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Review article

IL33 in rheumatoid arthritis: potential contribution to pathogenesis

Rafaela Bicalho Viana Macedo[a,*], *Adriana Maria Kakehasi*[b], *Marcus Vinicius Melo de Andrade*[c]

[a] *Faculdade de Medicina, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil*

[b] *Departamento do Aparelho Locomotor, Faculdade de Medicina, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil*

[c] *Departamento de Clínica Médica, Faculdade de Medicina, Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG, Brazil*

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ABSTRACT

A better understanding of the inflammatory mechanisms of rheumatoid arthritis and the development of biological therapy revolutionized its treatment, enabling an interference in the synovitis – structural damage – functional disability cycle. Interleukin 33 was recently described as a new member of the interleukin-1 family, whose common feature is its pro-inflammatory activity. Its involvement in the pathogenesis of a variety of diseases, including autoimmune diseases, raises the interest in the possible relationship with rheumatoid arthritis. Its action has been evaluated in experimental models of arthritis as well as in serum, synovial fluid and membrane of patients with rheumatoid arthritis. It has been shown that the administration of interleukin-33 exacerbates collagen-induced arthritis in experimental models, and a positive correlation between cytokine concentrations in serum and synovial fluid of patients with rheumatoid arthritis and disease activity was found. This review discusses evidence for the role of interleukin-33 with a focus on rheumatoid arthritis.

Ação da IL33 na artrite reumatoide: contribuição para a fisiopatalogia

Palavras-chave:
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RESUMO

A melhor compreensão dos mecanismos inflamatórios da artrite reumatoide e o desenvolvimento da terapia biológica revolucionaram o tratamento da doença, permitindo uma interferência no ciclo sinovite–dano estrutural–incapacidade funcional. A interleucina 33 foi recentemente descrita como um novo membro da família da interleucina 1, cuja característica comum é a atividade pró-inflamatória. Por estar envolvida na patogênese de uma grande variedade de doenças, incluindo doenças autoimunes, a interleucina 33 começa a ser estudada na doença reumatoide. Ela tem sido avaliada em modelos experimentais de artrite, no soro, no líquido e membrana sinoviais de pacientes com artrite reumatoide. Demonstrou-se

* *Corresponding author.*
E-mail: rafaelabicalho@yahoo.com.br (R.B. Macedo).

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que a administração da interleucina 33 exacerba a artrite induzida por colágeno em modelos experimentais, e concentrações dessa citocina no soro e no líquido sinovial de pacientes com artrite reumatoide correlacionaram-se positivamente com a atividade da doença. Esse manuscrito apresenta a interleucina 33 e discute as evidências do seu papel em diferentes doenças, com ênfase na artrite reumatoide.

Introduction

Rheumatoid arthritis (RA) comprises a symmetric polyarthritis affecting diarthrodial joints and periarticular structures, besides presenting several systemic manifestations. RA affects about 1% of the world population and is commonly associated with functional disability and reduced quality of life.[1,2]

The primary inflammatory site of RA is the synovial membrane (SM) which shows cell hyperplasia and an inflammatory process, settling a case of synovitis. When this disease progresses without treatment, or even in the most refractory cases, there is progressive joint destruction with cartilage and bone loss.[3]

The inner face of SM is in contact with the intra-articular cavity and, usually, this is a delicate two- or three-cell layer membrane. In RA, a large number of immune cells invade this structure, leading to cell proliferation, neovascularization and the formation of germinal lymphoid follicles. The mechanisms involved in the recruitment of inflammatory cells into the synovial membrane have been extensively studied.[4] Changes in the function of T and B cells, and an abnormal production of cytokines and antibodies have been recognized as processes present in RA.[5–8] Many cytokines responsible for regulating cell communication are expressed in the synovial membrane, being directly involved in immune processes in cases of RA.

