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REVIEW

Immunopathogenesis of reactive arthritis: Role of the cytokines

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Abstract

Reactive arthritis (ReA), also known as sterile postinfectious arthritis, belongs to the group of related arthropathies known as spondyloarthritis (SpA). ReA can arise 1-4 wk after a gastrointestinal or genitourinary infection, but once arthritis develops, the microorganism is not found in the joint. The classical microbes associated with ReA development include Gram-negative aerobic or microaerophilic bacteria containing LPS in their outer membrane. The immunopathogenic mechanisms involved in ReA development are still unknown. A hypothesis suggested that the bacteria probably persist outside the joint, at sites such as gut mucosa or lymph nodes, and bacterial antigens might then be transported to the joints. On the other hand, an altered immune response and the unbalanced production of cytokines have been reported in subjects with ReA. Currently, there is increased evidence to suggest that both mechanisms would operate in the immunopathogenesis of ReA. In this review we highlight recent advances on the role of cytokines in the ReA. Particularly, we discuss the roles of some pro- and anti-inflammatory cytokines involved in the immunopathogenesis of ReA.

Key words: Reactive arthritis; Cytokines; Immunopathogenesis; Infection; Interleukin-17; Interleukin-12; Interleukin-23; Interleukin-6; Tumor necrosis factor-α; Interleukin-10

Core tip: The immunopathogenic mechanisms involved in reactive arthritis (ReA) development are still unknown. However, in the last years, increased evidence suggests that the immune response in particular certain cytokines could be involved in the pathogenesis of ReA. Currently, the use of biological agents that block the action of certain cytokines has contributed to improving the treatment of some rheumatic pathology. Understanding the role of cytokines in the pathogenesis of ReA could contribute to the development of future treatments. In this review, we highlight recent advances on the role of certain cytokines in the pathogenesis of ReA.

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INTRODUCTION

Reactive arthritis (ReA), also known as sterile postinfectious arthritis, belongs to the group of related arthropathies known as spondyloarthritis (SpA)[1]. This group

also includes undifferentiated SpA, psoriatic arthritis (PsA), arthritis associated with inflammatory bowel disease and ankylosing spondylitis (AS). The SpA arthropathies have common several epidemiological, pathological, clinical and radiological features. ReA, as with other SpA, exhibits an absence of rheumatoid factor and has a genetic association with the molecule HLA-B27[1-3]. ReA can arise 1-4 wk after a gastrointestinal or genitourinary infection, but once arthritis develops, the microorganism is not found in the joint[2]. The ReA symptoms were recognized and studied in 1942 by Bauer and Engelmann, who associated these symptoms with those described in 1916 by the German physician Hans Reiter. At that time, Reiter described the clinical triad: arthritis, nongonococcal urethritis and conjunctivitis in a German soldier after an episode of bloody diarrhea. So, Bauer and Engelmann coined the term Reiter's syndrome to describe this new pathology[2]. However, most patients do not have the complete triad of symptoms. These observations drove Ahvonen to propose the name of ReA as the term most adapted to describe the "arthritis that happens during or after an infection in another site of the body without evidence of microorganisms in the joint"[4]. Yet, this operational definition of ReA has led to uncertain diagnosis in different clinical settings. Thus, several attempts have been made to create classification criteria; however, lack of consensus has led to a failure to achieve any universally validated diagnostic criteria. Based on discussions at the 4th International Workshop on ReA, this term should be used only in patients with clinical features of ReA and in cases where a pathogen known to cause ReA is implicated[5].

CLINICAL FEATURES

ReA most commonly affects young adults aged 20 to 40 years old and is rare in children[6-8]. Both sexes are equally affected by ReA after a gastrointestinal infection, while ReA is more frequent in men when triggered by a urogenital tract infection[3]. The presence of the HLA-B27 allele does not seem to be related to the onset of ReA; however, HLA-B27 positive patients have more severe arthritis with a tendency to progress to a chronic stage and they also have a greater chance of developing extra-articular symptoms. One hypothesis suggests that this molecule favors the cross-reaction between antigen and host, or it might be itself a target of the immune response[9].

