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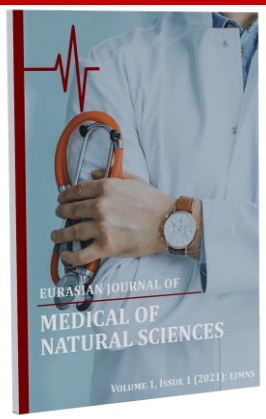

INTERLEUKIN -23, APPLICATION PROSPECTS (LITERATURE REVIEW)

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ABSTRACT

With the advent of new technologies, several new pro-inflammatory cytokines have been characterized, such as IL-23, which plays an important role in the pathogenesis of a number of inflammatory diseases. IL-23 pathways, as well as other proteins involved in the pathogenesis of inflammatory diseases, are currently under development and show promising efficacy and safety in early patient trials with minimal safety risks. Preliminary studies show that IL-23 therapy of the second generation is effective in the main inflammatory mechanisms.

Molecular and cellular immunology, combined with new ways of aggregating and using large sets of clinical data, are turning research ideas into new drugs for diseases that were considered incurable a few years ago. One of the main upcoming tasks is to test new concepts aimed at a wide range of signs of rare diseases of the skin, eyes, central nervous system, blood vessels and endocrine glands. To block the entire Th17 pathway, the drug must target IL-23R+ cells located in tissues (often behind the hemato-tissue barrier), as well as populations of migrating cells that interact with IL-23 and are reprogrammed to promote inflammation. These same cells are the driving force behind the response to chronic damage, responsible for many autoimmune diseases.

Interleukin-23 (IL-23) is a proinflammatory cytokine consisting of two subunits, IL-23A (p19) and IL-12/23B (p40), the latter being shared with interleukin-12 (IL-12). IL-23 is mainly produced by macrophages and dendritic cells in response to exogenous or endogenous signals and controls the differentiation and activation of T helper cells 17 (Th17), followed by the production of IL-17A, IL-17F, IL-6, IL-22 and tumor necrosis factor α (TNF-α). Although IL-23 plays a key role in the protective immune response to bacterial and fungal infections, its dysregulation has been shown to exacerbate chronic immune-mediated inflammation. Well-established experimental data confirm the concept that activation of the IL-23/IL-17 axis contributes to the development of a number of inflammatory diseases, such as psoriasis, psoriatic arthritis; As, Ankylosing spondylitis; IBD, inflammatory bowel disease; RA, rheumatoid arthritis; SS, Sjogren's syndrome; MS, multiple sclerosis. As a result, new clinical studies have focused on the blockade of this pathogenic axis as a promising therapeutic target in some autoimmune diseases; however, a deeper understanding of its contribution requires further study (Schinocca C, Rizzo C, Fasano S. And others 2021).

Sherlock JP, Cua DJ. (2021) IL-23 was discovered 20 years ago during the in silico bioinformatic search for new members of the IL-6 cytokine family. This immunomodulator is

a heterodimeric cytokine containing the p19 subunit associated with the p40 subunit shared with IL-12. It is important to note that the same common p40 subunit combines with the unique p35 subunit to form IL-12. Because of the common p40 subunit, much of the pathobiology attributed to IL-12 (1989-2002) was actually due to two different cytokines, IL-12 and IL-23. The discovery of IL-23 prompted a revision of the immune pathways regulating inflammatory diseases. At that time, it was believed that the classical IFN-γ response induced by Th1 cells was necessary for the induction and maintenance of autoimmune inflammation. Historically, Th1 cells have been thought to promote autoimmunity, mainly due to studies using p40-deficient mice and neutralizing antibodies to p40. However, there were inconsistencies. As discussed earlier, - / - , IFN-yR - / - , IL-12Rß2 - / - and IL-12p35 - / - mice) are very susceptible to autoimmune inflammation. When it was decided to revise the relative contribution of IL-12 compared to IL-23, using IL-23-deficient mice p19 - / - , p35 -/ - (IL-12-deficient) and p40 -/ - (IL-12-deficient) 12 and IL-23 deficient) it was shown that IL-23 plays an important role in autoimmune inflammation. It is noteworthy that disease-resistant IL-23p19-/- mice developed normal autoantigen-specific Th1 responses, while they had seriously impaired development of IL-17-producing T cells. In contrast, disease-susceptible p35-/-mice (lacking IL-12) showed impaired Th1 responses with a higher frequency of IL-17-producing pathogenic Th17 cells.