The study of the role of cytokines has led to the development of new therapeutic agents for the treatment of RA, including tumor necrosis factor alpha (TNF-alpha) and interleukin receptor (IL) 6 blockers. Recent observations in humans and experimental studies have shown the potential role of IL-33 and its receptor ST2 as mediators in the pathogenesis of RA.[9,10] IL-33 has been identified as a new IL-1 family member, which also includes IL-1alpha, IL-1beta, IL-18 and the antagonist of the IL-1 receptor (IL-1Ra).[11] This paper presents the actions of IL-33 and discusses its role in RA.

Interleukin 33

IL-33 was recently described as a new member of the IL-1 family, whose common characteristic is the pro-inflammatory activity.[11–13] IL-33 plays an important immune role associated with Th2 response, significantly stimulating the secretion of IL-5 and IL-13 by Th2 polarized cells.

The IL-33 gene is located on chromosome 9 (9p24.1). Messenger RNA (mRNA) of IL-33 is expressed in multiple cell types in different organs, both in humans and in mice. The IL-33 protein is mainly expressed in epithelial and endothelial cells, particularly in high endothelial venules.[14]

Similar to IL-1beta and IL-18, IL-33 is produced intracellularly as pro-IL-33 and, after undergoing cleavage, is secreted extracellularly as the mature form of IL-33.[14] Its bioactive form is released as a result of cell necrosis and serves as an inflammatory trigger through autocrine and paracrine action. Caspase-1, also known as IL-1 beta converting enzyme, is responsible by the cleavage of pro-forms of some cytokines of the IL-1 family, such as pro-IL-1beta and interferon gamma (IFN-gamma) inducing IL-18. It has also been demonstrated in vitro that IL-33 is cleaved by caspase-1, although the in vivo relevance of this enzyme is still under dispute.[15] Although IL-33 is structurally related to IL-1beta and IL-18, that activate Th1/Th17 cells, their biological functions result mainly in the production of IL-5 and IL-13.[11]

The IL-33 receptor is a complex formed by ST2 protein and by accessory protein for IL-1 receptor (IL-1RAcP), both expressed in most cells, mainly mast cells and in activated Th2 cells. Three isoforms of ST2 in humans are produced by differential processing of a single copy: membrane-anchored form (ST2), soluble form (sST2), and a form expressed mainly in gastrointestinal organs (ST2V). The sST2 form works as a decoy receptor of IL-33, by blocking its binding to the transmembrane receptor.[11]

The functions or effects of IL-33 are present in various cell types, and prompted studies on the participation of this interleukin and its receptor in different clinical conditions such as asthma, sepsis, atherosclerosis and rheumatoid arthritis.

IL-33 in in vitro and in experimental studies

Several experimental studies describe the cellular actions of IL-33. IL-33 secretion has been described in a monocyte lineage (THP-1 cells) in response to different stimuli: infection (*Listeria monocytogenes* and *Salmonella typhimurium*), lipopolysaccharide (LPS) with aluminum adjuvant, and LPS alone.[16,17]

Basophils activated by immunoglobulin E (IgE) produce IL-33 and release histamine and, additionally, basophil migration also appears to be regulated by IL-33. These findings aid in the understanding of independent immune responses of antigens present in tissues that express the mRNA of IL-33, for instance, smooth muscle cells in bronchial tissue and epithelial cells of the airways.[18,19]

In eosinophils, IL-33 regulates the activation, degranulation and increased adherence and survival.[16,20] In mice, after systemic administration, IL-33 is a powerful inducer of innate response type 2; this was demonstrated by the development of splenomegaly, eosinophilia and severe changes in the bowel

and lungs by the animals – effects accompanied by an increase of immunoglobulins E and A and of cytokines of the Th2 response.[11] An experimental study showed that IL-33 administration to mice was able to induce anaphylaxis.[21]

In mice sensitized with IL-33, there was an increase of IFN-gamma; this finding provided support for the conclusion that IL-33 may act as a costimulatory factor in cellular innate immune responses.[22]

Mast cells are very responsive to IL-33, which results in increased production of IL-6, IL-13, IL-1beta, TNF, prostaglandin D2 and MCP-1.[23–26] In addition, IL-33 promotes survival, adhesion and cytokine production in human mast cells and also in mast cell progenitors.[24,27]