The symptoms of ReA typically start between 1 to 4 wk after the gastrointestinal infection. However, the triggering infection could be asymptomatic, such as *Chlamydia*-induced ReA, resulting in underdiagnosis[2]. Clinical features of ReA are characterized by asymmetrical oligoarthritis, often in large joints of the lower extremities or in the upper extremities. A mild polyarticular form, particularly in the small joints, can also occur. Patients can have dactylitis. The typical extra-articular manifestations are enthesitis, tendinitis and bursitis. ReA share these clinical characteristics and inflammatory back pain with other members of SpA, such as AS and PsA[1]. Other extra-articular features include eye disease, where conjunctivitis is most prevalent, followed by acute anterior uveitis, and skin changes, such as erythema nodosum, keratodermia blennorrhagica and circinate balanitis[3].

The clinical diagnosis is made based on the clinical symptoms. Evidence for infection triggering the arthropathy is most convincing when microbe isolation or antigen detection is successful. In this respect, fecal culture of enteric pathogens associated with ReA or the finding of *Chlamydia trachomatis* nucleic acids in urine, cervical or urethral swabs are secondary criteria used to confirm the diagnosis.

Animal models

Animal models of ReA have complemented studies in human materials. However, these animal models are limited since even when they are developed after bacterial infection as in human ReA, in some of them the route of infection was intravenous instead of oral. Table 1 shows animal models of ReA similar to the human form of the disease[10-17]. We have described an experimental model useful for studying the pathogenesis of *Yersinia enterocolitica* (*Y. enterocolitica*) ReA. In our model, TNFRp55 deficient mice develop ReA after oral infection with *Y. enterocolitica* O: 3, the most common serotype associated with human ReA. *TNFRp55*$^{-/-}$ mice exhibited macroscopic signs of severe and progressive arthritis with significantly higher clinical score compared with wild-type mice from d 14 to 56 after infection[14]. Extensively, increased scores for inflammation and bone/cartilage degradation resulted when histopathological changes were analyzed in the joints. In these animals, we observed luminal disorganization of the synovial membrane, which was densely infiltrated with various types of leucocytes, sometimes concomitant with follicle formation. The articular cartilage and bone were degraded. Proliferation of synovial lining cells was also detected[14,15]. This evidence and the data presented in Table 1 indicate ReA development in animal models that resemble this disease in humans. Nevertheless, the convergence of these models with human studies will contribute to understand the pathogenic mechanisms of ReA.

TRIGGERING BACTERIAL AND PATHOPHYSIOLOGY

The classical bacteria associated with gastrointestinal ReA are *Yersinia*, *Salmonella*, *Shigella* and *Campylobacter*, while *C. trachomatis* is by far the most common cause of ReA associated with genital infection[3,18]. All these pathogens are Gram-negative aerobic or microaerophilic bacteria containing LPS in their outer membrane.

The immunopathogenic mechanisms involved in ReA development are still unknown. Even when bacterial

Table 1 Animal models of reactive arthritis similar to the human form of the disease

Animal	Bacteria	Route of infection	Arthritis onset/ remission	Clinical symptoms	Cytokine involved	Ref.
Lewis rats	*Y. enterocolitica* O:8[1]	*iv*[1]	1 wk/6 wk	Polyarticular arthritis, erythema	ND	Hill *et al*[10]
DBA/2 and BDF1 mice	*Y. enterocolitica* O:8 plasmid cured[1]	*iv*[1]	Day 31/3 wk	Polyarticular arthritis	ND	Yong *et al*[11]
SHR rats	*Y. enterocolitica* O:8[1]	*iv*[1]	1-4 wk/7-25 wk	Polyarticular arthritis, erythema, swelling and impaired movement of the joint	ND	Merilahti-Palo *et al*[12]
Swiss, BALB/c and C3H/HeJ mice	*Y. enterocolitica* O:3	*iv*[1]/*Oral*	1-3 wk/2-8 mo	Monoarticular arthritis, swelling redness, deformations and conjunctivitis	ND	de los Toyos *et al*[13]
C57BL/6 *TNFRp55*$^{-/-}$ mice	*Y. enterocolitica* O:3	*ig*	2 wk/chronic until 8 wk	Polyarticular arthritis, swelling, erythema	IL-17 IFN-γ IL-6 IL-1β	Di Genaro *et al*[14] Eliçabe *et al*[15]
BALB/c mice	*S. enteritides*	*ig*	1 wk/ND	Synovial inflammation	TNF-α IL-17	Noto Llana *et al*[16] Noto Llana *et al*[17]

