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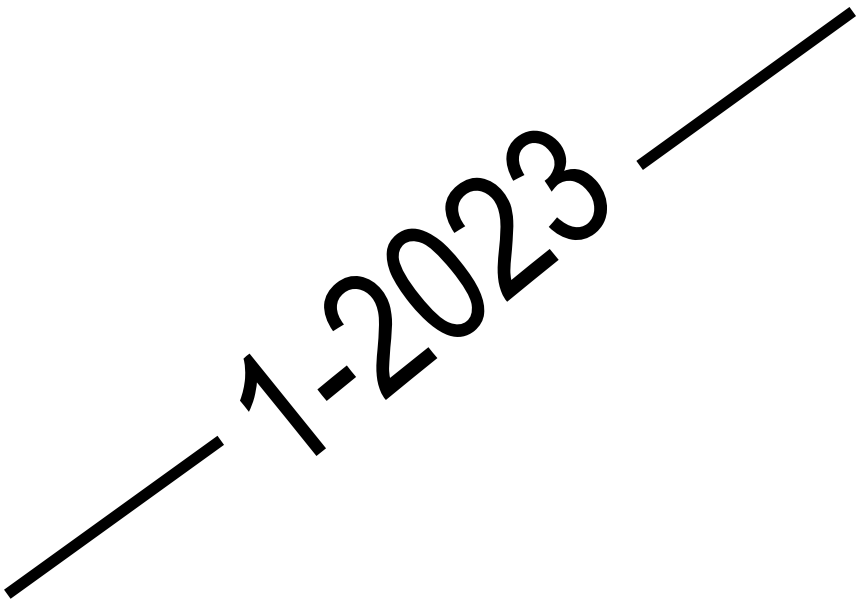

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REAKTIV ARTRITNING GENETIK JIHATLARI

GENETIC ASPECTS OF REACTIVE ARTHRITIS

ГЕНЕТИЧЕСКИЕ АСПЕКТЫ РЕАКТИВНОГО АРТРИТА

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Annotatsiya

Reaktiv artrit - bo‘g'imlarning eng keng tarqalgan surunkali yallig'lanish kasalliklaridan biri. Reaktiv artrit bilan og'rigan bemorlar revmatologik shifoxonalarda bemorlarning taxminan 10% ni tashkil qiladi va kasallikning surunkali shaklida bo‘g'imlarning funksional qobiliyatining sezilarli darajada yo‘qolishi va og'ir asoratlar paydo bo‘lishi mumkin, bu esa bemorlarning nogironligiga olib keladi. Reaktiv artritga bo‘lgan qiziqish, shuningdek, bir qator bemorlarda, ayniqsa, jarayon surunkali bo‘lsa, bo‘g'imlarda ankilozlanishgacha bo‘lgan destruktiv jarayonlarni rivojlanishi bilan bog'liq. Reaktiv artritga chalingan bemorlarning bo‘g‘imlarida va umurtqa pog‘onasida destruksiyaning rivojlanishi o‘z navbatida bemorlarning hayot sifatiga salbiy ta’sir etishi, ayniqsa navqiron yoshdagi insonlarning xastalanishi, ularning ish qobiliyatining pasayishi va nogironlik ko‘rsatkichining ortib borishi hanuzgacha dolzarb muammo sifatida namoyon bo‘lmoqda.

Аннотация

Среди хронических воспалительных заболеваний суставов одним из наиболее часто встречающихся является реактивный артрит. Пациенты реактивным артритом составляют около 10% больных ревматологических стационаров, причем при хронической форме заболевания может развиваться значительная утрата функциональных способностей суставов и возникновение тяжелых осложнений, что приводит к инвалидизации пациентов. Интерес к реактивному артриту связан также с тем обстоятельством, что у ряда больных, особенно при хронизации процесса развиваются деструктивные процессы в суставах вплоть до анкилозирования. Развитие деструкции суставов и позвоночника у пациентов с реактивном артритом, в свою очередь, отрицательно сказывается на качестве жизни пациентов, особенно у молодых людей, а также снижение их трудоспособности и увеличение заболеваемости остается актуальной проблемой.