Although initial studies of IL-23 biology focused on antigen-mediated T cell responses, it became apparent that the cytokine plays an important role in a cluster of seronegative diseases for which the role of specific antigens is less clear. Of great interest is that these diseases reveal a very close relationship between the biology of IL-23 and specific anatomical features. IL-23 not only plays a prominent role on external barrier surfaces, especially on the skin and intestines, but also causes inflammation in internal sterile areas such as joints. While the skin-intestinal barrier is characterized by the presence of an extensive microbiome, the fundamental feature of joints is the presence of a high biomechanical load. IL-23-sensitive cells appear to be specifically localized on these barrier surfaces and structures that transmit biomechanical force. These tissue-resident cells are present even in a healthy state and can play a role in the regulation of barrier function, as well as in the restoration and maintenance of tissues [Sandborn WJ, Ferrante M, Bhandari BR. et al. 2020].

IL-23 in the clinic

Today, a clinical evaluation of IL-17 and IL-23 inhibitors confirmed the initial opinion that the IL-23-Th17 pathway may contribute to the development of many immune diseases associated with the barrier and "high-stress tissues". Studies show clinical benefits in inflammation of the skin, joints and gastrointestinal tract. Drugs of both IL-17 and IL-23 class are effective for psoriasis, including secukinumab and ixekizumab (anti-IL-17A), brodalumab (anti-IL-17RA) and tidrakizumab, risankizumab and guselkumab (anti-IL-23p19). Currently, secukinumab, izekizumab and guselkumab are also approved for the treatment of PsA. It is important to note that data from long-term clinical trials showed that ≥80% of patients maintained a persistent response with ≥90% skin cleansing, and more than half of patients maintained a persistent response with complete skin cleansing [Griffiths C., Papp KA, Song M. et al. 2020].

Yang K, Oak ASW, Elewski BE (2021) American scientists are considering the use of IL-23 inhibitors for the treatment of plaque psoriasis and psoriatic arthritis. In recent years, a deeper understanding of the pathogenesis of psoriasis, especially the role of T-helper 17, has led to the development of new classes of biological drugs aimed at modulators of the pathway of its disease. Among them, interleukin-23 inhibitors (for example, ustekinumab, guselkumab, tildrakizumab and risankizumab) have become safe and effective treatment options for moderate and severe plaque psoriasis; ustekinumab and guselkumab are also approved for

the treatment of psoriatic arthritis. Selective interleukin-23 inhibitors require less frequent dosing than interleukin-17 inhibitors and may have a more favorable risk profile without an increased risk of candidiasis or inflammatory bowel disease. Extensive studies of the pathogenesis of psoriasis have opened access to new classes of drugs that change the approach to the treatment of psoriasis and PsA. As the role of the IL-23/Th17 axis was further revealed, IL-23 targeted therapy quickly came to the fore, setting a new standard for psoriasis outcomes. Over the past 3 years, guselkumab, tildrakizumab and risankizumab have consistently entered the market, demonstrating higher efficacy and favorable safety profiles compared to existing drugs.

The work of Chinese scientists Liu T, Li S, Ying S, Tang S. (2020) traces the path of IL-23/IL-17 in inflammatory skin diseases. Interleukin-23 (IL-23) plays a key role in stimulating IL-17 production by activating Th17 cells. The IL-23/IL-17 axis represents an important pathway for targeted therapy of inflammatory diseases. New clinical trial data have shown that monoclonal antibodies against IL-23, IL-17 and tumor necrosis factor are effective in the treatment of patients with psoriasis, atopic dermatitis, purulent hydradenitis, lichen erythematosus, pemphigus and systemic sclerosis. Here, scientists summarize the latest knowledge about the biology, signaling, and pathophysiological functions of the IL-23/IL-17 axis in inflammatory skin diseases. Currently available biologics targeting the axis are also discussed.

New and emerging targeted methods of treatment of purulent hydradenitis which are considered in the work of Croatian scientists (Markota Čagalj A, Marinović B, Bukvić Mokos Z.2022) Purulent hydradenitis (GG) is a chronic recurrent inflammatory skin disease originating from hair follicles. The formation of inflammatory nodules, abscesses, fistulas and fistula passages is characterized by a large influx of key pro-inflammatory mediators, such as IFN-γ, TNF-α, IL-1, IL-17 and IL-12/23. Adalimumab is currently the only biological drug approved by the FDA and the European Medicines Agency (EMA) for the treatment of moderate to severe HS in adults and adolescents.