Cardiomyocytes can also be activated by IL-33.[15,16,28] IL-33 produced by cardiac fibroblasts antagonizes the hypertrophic action induced by angiotensin II and phenylephrine on cardiomyocytes. Thus, it is believed that IL-33 might potentially exert a beneficial therapeutic effect on the regulation of myocardial response to overload.[28]

Regarding asthma, experimental models suggest that the ST2 receptor is involved in airway inflammation mediated antigen.[16,29] In the experimental asthma induced by ovalbumin, an IL-33 injection by intraperitoneal route resulted in eosinophilia and accumulation of macrophages in the lungs of animals. In contrast, ST2 receptor-deficient mice developed an attenuated inflammation in its airways and low levels of IL-5 and eosinophils in serum.[13,30]

Another prominent action of IL-33 seems to occur in relation to the defense against infection. Toll-like receptors (TLRs) participate in the inflammatory initiation mechanism in infectious processes, by recognizing Pathogen-associated molecular patterns (PAMPs) and endogenous ligands released by damage-associated molecular patterns (DAMPs). The binding of IL-33 to ST2 receptor can downregulate the activation of TLRs, by competing for the use of MyD88 signaling component.[31] Recently, Alves-Filho et al. found that IL-33 has a protective action in experimental cases of sepsis in mice, by showing that the inflammatory process was attenuated by treatment with recombinant IL-33. Since the activation of TLRs in neutrophils leads to suppression of the regulation of interleukin-8 beta receptor expression (CXCR2), critical for the recruitment of cells to the site of infection, the concurrent action of IL-33 by MyD88 protein decreases activation of TLRs and, in consequence, allows a greater expression of CXCR2, not inhibiting the influx of neutrophils to the infected site and providing an acceleration of bacterial clearance.[32]

IL-33 in human studies

As well as in experimental models, the participation of IL-33 and of its receptor ST2 has been investigated in several clinical conditions.

Serum levels of sST2 are increased in patients with acute asthma exacerbations, and patients with chronic asthma have high pulmonary concentrations of IL-33.[17] Bearing in mind that ST2 is preferentially expressed on Th2 cells and mast cells, this provides reasoning for explaining the association between high levels of IL-33 and asthma.[30]

In infectious processes, IL-33 promotes greater expression of surface receptor ligands of type CXCR2 cytokines, which are associated with migration of neutrophils to the site of infection and with bacterial clearance. It was shown that patients who have not recovered from a septic event expressed significantly lower concentrations of CXCR2 than those patients who have been healed. In addition, non-survivor septic individuals exhibited higher serum concentrations of sST2 as compared to those who survived. Given that sST2 is a decoy receptor for IL-33, these findings suggest that IL-33 is associated with a favorable outcome in a scenario of clinical sepsis.[13,32]

Recent studies suggest a protective role for IL-33/ST2 complex in cases of atherosclerosis and obesity, and also in cardiac remodeling in humans. IL-33 and its receptor ST2 seem to play a positive role in the progression of atherogenesis, and also protect the heart against the action of deleterious forces responsible for dilatation, muscle hypertrophy and fibrosis.[33] In humans, this cytokine reduces apoptosis of cardiomyocytes, improving left ventricular function through the suppression of caspase-3 and increased expression of inhibitor of apoptosis proteins.[34] It has been demonstrated that elevated serum levels of sST2 measured immediately after an acute myocardial infarction exhibited a direct correlation with serum creatine kinase levels and an inverse correlation with the ejection fraction of the left ventricle. In these patients, the levels of sST2 were higher in those patients who died or who have developed congestive heart failure.[34]

Complementarily, a clinical trial that evaluated patients in the first 12 h after an episode of acute coronary syndrome with ST-segment elevation showed that increased levels of sST2 at the initial assessment were predictors of heart failure. In addition, the combined evaluation of the ST2 and B-type natriuretic peptide (NT-proBNP) improved the prediction of cardiovascular death in these patients.[34]