[1]Different to the human form of the disease. ND: Not determined; *iv*: Intravenous infection; *ig*: Intragastric infection; IL: Interleukin; TNF: Tumor necrosis factor.

cultures of synovial fluids are negative in ReA, bacterial antigens have been found in the joints of patients. In *Chlamydia*-induced ReA, bacterial DNA and RNA have been detected in the joint, suggesting that live *Chlamydia* are present[19-21]. Positive reaction of antibodies specific to *Salmonella* and *Yersinia* antigens in synovial fluid cells of ReA patients suggests the presence of bacterial antigen in the joint[22,23]. Based on these findings, some authors have suggested that the bacteria probably persist outside the joint at sites such as gut mucosa or lymph nodes, and bacterial antigens might then be transported by monocytes to the joints[24,25]. On the other hand, an altered immune response and the unbalanced production of cytokines have been reported in subjects with ReA[26,27]. This altered immune response benefits the bacterial persistence and disfavors the elimination of the antigen by the host.

In this review, we highlight recent advances on the role of cytokines in ReA. Particularly, we discuss the roles of pro- and anti-inflammatory cytokines, especially interleukin (IL)-17, IL-12, IL-23, IL-6, tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ) as well as IL-10 in the pathophysiology of the ReA. Finally, we discuss the latest advances in the treatment of ReA based on the use of biological agents that neutralize the functions of certain cytokines, such as TNF-α or IL-6.

ROLE OF THE CYTOKINES IN ReA

Conflicting data have been reported on the production of cytokines in ReA patients. $CD4^+$ T cells mediate immunity as a balance between different lineages of T helper (Th)-1, Th2, Th3 and Th17 which secrete IFN-γ, IL-4, TGF-γ and IL-17, respectively, as the main cytokine for each profile. Some studies revealed low levels of Th1 cytokines in ReA, especially of TNF-α but also of IFN-γ in peripheral blood and synovium[28-34]. Since Th1 cells secreting IFN-γ and TNF-α have been proposed for bacterial clearance, defective Th1 response may contribute to bacterial persistence. Other data suggest that a Th2 cytokine profile and Th3 response with expression of TGF-β is common in ReA[32]. Temporal relationships of these different Th1 and Th2 cytokines or blunting of initial cytokine response might also be important in the disease manifestations and its maintenance. On the other hand, the discovery of Th17 cells and their importance in the pathogenesis of chronic inflammatory diseases suggested that these cells may have a pathogenic role in ReA. However, the available studies are not large enough to support the role of certain cytokines in the pathogenesis of ReA.

NOVEL CYTOKINES IMPLICATED IN PATHOGENESIS OF ReA

IL-17

IL-17 is a 15-20-kDa glycoprotein produced by a novel subset of Th cells, termed Th17 cells, and to a lesser extent by innate lymphoid cells, including T-cells, innate-like lymphoid cells, mast cells and neutrophils[35]. Th17 cells are critical in the pathogenesis of the arthritis, as demonstrated in several animal models[36-38]. Th17 differentiation, survival and expansion depend on a variety of cytokines and transcription factors that work in concert to drive the induction of increased Th17 numbers. TGF-β in synergy with IL-6 has been described as the central factor involved in generating Th17 cells in mice. It has been shown in humans that TGF-β, IL-1β and IL-6, combined with IL-21 or IL-23, can induce Th17 differentiation[39]. IL-17 binds to IL-17RA/IL-17RC, which is expressed by a variety of cells, such as monocytes, lymphocytes, lymphoid tissue inducer cells, epithelial cells, synoviocytes, fibroblasts and keratinocytes[35].

