased in both RA and PsA patients and correlate with their disease activity [44, 45]. Furthermore, IL-23 and IL-17A producing cells are present in autoimmune arthritic synovium [33, 46–49], while IL-17 producing γδ T cells are elevated in the skin of PsA patients. In the skin, secretion of IL-17 and IL-22 promotes keratinocyte differentiation and hyperproliferation which results in aggravation of psoriasis [50]. In addition to induction of synovitis and psoriasis, animal studies have suggested a role for IL-23 in supporting the development of enthesitis [42, 51].

Experimental models have played a pivotal role in investigating the role of IL-23 in arthritis [52]. In vivo overexpression of IL-23 results in systemic inflammation and chronic arthritis [53], while depletion of this cytokine completely protects mice from arthritis in the collagen-induced arthritis (CIA) model [54]. In this model, IL-23 is required for the development of pathogenic Th17 cells [54]. This indicates that IL-23 is crucial for the development of CIA. However, after onset of arthritis the requirement for IL-23 is limited. This was demonstrated by the finding that IL-23 inhibition did not prevent full-blown disease after onset of CIA [55]. The mechanism behind the IL-23-mediated induction of autoimmunity was reported in a recent study, which demonstrated that IL-23 is essential for CIA onset through the reduction of sialylation in autoantibodies [56]. IL-23 can thereby control the inflammatory

activity of autoantibodies. Autoantibody sialylation is reduced by cytokines of Th17 cells, IL-21 and IL-22, which may act on plasma cells. Previous studies demonstrated that IL-23 is required for the induction of IL-22 in Th17 cells [57]. In line with this, a role for IL-22 in the regulation of autoantibody formation has been reported showing less severe CIA in IL-22$^{-/-}$ mice with decreased serum autoantibody titers, germinal centers and germinal center B cell numbers [58]. Interestingly, reduced sialylation of antibodies is also detected in asymptomatic ACPA^{+} individuals who developed RA within 12 months compared to those who did not develop RA within this period [56].

These findings suggest that IL-23 is essential in disease onset through generation of pathogenic Th17 cells including Th17 cytokines, which are involved in regulation of autoantibody producing cells. In this context, IL-23 may be a driver of RA onset by mediating a shift toward a pro-inflammatory antibody repertoire.

In RA, relapses often occur in patients who have achieved remission [59]. With the antigen-induced arthritis model, arthritic flares can be mimicked. Interestingly, in the antigen-induced arthritis (AIA) model, blockade of IL-23 reduced disease severity after T-cell-mediated arthritic flare [55]. The mechanism behind this is not fully understood. However, relapses occur as a consequence of memory T cell reactivation and may resemble early disease onset which is driven by pathogenic Th17 cells downstream of IL-23 [60]. This suggests that in addition to autoimmune arthritis development, IL-23 may be important for driving disease relapses.

IL-23, osteoclasts, and bone loss

Juxta-articular bone damage around inflamed joints starts during the early phases of RA and is a radiological characteristic of autoimmune arthritis. In fact, the most progression in bone damage is detected during the first year of disease and bone erosions are associated with more severe disease course and increased disability [61]. Local and generalized bone loss during autoimmune arthritis may be accelerated as a result of increased pro-inflammatory cytokine production, such as IL-23, and potentially by autoantibodies including ACPAs, which contribute to increased formation of bone resorbing cells. Bone resorbing osteoclasts play a crucial role in the development and progression of bone loss and are directly or indirectly under the influence of the immune system [62, 63]. The finding that numerous osteoclasts are present in the inflamed synovium [64], suggests that both the precursor cells and the required stimulatory factors for osteoclast differentiation may also be present in the joint itself.