Abstract

Reactive arthritis is one of the most common chronic inflammatory diseases of the joints. Patients with reactive arthritis make up about 10% of patients in rheumatological hospitals, and in the chronic form of the disease, a significant loss of the functional abilities of the joints and the occurrence of severe complications can develop, which leads to disability of patients. Interest in reactive arthritis is also associated with the fact that a number of patients, especially when the process is chronic, develop destructive processes in the joints up to ankylosing. The development of destruction of the joints and spine in patients with reactive arthritis, in turn, adversely affects the quality of life of patients, especially in young people, as well as a decrease in their ability to work and an increase in morbidity remain an urgent problem.

Kalit so‘zlar: *reaktiv artrit, citokinlar, spondiloartrit, bo‘g‘im sindromi,* IL-17A rs2275913*, IL 18 gen.*
Ключевые слова: *реактивный артрит, цитокины, спондилоартрит, суставной синдром, ИЛ-17А rs2275913, ген ИЛ 18.*
Key words: *reactive arthritis, cytokines, spondyloarthritis, joints syndrome, IL-17A rs2275913, IL-18 gene*

INTRODUCTION

Reactive arthritis (ReA) is a "sterile" inflammatory joint disease in which infectious agents and their antigens are absent in the synovial fluid and synovial membrane of patients. ReA is a seronegative spondyloarthritis, which meets the criteria of the European Group for the Study of Spondyloarthritis. With the introduction into clinical practice in the early 90s of the reverse transcriptase polymerase chain reaction (RT–PCR) method, small amounts of Ch.trachomatis DNA and RNA were found in the joint cavity. The presence of these nucleic acids, which have a very short lifetime in tissues (several minutes), indicated the possibility of transcription and, consequently, active reproduction of bacteria in the joint cavity.

Later it was discovered that the joint is not normally a sterile environment. Thus, the DNA of various microorganisms was found in biopsies of the synovial membrane of healthy people and patients with osteoarthritis (in 9 and 20%, respectively). Genetic factors in the pathogenesis of ReA are being actively studied. In particular, a close association of the disease with the HLA–B27 antigen has been proven. There are several points of view about its role in the development of ReA.

MATERIALS AND METHODS

According to one of them, the HLA–B27 antigen is an antigen–presenting molecule capable of presenting arthritic peptides to cytotoxic CD8 T-lymphocytes. The object of lysis in this case is probably chondrocytes localized both in the cartilage tissue and in the entheses, where the inflammatory process also develops. According to Y. Sobao et al. (1999), for some bacteria (Yersinia, Salmonella), the presence of HLA–B27 is a factor that significantly facilitates their invasion into synovial membrane cells. In 2000, R.A. Colbert et al. a new theory of the pathogenesis of ReA was proposed, the essence of which is that under the influence of lipopolysaccharides of the cell wall of causal microorganisms during antigenic processing in human monocytes, an incorrect "assembly" of heavy chains of HLA–B27 is possible, which leads to the accumulation of HLA–B27 molecules in the endoplasmic network of these cells.

At the same time, despite the large number of studies conducted in genomic medicine devoted to the study of the mechanisms of development of reactive arthritis, the final answer to this question has not yet been formulated.

Endogenous immunomodulators, that is, cytokines are important in the regulation of almost all body systems. Compared with exogenous modulators (chemical, bacterial or plant origin), cytokines exert their abilities through specific receptors and manifest themselves as natural regulators of the functional activity of various types of tissue. This manifests itself due to the prospects for the use of cytokines in the treatment and prevention of various immunopathological diseases, as well as for the generation of various types of cells during cellular immunotherapy.

RESULTS

It is known that T-helper 17 (Th17) plays an important role in autoimmune processes, destruction of joints and connective tissue. Interleukin-17A (IL-17A) is one of six members of the IL-17 family, which includes IL-17A–F, which are cytokines produced by Th17 cells and other related immune cells. IL-17A stimulates the production of many factors, such as tumor necrosis factor-alpha (TNF-α), IL-6 and IL-1β, which play an important role in the inflammatory response.

It was studied by Shen L. that the relationship between six IL-17A polymorphisms and the risk of arthritis is the most suitable variant – IL-17A rs2275913, G-197A. However, a meta - analytical study conducted by Chen P. The results showed a significant relationship between IL-17A rs2275913 polymorphism and susceptibility to arthritis in the general population (allele model A versus G; heterozygous model GA versus GG); homozygous model AA versus GG; dominant model GA+ AA versus GG). When analyzing subgroups, IL-17A rs2275913 polymorphism was significantly associated with the risk of arthritis in Europeans (allele model A versus G; heterozygous model GA versus GG; dominant model GA + AA versus GG), but not in Africans or Americans. Since the results of these studies still remain inconclusive. And also according to the study of Marco A. Rocha Loures detected TNF and IL17 genotypes independently of these factors, which may provide more convincing evidence of a link between these polymorphisms and susceptibility to spondyloarthritis, AS disease and psoriatic arthritis. Moreover, the incidence is relatively severe in patients with spondyloarthritis bearing the IL17A A/G genotype and the A allele, as well as the IL17F T/C genotype and the C allele. Many people know that the association of these genetic polymorphisms with spondyloarthritis has not yet been proven.

