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Pharmacogenetics - A New Word in the Treatment of Rheumatoid Arthritis

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Abstract

As you know, rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease. Over the past few years, scientists have paid special attention to the close interaction of genetic and epigenetic mechanisms of the development of the disease. Research has focused on the effects of environmental factors, as well as the mechanisms of the innate and adaptive immune systems that can influence the various stages of RA. Coverage of various aspects of the pathogenesis of RA will help improve existing diagnostic methods of research and identify new opportunities for developing more specific points of application in the treatment of this serious disease.

Introduction

Rheumatoid arthritis (RA) is a chronic immune-inflammatory (autoimmune) disease manifested by progressive joint destruction, systemic inflammation of internal organs, and a wide range of comorbid diseases associated with chronic inflammation, and often with unwanted drug reactions (ADR) [1]. The pathogenesis of RA is determined by a complex interaction of environmental factors and genetic predisposition, which lead to global disorders in the system of innate and acquired immunity and are detected long before the development of clinical symptoms of the disease [2-4].RA still belongs to diseases with an incompletely understood etiology. In the literature, the issue of its multifactorial nature is widely discussed, where genetic, immunological, infectious and other factors are actively involved. The intensive study of biomarkers in rheumatology has arisen from the need to understand the mechanisms underlying some rheumatic diseasesJoint damage in RA develops as a result of chronic inflammation of synovia during the interaction of resident cells, such as fibroblast-like synoviocytes, with cells of innate (macrophages, dendritic cells, mast cells, neutrophils) and adaptive (B- and T-lymphocytes) immunity [5, 6, 7]. Defects in RA occur at three levels, culminating in persistent inflammation: level 1 — the site of inflammation, such as the synovium, where autoreactive and inflammatory cells proliferate; level 2 - the interface of regulatory processes, for example, the mechanism of peripheral tolerance and level 3 - the central level of regulation of autoimmunity [8].These levels are arbitrary and often overlap. Another major problem is that the changes that cause the disease and the subsequent process of its development can differ between groups of patients. Presumably, changes at regulatory levels leading to persistent inflammation, as well as changes that inhibit reversible processes, may be characteristic only of RA. Immune biomarkers.

A diagnostic biomarker, by definition, must be an objective, quantifiable characteristic of biological processes that aids in the accurate diagnosis of a condition. Currently, autoantibodies to rheumatoid factor (RF) and C-reactive protein (CRP) are well-known markers of RA. Numerous studies have evaluated the usefulness of RF [16,17,22,25-27], anti-CRP [16,17,22,26-32] and their variants.

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Antibodies (usually of the IgM class) to their own immunoglobulins of the IgG or RF class are one of the manifestations of a violation of tolerance to their own antigens, which characterizes the autoimmune process.It is believed that RF forms macroscopic immune complexes from IgG, which cause mechanical damage to the walls of blood vessels and synovial membranes, but this is not the only possible mechanism of RF pathogenic action.

Antibodies to cyclic citrullinated are often found in the serum of patients with rheumatoid arthritis. peptide (ACCP). Citrulline is one of the amino acids in the body, which is not encoded in DNA by a specific codon, but is formed from arginine after synthesis. Replacing arginine with citrulline affects the chemical properties of the protein and makes it more hydrophobic, which affects its spatial structure. Such unusually folded proteins can be seen by the immune system and autoantibodies are formed to them. Many proteins of the synovial fluid, including fibrin and fibrinogen, contain arginine residues, which are modified into citrulline under conditions of inflammation and cause an autoimmune response [11].

In the course of a study aimed at a comprehensive assessment of markers of inflammation in patients with rheumatoid arthritis, an increase in the level of C-reactive protein, calprotectin, IL6, IL-8, TNF-a was also revealed in comparison with the control [12].

Genetic aspect

The basis of the pathogenesis of RA is formed by a triad of genetic predisposition, environmental influences and autoimmunity, which is also rightly called the "Bermuda triangle". In this triad, a significant proportion is accounted for by heredity, as evidenced by studies on twins and monitoring of morbidity in families. To date, hundreds of genes are known whose polymorphism makes a significant contribution to the development of RA, and, as the Italian scientists C. Perricone et al. ., their discovery - "a never-ending story" [31]

Genome-wide search for associations has shown that certain variants of genes regulating the immune system have a significant effect on the onset and development of this disease. The genes of the main histocompatibility complex affect the predisposition to rheumatoid arthritis most of all. The proteins encoded by these genes are responsible for the binding of the antigen to T-lymphocytes. Some of their variants can carry out this process more efficiently against their own antigens, thereby promoting the initiation of the autoimmune process. One of the most interesting in this regard is the HLA-DRB1 gene, whose connection with rheumatoid arthritis has long been known. Various alleles of this gene, for example, encoding proteins for the self-acid motif QKRAA, are associated with the greatest susceptibility to disease. Variants from the DRB1 * 04 family (determining the HLA-DR4 serotype) are considered to be the most "unfavorable" ones [32].