In inflammatory rheumatic diseases, the immune system attacks and damages connective tissues and invariably internal organs. Over the past decade, significant advances have been made in our understanding of the cellular and molecular mechanisms associated with rheumatic diseases. The discovery of the IL-23/IL-17 axis and the determination of its important role in inflammation led to the introduction of many necessary new therapeutic agents.

Li H, Tsokos GC. (2021) present the rationale for therapeutic effects on the IL-23/IL-17 axis in rheumatic diseases and the clinical results that have been achieved so far. Over the past decade, the identification of the pro-inflammatory function of interleukin-17 (IL-17) and the discovery of a new subset of T helper cells called Th17 cells that stimulate inflammation by producing IL-17, a characteristic cytokine, has led to an important understanding of chronic inflammation. Interleukin-23 (IL-23), a heterodimeric cytokine consisting of two subunits (p19 and p40), controls the production of pro-inflammatory cytokines, including IL-17, IL-22 and GM-CSF, contributing to the development and spread of pathogenic Th17 cells. This relationship between IL-23 and Th17s led to the concept of the IL-23-IL-17 axis as the main pathway controlling various autoimmune processes. Genetic and experimental data support the concept that activation of the IL-23/IL-17 axis contributes to the development of a number of inflammatory rheumatic diseases, including psoriasis, psoriatic arthritis (PA), ankylosing spondylitis (AS), rheumatoid arthritis (RA).) and systemic lupus erythematosus (SLE) . Since IL-17 production is believed to be controlled by IL-23, it was expected that blockade of either IL-17 or IL-23 should have the same clinical effect. Although experimental data on animal models of chronic inflammatory diseases, including uveitis, lupus, multiple

sclerosis, collagen-induced arthritis and AS, have provided insight, clinical data obtained from human trials of this therapeutic concept are still limited. Currently, a number of antibody-based drugs targeting the IL-23/IL-17 axis have been developed, including drugs blocking IL-17A (ixekizumab, secukinumab and netakimab), IL-17 receptor subunit A (brodalumab and KHK4827), IL-23p19 (guselkumab, risankizumab, tildrakizumab, mirikizumab and brazicumab) or IL-23p40 (ustekinumab). Despite the success of these biologics targeting individual cytokines or cytokine receptors, bispecific antibodies targeting two cytokines with non-overlapping pro-inflammatory roles present an attractive opportunity. COVA 322 and ABT-122, two bispecific antibodies targeting both TNF-α and IL-17A, are currently undergoing clinical trials in patients with rheumatoid arthritis, and the results seem encouraging. In addition to synergism with TNF-α, the effects of IL-17A can also be potentiated by IL-17F, which exhibits 50% sequence homology and transmits signals through the same receptor. Related trials with various antibodies synergistically acting on two isoforms of IL-17 (bimekizumab, ALX-0761 and NI-1401) are ongoing.

Miossec P, Kolls JK (2012) After establishing the pathogenic role of the IL-23/IL-17 axis in various autoimmune and inflammatory diseases, the hard work of many groups of researchers, clinicians and colleagues in the industry has opened a new era of human treatment possibilities. who suffers from inflammatory rheumatic diseases. Although encouraging clinical results are emerging, the overall outcome remains challenging. Agents acting on IL-23/IL-17 are usually impressively effective in psoriasis and even surpass the effect of anti-TNF therapy, but they demonstrate only moderate therapeutic efficacy in people with PsA. Moreover, most of these biological drugs targeted at IL-23/IL17 have given negative results in the treatment of RA, despite the fact that convincing experimental data have demonstrated the involvement of this axis in the pathogenesis of RA. Last but not least, despite the fact that IL-17 inhibitors have proven their effectiveness, IL-23 blockers have not shown therapeutic value in the treatment of patients with AS. Despite the advances made with respect to the aforementioned diseases, little is known about the role of this axis in other rheumatic diseases, including Sjogren's syndrome, vasculitis and gout.