Th17 cell responses and IL-17 expression provide protection against bacterial and fungal pathogens through production and induction of inflammatory cytokines

and granulopoiesis, or by the recruitment of neutrophils. However, Th17 cells producing IL-17 have been suggested as the central effector lineage involved in the pathogenicity of ReA[40]. Thus, it has been shown that ReA patients have elevated levels of IL-17 in synovial fluid and that this cytokine contributes to the development of joint inflammation[40,41]. Furthermore, high expression of IL-17 was found in the synovial fluid of patients with SpA and an increased number of circulating memory Th17 cells has been recently reported in these patients[42,43]. Moreover, in patients with *C. trachomatis*-induced ReA, increased percentages of IL-17-positive $CD4^+$ T cells[44] and higher IL-17 concentrations were detected in synovial fluid[45].

Recent works suggest that *Salmonella*-induced ReA in mice dependent on $CD4^+$ T cells secreting IL-17[17]. Interestingly, these authors observed that the expression of IL-17 in the large intestine and in mesenteric lymph nodes (MLN) resembles that of popliteal and inguinal lymph nodes (ILN)[17]. Accordingly, previous results from our laboratory demonstrated that IL-17 plays a major role in *Yersinia*-induced ReA[15]. Furthermore, we detected a strong correlation among IL-17 levels in MLNs, ILNs and joints from *TNFRp55*$^{-/-}$ mice with arthritis, supporting a link between the intestinal mucosa and the articular immune response. In addition, we observed that neutralization of IL-17 resulted in the abrogation of synovitis[15]. In line with these results, other authors have reported recently that modulating intestinal IL-23/IL-17 expression by consumption of *Lactobacillus casei* prior to *Salmonella* infection in mice abolishes intestinal and joint inflammation[46].

These data in animal models and patients support the hypothesis that Th17 cells may be involved in ReA pathogenesis. However, there are few reports for understanding and elucidating the true role of IL-17 in the pathogenesis of ReA.

IL-12 and IL-23

IL-12 and IL-23 are heterodimeric cytokines that share subunits and have important roles in autoimmunity. These IL-12 family cytokines share some biological characteristics but have functional differences. IL-12 is composed of two covalently linked subunits, IL-12p35 and IL-12p40, while IL-23 is composed of two covalently linked subunits, IL-23p19, which is distantly related to IL-12p35, and the IL-12p40 subunit[47,48]. Furthermore, the receptors of IL-23 and IL-12 are also heterodimers that share the receptor 1 chain and have unique 2 chains[49]. IL-12 is released by antigen presenting cells such as dendritic cells (DCs) and monocytes/macrophages in response to bacterial products and immune signals. Furthermore, IL-12 is the main stimulator of IFN-γ production by inducing development of Th1 responses[49,50]. In addition, IL-23 is produced by macrophages and activated DCs and plays a crucial role in the generation of the Th17 cells. Since IL-12 has the ability to orchestrate the Th1 response, this cytokine plays a crucial role in the protective immunity against many pathogens associated with ReA. Thus, the low concentrations of IL-12 have been linked to the bacterial persistence hypothesis and then to the pathogenesis of ReA[28]. On the other hand, data on IL-23 concentrations in synovial fluid or serum of patients with ReA are limited, but high levels of IL-17 found in synovial fluids and sera of patients with ReA may reflect IL-23 activity. Moreover, abnormality of IL-12p40 gene expression in humans has been reported and IL-12 deficiency has been detected in patients with ReA[51,52]. Yin *et al*[28] found that the balance of anti-inflammatory cytokines (IL-10) and IL-12 in the synovial fluid is also important. This may contribute to the decreased clearance of the bacteria or their components from the joint and lead to ReA[28]. In relation to these findings, a recent study has shown that monocyte-derived macrophages from subjects with a history of ReA show low IL-12 and IL-23 production[53]. Conversely, some authors have reported that IL-12/23p40 levels in synovial fluids of patients with ReA and other SpA are higher compared to synovial fluids of patients with osteoarthritis (OA) used as control[41,54].