Both animal and human studies have demonstrated pro-osteoclastogenic roles for the IL-23 pathway. IL-23 induces the formation of pathogenic autoantibodies during the early development of CIA [56] and may thereby further promote bone erosion. Pathogenic APCAs are involved in bone loss as ACPA positivity correlates to reduced bone mineral density (BMD) in both the spine and the hip in early RA patients [65]. This may be explained by the notion that ACPAs directly activate osteoclasts by binding to

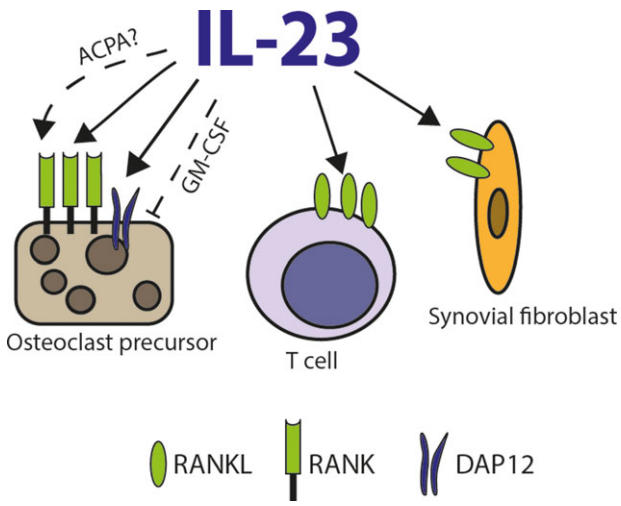

Figure 2. Schematic overview of the role of IL-23 on osteoclast formation. IL-23 can stimulate osteoclastogenesis in several ways: (i) increase of RANK expression on osteoclast precursor cells; (ii) increase of RANKL expression on T-helper cells or fibroblasts; (iii) activation of DAP12 ITAMs. IL-23 may also induce pathogenic ACPAs which can stimulate osteoclastogenesis. IL-23 indirectly inhibits osteoclasts through GM-CSF. Pointed arrows indicate stimulatory actions of IL-23 and blunt arrows show suppressive effects. Dashed lines indicate indirect effects of IL-23.

citrullinated vimentin, which is present on osteoclasts and their precursor cells [65–67].

Other indirect actions of IL-23 on osteoclasts are mediated through T cells, synovial fibroblasts and osteoclast precursor cells. Osteoclasts emerge from hematopoietic myeloid precursor cells and require RANK signaling for their differentiation. In this context, IL-23 stimulates osteoclastogenesis by enhancing RANK expression in osteoclast precursor cells [68] and RANKL on T cells and RA synovial fibroblasts (Fig. 2) [37, 69]. However, it should be noted that IL-23 has also been reported to reduce osteoclastogenesis via the induction of GM-CSF in murine T cells, which can inhibit osteoclast formation [70]. This indicates that although IL-23 has mainly pro-osteoclastogenic roles, it can also suppress osteoclast formation.

In addition to inducing the RANKL pathway, IL-23 acts on osteoclast precursors through activation of DNAX activating protein of 12kDa- (DAP12) ITAMs to stimulate osteoclast formation independent of RANKL [71]. Accordingly, bone marrow cells of IL-23p19$^{-/-}$ mice have reduced differentiating capacity toward osteoclasts and less dentine resorptive activity in vitro [53]. In line with the in vitro studies, overexpression of IL-23 leads to arthritis and systemic bone loss in mice [53, 72], whereas inflammation-mediated bone destruction is less pronounced with reduced osteoclast formation in mice lacking IL-17 or IL-23 [73–75].

Together these findings suggest that IL-23 has mainly pro-osteoclastogenic capacity via both RANKL/RANK dependent and independent pathways, thereby aggravating joint damage and systemic bone loss.