The binomial IL-33/ST2 has been investigated in several rheumatic diseases. In patients with systemic lupus erythematosus (SLE), serum sST2 was higher than in healthy controls and, in addition, showed a positive correlation with disease activity (by SLEDAI index and serum anti-DNA antibody). SLE patients showed an inverse correlation between sST2 and serum levels of complement C3, suggesting that sST2 is a marker of disease activity. Serum IL-33 was comparable to healthy controls, and showed no correlation with levels of sST2, lupus activity, or involvement of a specific organ.[35] In spondyloarthritis, serum IL-33 levels were significantly higher in patients versus controls. Serum levels of ST2 differ between patients with ankylosing spondylitis and controls, but with no correlation with disease activity. Contrary to what occurs in patients with SLE, in cases of spondyloarthritis the ST2 receptor appears to act as a disease activity marker.[36]

Terras et al. found elevated serum levels of IL-33 in patients with systemic sclerosis versus healthy controls. In these patients, IL-33 was associated with early disease and microvascular involvement. These authors believe that, in the future, IL-33 will help to predict the onset of recurrent digital ulcers.[37]

In young people with juvenile idiopathic arthritis (JIA), the action of IL-33 and its receptor was evaluated. In 24 patients with the systemic type, five patients with polyarticular JIA associated with rheumatoid factor, four patients with macrophage activation syndrome and 20 healthy controls, serum levels of IL-33 and sST2 were measured. In patients

with systemic JIA, serum levels of IL-33 were detected in only four of 24 patients analyzed, and this cytokine did not correlate with disease activity or to sST2 levels. Moreover, serum levels of IL-33 were significantly increased in patients with rheumatoid factor-positive polyarticular JIA, compared to healthy controls. Serum levels of sST2 in patients with macrophage activation syndrome and in patients with active systemic JIA were significantly higher versus patients with polyarticular JIA associated with rheumatoid factor and versus healthy controls. In cases of systemic JIA, the sST2 levels were normalized in the remission stage. In cases of macrophage activation syndrome, serum levels of sST2 rose rapidly, with a gradual decrease after clinical resolution. The mechanisms proposed to explain the discrepancy between IL-33 and SST2 levels in systemic JIA are: formation of immune complexes of IL-33 with sST2, or as a result of the decoy receptor function assigned to sST2, as already discussed. The authors conclude that despite the small number of patients studied, the ST2 receptor may be an important mediator in cases of systemic JIA, providing a promising marker of disease activity, or even a new therapeutic target.[38]

Also in the group of rheumatic diseases, IL-33 and its receptor have been associated with systemic vasculitis. In patients with Behcet's disease, IL-33 serum levels were higher in patients with active disease compared to healthy controls or patients with inactive disease.[39] Ciccia et al. identified significantly higher levels of ST2 and IL-33 in inflamed arteries of patients with giant cell arteritis, and the major sites of expression of IL-33 were found in the neovascularization. In addition, the arteries of patients treated with glucocorticoids showed lower expression of this cytokine. It was noteworthy that increased expression of IL-33 was not related to a concomitant increase in cytokines of Th2 group, suggesting that IL-33 could act early in the disease, promoting arterial inflammation and angiogenesis, as well as modulating the innate immune response by a regulation of macrophage action.[40] Evaluating patients with Henoch-Schönlein purpura, Chen et al. demonstrated that serum levels of IL-33, but not of sST2, were higher in these patients during the acute phase, but returning to normal values in the convalescent phase. In this analysis, the serum levels of this cytokine were correlated with the severity of the disease and serum concentrations IgA-type anti-endothelial antibody and IgA anticardiolipin antibody.[41]

Furthermore, the involvement of IL-33 has been described in several other diseases of different etiopathogenesis as shown in Table 1.[13,42–49]

Table 1 – Participation of interleukin 33 and its receptor ST2 in infectious, metabolic and inflammatory diseases.