Interestingly, we demonstrated that the p40-deficient mice develop acute ReA after oral infection with *Y. enterocolitica*, suggesting that IL-12 or IL-23 could exert a protective effect on the development of ReA[55]. However, we have observed elevated levels of p40 in regional lymph nodes to joints of *TNFRp55*$^{-/-}$ mice with *Yersinia*-induced ReA. This effect has been accompanied by high levels of IFN-γ and IL-17 in affected joints[15]. These results are in accordance with the concept that the IL-12/IL-23 pathway plays a dual role protecting from infection and eliciting tissue damage, and support future study to determine whether IL-12/23p40 could be a possible target for ReA treatment.

IL-6

IL-6 is a pleiotropic cytokine that is involved in numerous biological processes. The pleiotropy and redundancy of IL-6 functions have been identified by characterizing a unique receptor system comprising two functional proteins: a receptor specific for IL-6 (IL-6R)[56] and gp130, the common signal transducer of cytokines related to IL-6, including the IL-12 family cytokines IL-27 and IL-35[57,58]. In the early phase of infectious inflammation, IL-6 is produced by monocytes and macrophages immediately after the stimulation with distinct pathogen-associated molecular patterns. In noninfectious inflammation, damage-associated molecular patterns from damaged or dying cells stimulate monocytes and macrophages to produce IL-6. The pathogenic role of IL-6 in rheumatic diseases like rheumatoid arthritis (RA) has been well established. The critical role for IL-6 in the pathogenesis of RA is provided by clinical trials, in which tocilizumab, a humanized mAb specific for IL-6R, has been shown to suppress disease activity and erosive progression in patients with RA[59]. In ReA, elevated IL-6 concentrations in the plasma and sera of the patients has been reported[60,61]. Moreover, synovial fluid concentrations of

IL-6 were higher in patients with ReA[41]. Interestingly, we found that mice TNFRp55-deficient macrophages are hyperactivated to secrete common pro-inflammatory mediators such as NO and IL-6 following stimulation with *Yersinia* antigens. The higher concentrations of IL-6 production detected in stimulated *TNFRp55*$^{-/-}$ macrophages may be associated with our previous *in vivo* results demonstrating the increased susceptibility of *TNFRp55*$^{-/-}$ mice to *Yersinia*-induced ReA[14]. Furthermore, higher concentrations of IL-6 were detected in the joints of these mice which showed a severe chronic synovitis[15]. This data suggests that over-synthesis of IL-6 may be related to the development of ReA.

TNF-α

TNF-α is a cytokine prototype of a large family of over 40, known as TNF superfamily, and TNF receptor (TNFR) proteins. TNF-α is a cytokine with pleiotropic functions produced by a large number of cells, but are monocytic lineage cells (macrophages, astroglia, microglia, Kupffer cells and alveolar macrophages) major sources. Initially, this cytokine is produced as a pro-TNF and is expressed on the cell surface. Subsequently it is cleaved by the action of a metalloproteinase (TACE) and released into the extracellular medium as a soluble protein[62]. Often, TNF-α is not detected in high concentrations in serum or tissues, but increases intensively on various inflammatory and infectious conditions. Two receptors, TNF-R1 (TNF receptor type 1; CD120a; p55/60) and TNF-R2 (TNF receptor type 2; CD120b; p75/80) bind to membrane-integrated TNF (memTNF) as well as soluble TNF-α (sTNF-α). In the vast majority of cells, TNF-R1 appears to be the key mediator of TNF-α signaling, whereas in the lymphoid system, TNF-R2 seems to play a major role. Low TNF-α secretion by blood mononuclear cells may be related to ReA development since TNF-α deficiency may interfere with eradication of bacterial infection in its early stages[34,63-66]. However, other studies suggest that TNF-α could have a pathogenic role during the chronic stage of ReA in line with the role of this cytokine in RA. In this regard, some studies have revealed significant increase of TNF-α production in chronic ReA compared with acute ReA[66]. These data support the possibility that anti-TNF-α treatment in ReA during the chronic phase of the disease could be beneficial. However, considering that TNF-α may be required for the elimination of ReA-associated bacteria, anti-TNF-α biologics might favor bacteria growth. Results obtained in our laboratory showed that TNFRp55 deficiency favors the development of ReA after infection with *Y. enterocolitica*[14]. These data support the idea that the relative lack of TNF-α may play a protective role in ReA at acute phase of disease. On the other hand, we have demonstrated an *in vivo* regulatory role for TNFRp55 signaling in fine-tuning of Th17 and Th1 programs during bacterial-induced ReA through modulation of the common p40 subunit of IL-23 and IL-12[15]. This evidence suggests that TNF-α might have a dual role in ReA, playing a protective role first and during the initial stage. However, during the chronic stage of the disease, TNF-α would act as a pro-inflammatory cytokine.