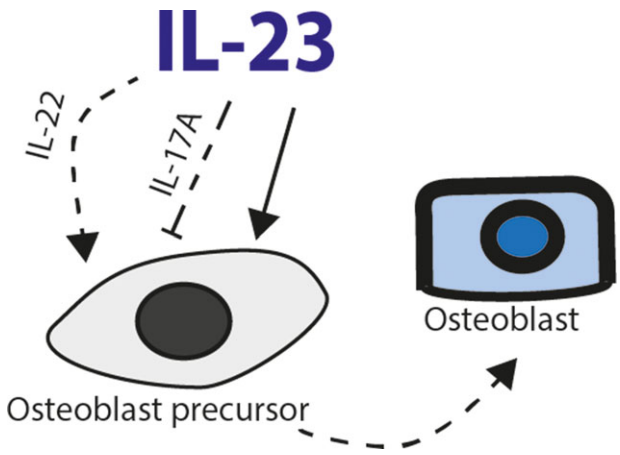

Figure 3. Schematic overview of the role of IL-23 on osteoblast precursor cells. IL-23 acts directly on osteoblast precursor cells to stimulate formation of osteoblasts. IL-23 can indirectly inhibit or stimulate osteoblast formation via IL-17 or IL-22 respectively. Pointed arrows indicate stimulatory actions of IL-23 and blunt arrows show suppressive effects. Dashed lines indicate indirect effects of IL-23.

IL-23, osteoblasts, and bone formation

A distinguishing feature between RA and PsA is the occurrence of new bone formation in the form of syndesmophytes (inside spinal ligament) and enthesophytes (at the attachment of tendons or ligaments to the bone) in PsA [76]. Although the role of IL-23 in osteoclasts has been studied extensively, studies on its role in bone forming osteoblasts are limited and report mainly indirect effects of IL-23 on these cells (Fig. 3). Messenger RNA expression of IL-23Rα subunit is found on murine osteoblasts, but no protein expression could be detected [77]. Supporting this, no effect of IL-23 stimulation on osteoblasts was shown and IL-23p19$^{-/-}$ osteoblasts were not functionally impaired in vitro [70]. Nevertheless, IL-23 can exert indirect effects on osteoblasts through downstream cytokines such as IL-17A or IL-22 [42, 78].

IL-17 can inhibit osteoblast formation by increasing antagonists of the Wnt/B-catenin pathway. This pathway promotes Runx2, which is the key transcription factor for osteoblast development. An antagonist of the Wnt pathway, secreted frizzled related protein 1 (sFRP1), is induced in differentiating osteoblasts upon in vitro IL-17A stimulation. This increase in sFPRP1 contributes to impaired osteoblast formation [78]. Accordingly, arthritic IL-17$^{-/-}$ mice develop increased periosteal bone formation [78]. In line with the experimental study, sFRP1 is increased in RA synovial fluid compared to osteoarthritis and correlates with increased synovial IL-17A [79]. Interestingly, in vitro stimulation of Th17 cells with sFRP1 results in increased IL-17A production and IL-23R expression. This suggests that there may be a positive feedback loop between IL-17 and sFRP1.

Another Wnt antagonist, Dickkopf-1 (DKK-1), is also induced by IL-17A together with TNFα in murine synovial fibroblasts [78]. DKK-1 is increased in RA joint compared to osteoarthritic joint and correlates with disease activity [80] and decreased BMD [81]. The findings of dysregulated expression of Wnt antagonists may also explain the absence of bone repair in RA joint.

In PsA patients, co-occurrence of joint erosion and new bone formation is often observed. Interestingly, serum DKK-1 levels are lower in PsA compared to RA and healthy controls, potentially contributing to new bone formation [82]. This also suggests that there may be a shift in the IL-17A/IL-22 balance in PsA compared to RA.

Another cytokine which acts on osteoblasts downstream of the IL-23 signaling pathway is IL-22. This cytokine is associated with bone formation and is found to be elevated in synovial fluid of PsA patients compared to patients with osteoarthritis. In this context, systemic overexpression of IL-23 leads to new entheseal bone formation and osteoblast expansion via upregulation of IL-22, which induces osteoblast-related genes in the enthesis. Similar to IL-23, overexpression of IL-22 leads to new periosteal bone formation through STAT3 activation and increased expression of genes that regulate bone formation, including the Wnt family members [42]. These findings are further supported by a recent study demonstrating that IL-22 stimulates human mesenchymal stem cell proliferation and migration and increases osteogenic genes such as ALPL and Runx2 [83]. Interestingly, IL-23 has also been reported to directly regulate osteoblast formation as its binding to the IL-23R on human mesenchymal stem cells leads to increased expression of osteoblast-related genes and formation of osteoblasts in vitro (Fig. 3) [84].