Disease	Role of IL-33 and ST2 receptor
Alzheimer's disease	Reduced brain expression of IL-33 gene
Inflammatory bowel disease	Increased IL-33 regulation in colonic cells
Autoimmune encephalitis	Increased expression of ST2 in the spinal cord of mice with autoimmune encephalitis
Hepatitis B	Severe encephalitis induced by IL-33 in experimental model
Hepatitis C	Exacerbation of encephalitis in ST2-deficient mice
Chronic renal failure	IL-33 and sST2 serum levels are elevated compared to healthy controls
Leishmania major	Reduced serum levels of IL-33 with treatment
Acute pancreatitis	IL-33 and sST2 serum levels increased compared to controls and to those with spontaneous resolution of hepatitis C
Pseudomonas aeruginosa	Positive correlation between IL-33 and serum transaminases
Toxoplasma gondii	Elevated serum concentration of sST2 compared to healthy controls
Trichuris muris	Relationship between sST2 and disease severity
Human immunodeficiency virus	Increased resistance conferred by anti-ST2 in an experimental model
Influenzae virus	Early elevation of serum sST2
Respiratory syncytial virus	Correlation between sST2 and severity parameters

Interleukin-33 and rheumatoid arthritis

The role of IL-33/ST2 complex has been much discussed in RA, mainly from the findings that IL-33 expression is increased in synovial membrane.[50]

Several studies using experimental models of arthritis have evaluated the participation of IL-33 in pictures of joint inflammation. The first study to evaluate the association of IL-33 with joint inflammation in animal models of arthritis was Damo et al., who described the role of IL-33 in experimental collagen induced arthritis (CIA) in mice. These authors demonstrated that IL-33 increased the response in a CIA model by activating mast cells, which express high density of ST2. Proposed mechanisms for joint inflammation induction by IL-33 were activation of mast cells, and therefore, the production of inflammatory cytokines; increased secretion of IL-6 and IL-1beta by activated mast cells; or CD4+ T cells stimulation that would lead to production of IL-5 and IL-13. This latter mechanism would increase the activation of B cells and immunoglobulin production, worsening the joint inflammation process and stimulating mast cell degranulation and the formation of immune complexes with collagen. These authors also demonstrated that, in this experimental model, mast cells are important, albeit not essential for the development of arthritis.[23]

In contrast, Lee et al. showed that mast cell-deficient mice were completely resistant to the induction of arthritis.[51] The reasons for this difference are not clear, but may be due to the fact that the animals used by Lee et al. were also deficient in neutrophils, unlike the experiments conducted by Damo et al. This could explain the different results, especially considering the critical role of neutrophils in the pathogenesis of CIA.[23,51]

Strengthening the role of neutrophils in this process, Verri et al. demonstrated that IL-33 is a potent chemical attractor for neutrophils in an experimental model of arthritis induced by methylated bovine serum albumin. IL-33 was produced mainly by FS and macrophages through the adaptive immune response. Although the exact nature of the induction of IL-33 synthesis in these cells is still unknown, it is likely that there is

involvement of the effect of inflammatory cytokines produced by T cells and macrophages after challenging with a specific antigen. In the presence of IL-33, occurs a recruitment of neutrophils to the joint site via at least two mechanisms: stimulating the production of TNF and IL-1beta by macrophages and synoviocytes, in addition to the surface receptor ligands of cytokines of types CXCL1 and CCL3, which, in turn, would allow the recruitment of neutrophils to the joint space; or IL-33 could directly activate neutrophils, recruiting these cells to the site of inflammation.[52]

Paradoxically, in a recent experiment in mice with CIA receiving IL-33 intraperitoneally, these authors showed the occurrence of inhibition of the development of arthritis after administration of this cytokine. This effect was associated with an improved immune response type 2, including the expansion of eosinophils, innate lymphoid cells type 2 and cells and cytokines from Th2 group. Since IL-33 acts directly on Treg cells via ST2, it was proposed that the treatment of these animals with IL-33 would enhance the suppressive capacity of such cells. Thus, these authors believe that IL-33 might exert anti-inflammatory properties in CIA.[53]