Allelic variants of the genes of many proteins involved in the activation of T-lymphocytes are also responsible for the predisposition of their carriers to rheumatoid arthritis. Among these proteins are molecules associated with a co-stimulating signal (CD28, CTLA-4), pro-inflammatory cytokines and their receptors (IL2, IL2RA, IL21), which are necessary for the functioning of T cells, as well as various enzymes that are important intracellular players in the activation of lymphocytes (PTPN22, PRKCQ, TAGAP). The interaction of specific allelic variants of different genes (for example, HLA-DRB1 and PTPN22) increases the likelihood of disease [34]. Berglin et al. Tried to analyze the predictability of RA development using a combination of an autoantibody (anti-CCP) and a common epitope allele: HLA DRB1 * 0401 or B1 * 0404 (SE HLA DR). They demonstrated increased predictability as well as similar specificity in predicting RA. Likewise, the combination of a single nucleotide polymorphism in the PTPN22 gene encoding lymphoid protein tyrosine phosphatase and the presence of a detectable level of anti-CCP demonstrated improved predictability of RA development as well as increased prediction

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specificity. The presence of the PTPN22 1858T (CT + TT) variant and anti-CCP had 100% specificity with an almost 20-fold increase in the power of predictability [35]. These studies highlight the fact that the presence of susceptibility markers improves the predictive value of a positive additional test.

Epigenetic mechanisms can also regulate the immune system, increasing the risk of rheumatoid arthritis. The action of regulatory RNAs, histone or DNA modification can lead to a change in the usual "schedule" of the work of key genes involved in pathogenesis.

Pharmacogenetics

For the best long-term results, it is very important that the patient starts taking basic anti-inflammatory drugs (DMARDs) as early as possible. These drugs have immunosuppressive properties, respectively, the autoimmune process, literally eating a joint affected by rheumatoid arthritis, can be limited at an early stage [45,48].

When using methotrexate, the best ratio of efficacy and toxicity is noted compared to the use of other basic anti-inflammatory drugs.The immunomodulatory and anti-inflammatory effect of the drug is based on the induction of apoptosis of rapidly proliferating cells (activated T-lymphocytes, fibroblasts, synoviocytes), inhibition of the synthesis of anti-inflammatory 1 cytokines (IL- a), increased synthesis of anti-inflammatory cytokines (IL-4 and IL-10), suppression of the activity of metalloproteinases. However, the high incidence of adverse reactions, the development of resistance often become the main reason for its cancellation. [47].

It is known that the effectiveness and frequency of adverse reactions are determined primarily by genetic characteristics and the ability of the body to metabolize the drug. A change in the structure of a gene can influence proteins involved in pharmacodynamics and drug metabolism.

A new direction in clinical pharmacology, pharmacogenetics, allows using genotyping to determine which drug or which dose is the most effective and safe.

The methotrexate molecule alters the metabolism of folic acid by interacting with intracellular enzymes. The activity of these enzymes directly affects the entry of the drug into the cell, its intracellular metabolism and the rate of excretion from the cell, and therefore the concentration of the drug, which determines both its effectiveness and the implementation of toxic properties. [49].

It is known that, in addition to interaction with their own activators and inhibitors, the activity of enzymes is affected by conformational changes in the protein structure, in particular, the structure of the active center. The latter depends on the amino acid sequence of the linear chain, in turn, the amino acid series from gene polymorphism.

findings

A dynamic disease like RA is unlikely to have a single unique biomarker for diagnosing or predicting disease progression. The selected factor or molecule must be specific for RA, susceptible to disease progression, and cover a wide range of RA patients to qualify as a suitable biomarker.

Thus, any changes in genes affect the metabolism of methotrexate. Certain cellular components, soluble neurotransmitters and autoantibodies contribute to the development of inflammation and structural changes in joints and internal organs. Recently, studies at the molecular and cellular levels have elucidated some of the mechanisms that regulate innate and adaptive immunity in RA. In particular, genetic and immunological research has allowed us to identify new mechanisms that may explain the development of the disease. Research aimed at improving the identification of the mechanisms underlying the pathogenesis of RA will allow the development of new and more specific immunological parameters of RA, and hence a new modifying therapy. Multicenter studies examining these factors should help improve the detection of early RA biomarkers.

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