IFN-γ

IFN-γ is produced mainly by natural killer (NK) cells and a particular subset of T cells, namely Th1 cells[67]. As previously mentioned, IL-12 is the main stimulator of IFN-γ production[47,50]. Thus, IL-12 and IFN-γ coordinate the link between pathogen recognition by innate immune cells and the induction of specific immunity by mediating a positive feedback loop to amplify the Th1 response. The functional IFN-receptor (IFN-R) consists of 2 ligand-binding IFNGR1 chains and 2 signal-transducing IFNGR2 chains[68]. Mice deficient in IFN-γ or its receptor are susceptible to an array of intracellular pathogens[69-71]. It was thought that Th1 cells cause damage in the joints mainly through IFN-γ driven inflammatory mechanisms. However, similar to TNF-α, conflicting data have been reported about the role of IFN-γ in ReA. As previously mentioned, some authors have reported an aberrant lower production of IFN-γ in patients with ReA[28-34,52]. In contrast, in patients with *C. trachomatis*-induced ReA, the synovial fluid concentrations of IFN-γ were significantly higher than in OA patients but no significant differences were found between ReA and RA patients[45]. Similar results were reported by Singh *et al*[41]. Other studies have shown that the percentages of IFN-γ positive CD3$^+$ cells were significantly higher in peripheral blood and synovial fluid of chronic ReA patients[66]. These data support the idea that, as with TNF-α, IFN-γ may play a significant protective role in ReA in the acute phase of disease. However, in the chronic phase, this cytokine, as in RA, could play a pathogenic role in ReA.

IL-10

IL-10 is an anti-inflammatory cytokine with a major role in preventing inflammatory and autoimmune pathologies[72]. Based on a large body of evidence, T cells are thought to be the main source of IL-10 *in vivo*. Regulatory T (Treg) subsets are also a key source of IL-10 *in vivo* and play a central role in mediating the inflammation control. However, it is now accepted that IL-10 is expressed by subsets of all CD4$^+$ T helper populations, including Th1, Th2 and Th17[73]. Nevertheless, this cytokine is also expressed by B cells and cells of the innate immune system (DCs, stimulated macrophages, mast cells, NK cells, eosinophils and neutrophils)[74]. This cytokine binds to IL-10 receptor (IL-10R), which consists of two subunits. They are members of the interferon receptor family and belong to JAK/STAT3 class of receptors[74]. Extensive studies have demonstrated that IL-10 inhibits the production of pro-inflammatory cytokines and chemokines in activated monocytes/macrophages and inhibits proliferation of CD4$^+$ T cells[75]. However, the role of IL-10 in ReA is less clear. Appel *et al*[32] reported that the amount of IL-10 and TGF-β secreting cells was higher in ReA than in RA patients. This result was accompanied by a lower level of TNF-α secretion in ReA patients. Interest-