Concurrently with experimental studies, the demonstration of the presence of IL-33 and ST2 in the synovium of patients with RA has aroused great interest for the role of this complex in the pathogenesis of the disease.[10]

Palmer et al. detected an expression of IL-33 in human synovial tissue samples, in SF cultures of patients with RA, and in FS cultures of mice with arthritis. IL-33 was also found in endothelial cells of normal and inflamed synovial tissue. Human SF of RA patients constitutively expressed low levels of this cytokine, and the expression of mRNA and IL-33 protein increased after treatment with IL-1beta or TNF-alpha. These authors concluded that IL-33 is locally produced in inflamed tissues and that its neutralization may exert therapeutic effects in RA.[54]

The precursor of IL-33 was detected in the supernatant of FS cultures stimulated with TNF and IL-1beta. These results indicate that IL-33 is locally produced in inflamed joints and that, furthermore, the neutralization of IL-33 action has a therapeutic effect in the course of arthritis. In the CIA animal model, administration of a blocking antibody of ST2 attenuated the severity of arthritis and decreased joint destruction associated with the decreased production of IFN-gamma, as well as a reduction in IL-17 production. In addition, the levels of mRNA of the receptor activator of nuclear factor kappa B ligand (RANKL) diminished with the use of anti-ST2. These results indicate that IL-33 is locally produced in inflamed joints, and that the neutralization of IL-33 action has a therapeutic effect in the course of arthritis.[22,54]

In vivo, the expression of IL-33 is also induced in stimulated FS, suggesting that this expression can be maintained in an environment filled with cytokines, promoting the maintenance of chronic inflammation.[10]

The first study to identify high levels of IL-33 in serum and synovial fluid of patients with RA was that of Matsuyama et al., comparing these levels versus patients with infectious diseases and healthy individuals. In RA patients, a positive correlation between serum levels of IL-33 to disease activity using the Disease Activity Score 28 (DAS28) was observed. The number of painful and swollen joints was highest in the group positive for IL-33, while C-reactive protein (CRP), IL-1beta, IL-6 and TNF-alpha did not differ between groups.[55]

Hong et al. also found serum levels of IL-33 and sST2 significantly higher in patients with RA versus healthy controls.[10] It is worth mentioning the fact that serum levels of IL-33, sST2 and CRP were assessed before and after treatment with disease-modifying anti-rheumatic drugs (DMARDs). Of the ten patients, nine have received more than one type of synthetic DMARDs. Serum IL-33, sST2 and CRP decreased after treatment with DMARDs in patients with RA; furthermore, the authors found a positive correlation between the reduction of IL-33 concentration and the level of CRP after treatment. No relationship was found between sST2 values and CRP concentration changes.

Xiangyang et al. analyzed IL-33 levels in serum from RA patients and additionally investigated the pathophysiological importance of this cytokine (reference). Serum levels of this cytokine were higher in RA patients versus healthy controls, and these authors also observed a positive and significant correlation between IL-33 levels, positivity for anti-citrullinated protein antibodies and rheumatoid factor, and levels of matrix metalloproteinase (MMP) 3. In that study its authors also noted a strong correlation between serum levels of IL-33 and the Sharp score (modified) in patients with RA. These data arouse great interest in the use of IL-33 as a prognostic marker in patients with RA, although this study did not find any correlation between IL-33 levels and other clinical parameters, such as erythrocyte sedimentation rate, CRP and DAS28. In this study it was also demonstrated that the serum level of IL-33 was significantly increased in patients with interstitial lung disease, as compared to patients without lung involvement, suggesting that IL-33 would be associated with interstitial lung disease of RA.[56]

Perspectives

RA is a chronic arthropathy associated with joint damage and disability and functional decline.[57] Along with a better understanding of the pathophysiology of RA, the incorporation of genetic and molecular technologies has allowed the development of therapeutic procedures and improved the prognosis of patients.[58] The identification of the pro-inflammatory role of IL33 demonstrated by its expression in the synovium of patients with RA, indicates that this interleukin may be a therapeutic target.[23]

Conflicts of interest

The authors declare no conflicts of interest.

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