To summarize, IL-23 has pleiotropic roles on bone forming osteoblasts either by directly acting on the precursors of these cells or through induction of IL-17 and IL-22.

A role for IL-23 in physiological bone remodeling?

In healthy individuals, bone forming osteoblasts and bone resorbing osteoclasts maintain bone homeostasis through balanced activity. In vivo studies using IL-23p19$^{-/-}$ mice have reported contradictory findings about the role of IL-23 in bone homeostasis. Illustrating this, Sato et al. reported no bone abnormalities in 12 weeks old IL-17$^{-/-}$ and IL-23p19$^{-/-}$ mice [73]. In contrast, Quinn et al. did find bone defects in 12 and 26 weeks old IL-23p19$^{-/-}$ mice as shown by lower trabecular BMD [70]. Along this line, IL-23p19$^{-/-}$ mice had shorter femurs and histological analysis of the tibial growth plate region revealed that IL-23p19$^{-/-}$ mice had smaller hypertrophic zones. This is possibly due to increased resorption of the hypertrophic cartilage by osteoclasts. This increased activity of osteoclasts may be explained by the finding that under normal condition IL-23 can inhibit osteoclast formation through induction of GM-CSF production in T cells [70].

Similarly to the study by Quinn et al., data from Adamopoulos et al. suggested that IL-23 might have a role in bone remodeling. However, these authors observed a slight increase in bone mass of 26 weeks old IL-23p19$^{-/-}$ mice which may have resulted from impaired osteoclastogenesis in the absence of IL-23 [53].

Interestingly, bone defects of IL-23p19$^{-/-}$ mice are not congenital as no abnormalities were found in 4 and 8 weeks old mice [53, 70].

An explanation for these different findings may be the use of different mouse strains, differences in gut microbiota of the mice or the sensitivity of the equipment used for the analysis of the bone. Nevertheless, despite the differences observed, these studies suggest that IL-23 signaling may play a role in bone homeostasis. However, further studies are required to confirm this and to unravel the potential mechanism.

Targeting the IL-17/23 pathway during autoimmune arthritis: clinical implications

IL-23 is required for the maintenance, stability and pathogenicity of Th17 cells, which are well known key effectors in inflammation and tissue damage in several autoimmune diseases. Therefore, targeting this pathway through biologic disease modifying anti-rheumatic drugs (bDMARDs) including antibodies against IL-17A or IL-23 might be beneficial as they have strong anti-inflammatory properties. Currently, treatment with anti-TNFα biologicals for autoimmune arthritis has proven beneficial in both dampening of the inflammation and reduction of bone loss. Aggressive anti-inflammatory treatment of early RA patients with synthetic and biologic DMARDs results in reduced rate of annual bone loss in 2–10 years period of follow up compared to 0–2 years [85].

While TNF-α inhibitors have shown efficacy in treatment of autoimmune arthritis, there is still a substantial proportion of patients who remain unresponsive to these drugs or suffer from loss of efficacy over time. Therefore in recent years, biologicals targeting the IL-23/IL-17A pathway have emerged as alternative therapy. IL-17A inhibition with Secukinumab showed moderate clinical improvement in rheumatoid arthritis. In a phase II clinical trial, Sekukinumab demonstrated improved efficacy in reducing disease activity (DAS28) over placebo in patients with inadequate response to methotrexate at week 12 [86]. However, the primary endpoint, a 20% improvement in disease activity according to the American College of Rheumatology (ACR20), was not met in this study. In contrast to this, Secukinumab demonstrated ACR20 achievement at week 24 in a phase III study with RA patients who responded inadequately to TNFα inhibitors [87]. Nevertheless, IL-17A inhibition did not have an additional benefit over Abatacept (a CTLA-4-Ig fusion protein that prevents CD80/86 interaction with CD28 receptor) [87], which is already approved by the FDA for RA treatment.