Vukelic M, Laloo A, Kyttaris VC. (2020) IL-23 levels track the activity of SLE disease mainly in the renal, dermal and musculoskeletal regions. IL-23 levels positively correlated with the overall activity of SLE disease measured using SLEDAI. Moreover, IL-23 correlated with cutaneous, renal SLEDAI domains and arthritis, but not with cytopenia or serositis. IL-23 also correlated with the positivity of antibodies against double-stranded DNA and inversely correlated with C3 levels. We found no association between the demographic data of patients, previous manifestations of the disease, medications or autoantibody profile and IL-23 levels. No immunomodulatory drugs appeared to affect IL-23 levels, which indicates that modern drugs used in SLE are not as effective for disabling the IL-23/IL-17 axis. The authors of the study also found that IL-23 levels are elevated not only in patients with lupus nephritis, but also in patients with non-renal lupus and, in particular, in patients with arthritis and skin diseases. Serologically active patients with positive antibodies against double-stranded DNA and/or low C3 levels are also more likely to have elevated IL-23 levels. Future studies will be required to find out whether serum IL-23 levels can serve as a biomarker of renal, dermatological and musculoskeletal exacerbations in lupus, as well as a predictor of reaction to biological drugs that affect the IL-23 pathway.

Katayama H.(2021) Antibodies to interleukin-17A and anti-interleukin-23 may be effective against Alzheimer's disease. Amyloid β (Aß) is an agonist of the formylpeptide receptor 2, indicating that Aß is a potent chemoattractant for phagocytic leukocytes. Therefore, in all likelihood, Aß attracts peripheral blood neutrophils, monocytes, as well as microglial cells in the parenchyma of the brain and activates them. However, the role of

microglial cells and their monocyte precursors in the pathogenesis of AD remains unclear. Neutrophils have recently been found to be present in areas with Aß deposits in the brain of AD and in transgenic mice with the AD model. Since the brain is vulnerable to the effects of reactive oxygen species (ROS), and neutrophils secrete a large amount of ROS, neutrophils appear to be the driving force of AD. Therefore, it is possible that anti-IL-17A and anti-IL-23 antibodies are effective against AD, since it can be assumed that these antibodies prevent the transfer of neutrophils from the bone marrow into the bloodstream and, thus, inhibit the infiltration of neutrophils into the brain in AD. IL-17A stimulates bone marrow stroma (BM) cells to secrete G-CSF, and G-CSF mediates granulopoiesis. Neutrophils in the bone marrow are attached to factor-1a derived from stroma cells (SDF-1a), which is present in the bone marrow stroma or on the surface of osteoblasts, reticular cells and endothelial cells. Attachment is mediated by CXCR4 on the neutrophil surface. G-CSF suppresses the expression of CXCR4 on neutrophils and reduces the level of SDF-1a in the bone marrow, disrupting attachment. Neutrophils released from SDF-1a migrate into the peripheral circulation to maintain neutrophil homeostasis. Antibodies to IL-17A prevent IL-17A-mediated granulopoiesis and neutrophil migration from the bone marrow and presumably interrupt neutrophil infiltration into the brain in AD. Clinical studies using antibodies to IL-17A and anti-IL-23 in patients with AD are needed.

As already noted, convincing data have now been obtained on the important role of the Thn immune response in the pathogenesis of a wide range of human IVZ [Beringer A, Noack M, Miossec P. 2016]. Psoriasis is the most frequent IVZ of a person, characterized by a high frequency of comorbid diseases, including cardiovascular pathology and diabetes mellitus, metabolic syndrome, depression, and possibly PsA, within the framework of the so—called psoriatic disease. The characteristic features of psoriasis are the proliferation of keratinocytes and the accumulation of immune cells (T cells, macrophages, leukocytes) and myeloid (CD11+) dendritic cells (DC) in the affected skin, which are involved in the polarization of the immune response by both Th17- and TM-type. These cells produce a wide range of cytokines, which, acting on keratinocytes and other skin resident cells, induce hyperproliferation of the epidermis, neoangiogenesis and inflammation of the skin as a whole. A unique place in the immunopathogenesis of psoriasis is occupied by two autoantigens: cathelicidin (cathelicidin/LL-37) and ADAMTS-like protein 5, the presentation of which DC induces the synthesis of IL23. In the skin of patients with psoriasis, an increase in the content of Thn cells, ubT cells, SHC3 cells, EC cells, mast cells synthesizing IL17, IL23, IL22, IL23P and TNFa was noted. The integral and individual action of IL17, IL22 and TNFa on keratinocytes leads to the induction of transcription of genes encoding the synthesis of antimicrobial proteins (8100A7) and peptides (C-37 — cathelicidin), as well as "pro—inflammatory" mediators - chemokine ligand 20 (C^20), CX^1,2,3,8, IL19, IL20, IL15, IL36. The development of epidermal hyperplasia and vascular proliferation are caused by the action of both cytokines (IL22, IL19, IL36) and "classical" growth factors such as epidermal growth factor, TFR, fibroblast growth factor, endothelial growth factor and platelet growth factor. It is noteworthy that according to genetic studies, the carriage of a specific single-stranded polymorphism of the IL23P and IL22B genes is associated with "sensitivity" to the development of psoriasis, which brings psoriasis closer to other diseases associated with the activation of the IL23/IL17 axis.