As a result of many studies conducted, it was found that IL 18 has an important role in the humoral immune response, thereby its significantly higher serum level in patients with Spondyloarthritis. IL 18 belongs to the IL1 family, because of the homology with the IL1 family, IL18 was named IL1u, but as

it turned out later, IL18 does not bind to the IL 1 type I receptor and is therefore isolated as a new cytokine, IL18.

According to Yakushenko E.V.'s research, IL 18 is produced mainly by macrophages, including Kupffer liver cells, and dendritic cells. The presence of IL-18 mRNA is detected in many cell types, in particular in CD4(+), CD8(+), B- and NK cells. In addition, IL-18 mRNA in humans is found in skeletal muscle cells, keratinocytes, myelomonocytic hematopoietic and human cell lines. It has been proved that in the MyD88-mediated signal activating the inflammatory response cascade, the effects of IL-18 are realized through interaction with a receptor consisting of an auxiliary protein of the IL-18 receptor (IL-18RAP) and the IL-18 receptor protein (IL-18R1). The IL-18RAP/IL-18R1 receptor complex forms a signaling chain and mediates signal transduction initiated by IL-18. Polymorphism of IL18RAP and IL-18R1 genes is associated with a variety of immuno-mediated diseases, which suggests the extreme importance of the balance of IL-18 signaling pathways in connection with the activation of innate and acquired immune response. The expression of the IL 18 gene is so widely represented in various cell types, indicating the participation of this cytokine not only in the formation of the immune response, but also in the regulation of other physiological processes in various tissues and organs. IL 18 has various effects on immunocompetent cells. The main effect of IL 18 is the induction of IFNy T- and NK production by cells, which is why IL 18 was originally called the IFNy inducing factor.

The analysis of the amino acid sequence showed the similarity of the structure of IL18 and IL1ß by 18%, IL18 and IL1a or IL1PA by about 15%. Both cytokines have a unique β-folded structure. IL1ß and IL18 are synthesized initially as precursor molecules, then a mature biologically active peptide is produced using the IL1ß converting enzyme (caspase 1). However, despite the partial similarity of the structure of IL1 and IL18, the specific biological functions and receptor systems of these two cytokines are different. If IL18 activates the maturation of type 1 T helper cells (Th1) and does not affect the proliferation of type 2 T helper cells (Th2), whereas IL1 does not affect the proliferative response and production of type 1 cytokines and induces the proliferation of type 18 Th2, its receptor and IL 18 binding protein are a polymorphic structure that is formed as at the level of allelic polymorphism of the genes of these proteins. According to the literature, IL 18 genes were found in more than 9 allelic variants, as well as in IL 18 binding protein more than 11 allelic variants. The presence of any allelic variant of IL 18 or IL 18 binding protein is associated with an increase in the frequency of various pathological processes.

It is known according to K.F.Nolan, the gene encoding IL 18 is located on chromosome 11, locus 1q22.2-q22.3., has 6 exons, 5 introns and one promoter. Despite the fact that the exons and intron-exon boundaries of IL18 were sequenced repeatedly in different populations, no non-synonymous SNPs were found in the gene structure. In addition, no SNPs were found that could interfere with mRNA splicing. This indicates a high conservatism of the gene, most likely directly related to the regulation of the inflammatory response. However, there is a variation in the gene structure within the 5'-untranslated region (UTR) and 3'UTR, which can cause differences in the translation rate and stability of mRNA, as well as changes in the proximal promoter, which affects the transcription rate.

DISCUSSION

However, in order to further determine the role of polymorphic variants and the significance of variations in serum concentrations in the pathogenesis of the progression of diseases of the spondyloarthritis groups, it is necessary to prospectively monitor patients with reactive arthritis, as well as individuals who carry risky genotypes, but do not have joint syndrome at the time of ehamination.

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