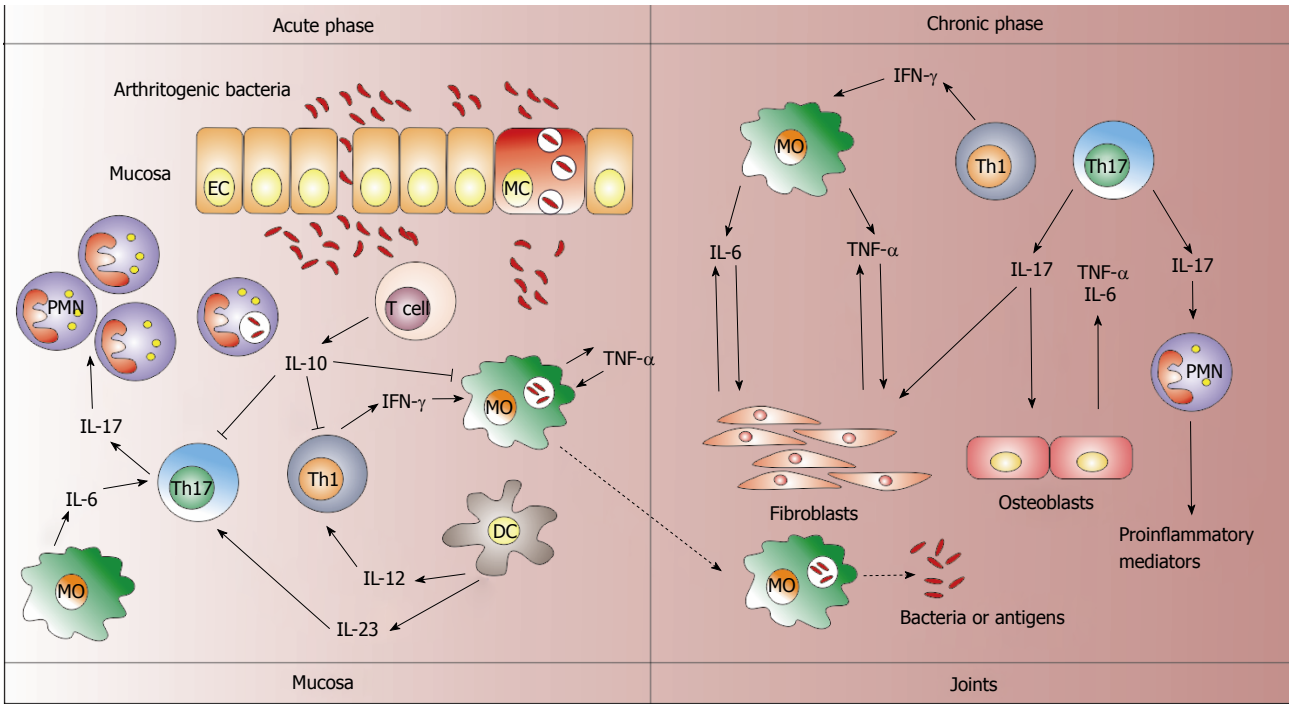

Figure 1 The role of cytokines in reactive arthritis depending on the state of disease. Arthritogenic bacteria enter through the gastrointestinal or genitourinary mucosa using different strategies (M cells; epithelial cells) and induce an inflammatory response. During the acute stage, interleukin (IL)-12 and IL-23 plus IL-6 promote the development of Th1 and Th17 cells, respectively. These cells are a major source of interferon (IFN)-γ and IL-17, favoring the bacterial clearance. The IFN-γ activates macrophages to kill phagocyted bacteria and secrete tumor necrosis factor (TNF)-α. IL-17 induces the migration of polymorphonuclear cells to the site of infection. However, this effect could be disrupted by the action of regulatory T cells producing IL-10. This regulatory event contributes to the bacterial persistence in the mucosa. Then, the bacteria could reach the joint transported by macrophages. In chronic stages, IL-6, TNF-α, IFN-γ and IL-17 exert pro-inflammatory roles in the joint. These cytokines stimulate articular cells (*e.g.*, fibroblasts, osteoblast) and immune cells to produce more cytokines and pro-inflammatory mediators that contribute to chronic articular inflammation. These effects may be enhanced by the presence of bacteria or bacterial antigens in the joint. EC: Epithelial cell; MC: M cell; MO: Macrophage; PMN: Polymorphonuclear cell; DC: Dendritic cell.

ingly, all ReA patients had a disease course of less than 6 mo. These authors suggest that this cytokine milieu might contribute to the lack of elimination of the triggering agent. Similar results were reported by Yin *et al*[28]. These authors found that synovial fluid mononuclear cells secreted low amounts of IFN-γ and TNF-α, but high amounts of IL-10 upon stimulation with specific bacteria, which was responsible for the suppression of IFN-γ and TNF-α[28]. There is also evidence indicating association of the IL-10 promoter region with the development of ReA. This raises the possibility that high levels of IL-10 in the joints of patients with ReA may be genetically determined, making these individuals more prone to the persistence of arthritogenic bacteria[76].