There is an opinion that psoriasis without joint damage and PsA should be considered as variants of the development of "psoriatic disease", the differences between which are determined by the "profile" of cytokine synthesis and genetic factors. In any case, along with psoriasis, AS and PsA are classic examples of diseases whose pathogenesis is associated with the activation of the IL23/IL17 axis. As with psoriasis, there was a connection between the development of PsA and the carrier of single-nucleotide (protective) polymorphism of the

genes encoding IL23YA and IL23, as well as polymorphism of the AST1 gene (TCAR31P2) involved in IL17YA-mediated signaling. In the affected skin and synovial membrane of patients with PsA, an increase in the expression of IL12p19—IL23P, IL17A—IL17P was noted. In vitro experiments have shown that IL17 induces hyperproduction of IL6, IL8 and matrix metalloproteinase 3 (MMP3) by synoviocytes isolated from the joints of patients with PsA. In the peripheral blood of patients with psoriasis and PsA, an increase in the number of IL17+ cells and CD22+CD4+ cells was noted. There is evidence of a correlation between the content of another subpopulation of IL17 cells - CD8+ — in synovial tissue, the activity of inflammation and the severity of joint destruction. In the synovial fluid of patients with PsA, an increase in the content of 1Y17 cells and the concentration of IL17, IL17P, IL23 was noted, correlating with the severity of arthritis.

With the advent of new technologies, several new pro-inflammatory cytokines have been characterized, such as IL-23, IL-31 and IL-33, which play an important role in the pathogenesis of the psoriatic process. It was determined that single nucleotide polymorphisms (SNPs) in the promoter regions of the IL23, IL31 and IL33 genes play an important role in controlling the expression of the corresponding cytokines involved in the immunopathogenesis of psoriatic disease. By the authors (Smolnikova M. V. 2020) analyzed the frequency of genotypes and allelic variants of polymorphisms IL23A (rs2066808), IL23R (rs2201841), IL31 (rs7977932) and IL33 (rs7044343), in order to search for genetic markers of predisposition to psoriasis and psoriatic arthritis. Genotyping of patients with psoriasis (PS, n = 77), median age 31.0 years (27.0-43.0), psoriatic arthritis (PsA, n = 99), median age 49.0 years (39.0-56.0) and practically healthy residents of Krasnoyarsk (n = 103), median age 32.0 years (24.0-38.0). DNA extraction from whole venous blood was carried out using a standard set with a sorbent. Genotyping of single nucleotide polymorphisms IL23A (rs2066808), IL23R (rs2201841), IL31 (rs7977932), IL33 (rs7044343) was carried out using real-time PCR using specific oligonucleotide primers and fluorescently labeled probes. The frequencies of allelic variants of the studied cytokine genes in the control group obtained during the study correspond to their distribution in the Caucasian populations - the IL23A*T, IL23R*T, IL31*C, IL33*C alleles predominate. When comparing the frequency of distribution of allelic variants of the IL23A, IL23R, IL31, IL33 genes, we did not obtain statistically significant differences between patients and the control group. Despite the fact that when comparing the frequency of distribution of allelic variants of the IL23A, IL23R, IL31, IL33 genes, we did not obtain statistically significant differences between patients and the control group, there are results worthy of attention. Thus, in patients with PS, the frequency of the allelic variant C* IL23A (rs2066808) is lower than in the population sample, which may indicate its specific role in relation to the development of the disease. All this dictates the need to continue research with the assessment of other ONPS and to increase the sample of patients in search of potential genetic markers of psoriatic disease.