Treatment of RA patients with IL-23 inhibitors has so far not shown clinical benefit. A recent randomized placebo controlled phase II study showed no treatment benefit of ustekinumab, a monoclonal anti-IL-12/23 p40 antibody, and Guselkumab, a monoclonal anti-IL-23p19 antibody, over placebo treatment in patients with active RA on methotrexate [14].

These findings suggest that the role of IL-23 in established RA is limited. However, IL-23 may be essential in the early autoimmune development including the production of pathogenic autoantibodies, which is demonstrated to be IL-23-dependent [56]. In addition, IL-23 may be an important driver of disease relapse in patients as suggested by experimental studies since IL-23 plays a role in reactivation of memory T cells that are involved in arthritic flares [55]. Therefore, future research should reveal whether targeting the IL-23 signaling pathway in RA patients can prevent an arthritic relapse.

In contrast to RA, both anti-IL-17A or anti-IL-23 treatment (Secukinumab and Ustekinumab, respectively) have shown beneficial effects in psoriasis and PsA and are currently approved for treatment of both disorders [15, 88]. Ustekinumab treatment resulted in sustained inhibition of radiographic progression of joint damage in patients with active PsA [89]. Likewise, a phase III clinical trial demonstrated less joint damage progression at week 24 and 52 in PsA patients treated with Secukinumab compared to those receiving placebo [90]. Guselkumab is currently under study with active PsA patients in a phase II trial and has so far yielded improvement in joint symptoms, physical function, psoriasis, enthesitis and quality of life for patients undergoing this clinical trial [91]. It would be of interest in future long-term studies to investigate if targeting IL-23/IL-17 also inhibits systemic loss of BMD and how it would affect new bone formation in patients with inflammatory arthritis.

The finding that anti-IL-23 biologicals are effective in established PsA but not in RA, points toward a difference in the immunopathology of both diseases. In established RA, the requirement for the IL-23/IL-17 pathway is limited compared to its role in the early autoimmune phase of the disease and possibly also during arthritic relapses.

In addition to targeting IL-23 and IL-17A for the treatment of erosive inflammatory arthritis, an anti-RANKL monoclonal antibody (Denosumab) is approved for patients with osteoporosis, and inhibited bone erosion and systemic bone loss at 12 months compared with placebo in a phase II study with RA patients [92].

Conclusion

Increasing evidence suggests that the IL-23 pathway may act as a checkpoint during autoimmune arthritis development, where it can shift the balance of subclinical inflammation in favor of autoimmunity. On the other hand, in established RA the role of this pathway might be limited as indicated by clinical and experimental studies which report lack of efficacy of anti-IL-23 treatment during the effector phase of disease. However, few experimental studies have suggested that this pathway is involved in the reactivation of memory T cells which may drive disease relapses. This may offer new possibilities of using anti-IL-23 biologicals to suppress or even prevent relapses in these patients.

Chronic arthritis leads to joint damage due to increased activation of bone resorbing cells. Several studies have demonstrated that IL-23 acts on bone resorbing osteoclasts and bone forming osteoblasts by either directly targeting precursors of these cells or through induction of downstream cytokines such as IL-17A and IL-22. IL-23 can exert pro-osteoclastogenic effects via IL-17A,

while it may play a role in bone formation by inducing IL-22. The role of IL-23 in physiological bone remodeling together with its underlying mechanism still remains to be fully elucidated.

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Author contributions

W.R. performed literature research, prepared the review lay-out and wrote the review. M.vD. revised the manuscript. E.L. prepared the review lay-out and revised the manuscript.

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Abbreviations: **ACPAs**: anti-citrullinated protein antibodies · **BMD**: bone mineral density · **CIA**: collagen-induced arthritis · **IL-23R**: IL-23 receptor · **PsA**: psoriatic arthritis · **RA**: rheumatoid arthritis · **RANK**: receptor activator of NF-κB · **Th17**: T helper-17

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