Despite these clinical findings suggesting a pathogenic role of IL-10 in human ReA, IL-10 depletion and IL-10 treatment in other types of arthritis models have demonstrated the anti-inflammatory properties of IL-10 in arthritis[77-80]. Results obtained in our laboratory showed that the number of Treg cells as well as the *FoxP3* mRNA expression and IL-10 levels were significantly decreased in joint regional lymph nodes of *TNFRβ55*$^{-/-}$ mice at the arthritis onset[81]. These results would indicate that IL-10 plays a protective role during the acute phase of arthritis. However, the clinical evidence suggests that high levels of IL-10 could promote bacterial persistence, favoring the development of ReA.

TREATMENT BASED ON BIOLOGICAL AGENTS

IL-6 antagonists

Published data on the effects of IL-6 blockade in patients with SpA are very scarce. Thus, in 1996 a report describes a patient with ReA who received a murine anti-IL-6 antibody[82] and, in 2009, tocilizumab was reported to be successful in another patient with ReA[83]. Only two injections of tocilizumab led to complete clinical remission from symptoms caused by ReA[83]. Recently, Kwan *et al*[84] reported successful results of tocilizumab in the treatment of a case of ReA precipitated by intravesical bacillus Galmette-Guèrin (BCG) which did not respond completely to disease modifying antirheumatic drugs (DMARDs). As previously mentioned, IL-6 is one of the cytokines that favor the differentiation of naïve T cells into Th17 cells[39]. Therefore, it is possible that the inhibitory action of tocilizumab is exerted indirectly interfering with the differentiation of Th17 cells. These data indicate that IL-6 may play a pivotal role directly or indirectly in the pathogenesis of ReA and tocilizumab treatment can be an option for an alternative treatment.

TNF-antagonists

The pathogenic role during the critical stage of the disease supports the idea that TNF-α blocking agents could be an effective treatment for patients with ReA who develop severe arthritis that does not respond to conventional lines of treatment. Thus, Kaipiainen-Seppönen *et al*[85] reported two cases of ReA post *Y. enterocolitica* treated early with infliximab (an anti-TNF-α antibody). One patient that received this treatment within 2 mo after the disease onset exhibited an improvement after the third infusion. The second patient that was treated after one month of evolution showed an immediate clinical improvement with almost complete regression after 15 d[85]. Recently, Thomas-Pohl *et al*[86] obtained the same result in one patient with ReA triggered by a gastrointestinal infection. Similar results were reported by Edrees in a patient with a severe case of *C. trachomatis*-related ReA that was successfully treated with etanercept (a fusion protein of TNFRp75)[87]. Thus, anti-TNF-α therapy has proved efficacious in some cases. However, sufficient data are lacking and theoretical concerns with their use remain. Large controlled trials are needed to evaluate the role of TNF-α blocking agents in ReA.

CONCLUSION

The network of cytokines is complex with feedback regulatory circuits that make it difficult to elucidate the role of a particular cytokine in ReA. In addition, the clinical reports of cytokine levels in patients with ReA have included patients in different stages of the disease or they are not large enough to support the role of different cytokines in ReA development. However, the current evidence in patients with anti-cytokine treatments suggests that IL-6 and TNF-α may play central roles in ReA pathogenesis. Furthermore, the IL-17/23 axis should be considered in the picture of ReA development, although further investigations are necessary for these cytokines. According to the presented evidence in this review, Figure 1 shows the different functions of the cytokines in ReA depending on the disease phases. Moreover, animal models may contribute to provide insight into the immunopathogenic mechanisms mediated by a particular cytokine in ReA and to support anti-cytokine treatments.

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