Novikov Yu.A. et al. (2019) present the results of the use of immunological markers of nerve tissue damage as an element of a prognostic model of nervous system damage in syphilis. A comprehensive laboratory examination of patients with neurosyphilis and syphilis without a specific lesion of the nervous system was carried out, which were observed in the venereological department of the Public Health Institution "Clinical Skin and Venereological Dispensary" in Omsk. All patients underwent serological blood examination, serological and clinical examination of cerebrospinal fluid, immunological examination of cerebrospinal fluid (interleukins - 23, 12p40, GFAP). Based on the study of IL-23, IL-12p40, GFAP, protein levels and pleocytosis in the cerebrospinal fluid, a prognostic model of the development of neurosyphilis in patients with syphilis without specific damage to the nervous system is proposed. The analysis of immunological changes in the cerebrospinal fluid of patients

showed that an integral part of the diagnosis of neurosyphilis can also be the study of a number of cytokines and markers of nerve tissue damage in the cerebrospinal fluid as the most specific and reliable, especially in the absence of clinical symptoms from the central nervous system.

Recently, when studying the pathogenesis of ovarian malignancies, scientists around the world have been of great interest in studying the role of immune response and inflammation genes. The article (Mingazheva E. T. et al., 2019) presents the results of a study of the role of allelic variants of the genes NFKB1 (rs28362491), IL6 (rs1800795), IL18 (rs1946518) and IL23R (rs7517847, rs10889677) in the pathogenesis of breast cancer in women from the Republic of Bashkortostan. DNA samples of women with an established diagnosis of ovarian cancer (n=238) and healthy individuals (n=284) served as the material for the work. Genotyping of DNA samples was carried out by polymerase chain reaction (PCR) with subsequent analysis of the polymorphism of the lengths of restriction fragments and allele-specific PCR. It was found that the genetic markers of ovarian cancer risk for premenopausal women of Russian ethnicity are the genotypes rs28362491*ID in the NFKB1 gene and rs1946518*CA in the IL18 gene. The carriage of the rs1800795*GG genotypes in the IL6 gene and rs10889677*CC in the IL23R gene for postmenopausal Tatar women is a protective factor. For Tatars with the rs10889677*CA genotype in the IL23R gene in postmenopause, on the contrary, an increased risk of developing the disease was shown. The markers of a reduced risk of developing RS in Russians also include the rs1946518 *AA genotype in the IL18 gene, which was noted as a protective factor for both pre- and postmenopausal women, as well as in patients with this oncopathology with the initial and advanced stages of the disease. A comparative analysis of the frequency distribution of alleles and genotypes of the polymorphic variant rs7517847 in the IL23R gene among patients with RS and healthy donors revealed no statistically significant differences between the study groups.

Among the interleukins that can take part in antitumor protection, as mentioned above, is IL-23, a member of the IL–12 family, which has the properties of pro-inflammatory cytokines. Its biological activity is associated with the ability to enhance the proliferation of T-lymphocytes at the initial stages of activation of naive CD4+ and CD8+ T cells, increased production of IFN-γ, secretion of IL-17, increased production of IL-10 by these cells, increased activity of dendritic cells, etc. In experiments using adenocarcinoma cells of mice ST26 and melanoma B16F1, which underwent transfection of the IL-23 gene, followed by the introduction of these cells to mice, an increase in antitumor activity was noted. The obtained data allowed the authors to conclude that IL-23, like IL-12, can be an effective antitumor effect, however, the antitumor effect of IL-23 is carried out by other mechanisms compared to IL-12, since CD8+ T-lymphocytes play the main role in the action of the latter [Barilo A.A., Smirnova S.V., Smolnikova M.V.2018].

Thus, the literature data provide an assessment of the main properties of interleukin - 23. IL-23 is produced mainly by activated macrophages and dendritic cells. It is a pro-inflammatory cytokine. Researchers show the role of IL-23 signaling in inflammation based on experimental work on animal models, and is currently being used with great success to treat a diverse set of inflammatory diseases. It is a heterodimer consisting of p19 and p40 subunits. Its functional receptor is also a heterodimer consisting of the IL-12 β1 and IL-23R α receptor, which is expressed mainly on activated T cells. 56IL-23 regulates the differentiation and maintenance of IL-17-producing T-lymphocytes (Th17 and γδT17) depending on JAK2/STAT3.57-59 Disregulation of the IL-23/IL-23R pathway has been implicated in various inflammatory and/or autoimmune diseases, such as Crohn's disease and psoriasis, among others. Although the role of IL-23R+ γδT cells in hypertension has not yet been studied, there

is a report showing that IL-23 increases the expression of the SGK1 gene in the intraepithelial cells of γδT.69 As mentioned above, SGK1, in turn, is able to induce IL-23R in Th17 cells by phosphorylation of the fork box of transcription factor O1,16 indicating the presence of a direct transmission along the IL-23/IL-17 axis.

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