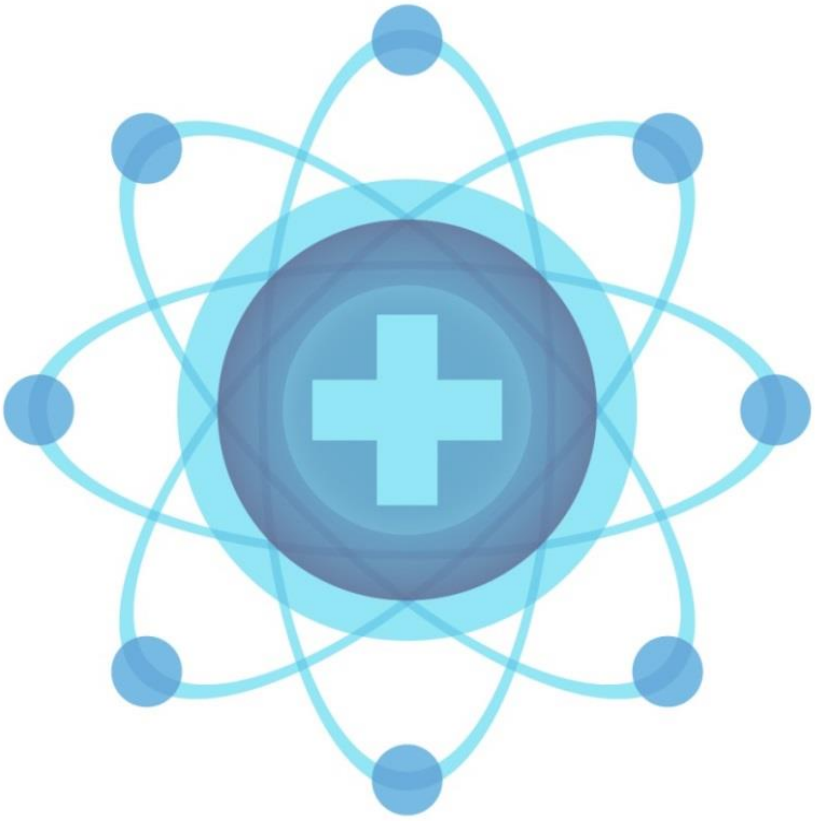

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RHEUMATOID ARTHRITIS OF MOLECULAR GENETIC ORIGIN

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Abstract. The causes of rheumatoid arthritis (RA) are largely unknown. However, RA is most likely a multifactorial disease with contributions from genetic and environmental factors. The search for genes affecting RA was carried out both in human and experimental model materials. Both types of studies confirmed the polygenic inheritance of the disease. This article deals with the pathogenesis of rheumatoid arthritis of molecular genetic origin.

Keywords: rheumatoid arthritis, internal factors, genetic and environmental factors, human leucocyte antigen (HLA)-D MHC locus, hereditary predisposition

Introduction

Rheumatoid arthritis (RA) is a chronic systemic progressive disease that manifests itself in the form of inflammation mainly of small joints. It is not associated with an infection, but with a breakdown of the immune system. Connective tissue is affected, so this disease is called systemic. The pathological process often spreads and internal organs (heart, blood vessels, kidneys) are extra-articular manifestations of the disease.

In total, about 1% of the population suffers from rheumatoid arthritis in the world. You can get sick at any age, but more often it happens at 35-55 years old in women and a little later (at 40-60 years old) in men. Women are diagnosed with rheumatoid arthritis three times more often than men.

The cause of rheumatoid arthritis is unknown. Recently, researchers are inclined to believe that the leading cause of the development of rheumatoid arthritis is a combination of internal factors (genetics, production of sex hormones) and environmental factors (bacterial and viral infections, occupational hazards, stress).

It is proved that smoking is the leading external factor in the development of pathology. A large study has been published showing that secondhand smoke in childhood also significantly increases the risk of developing rheumatoid arthritis in adulthood [1].

Methods and literature review

One of the first known suitable clinical descriptions of RA is found in written sources from 1782 in a textbook written by the Icelandic physician Jon Pétursson [4]. However, the skeletons of people who lived in the Mississippi Valley about 5000 years ago indicate that RA could have arisen before our time [5]. It was not until 1978 that the first genetic association was reported [6] when an association with B cell allotypes was observed [later known to be encoded by the human leucocyte antigen (HLA)-D MHC locus]. It is now clear that the genetic predisposition to RA is polygenic and complex, and new methods must be used to identify the underlying genetic factors.

A person develops RA as a result of a combination of genetic and environmental factors. In addition, changes in the environment can affect not only the overall incidence of the disease, but also its phenotypic appearance. The difficulty in

obtaining fully informative pedigrees in a disease as common as RA may reflect a very complex genetic influence in which many genes that promote development have low penetrance. Poor disease subtyping and environmental influences on disease also make it difficult to find the most important genes associated with pathogenic events leading to RA [7]. However, monozygotic twin matching (the frequency of monozygotic twin pairs in which both twins are affected) is 12-15% compared to 2-4% dizygotic twin matching [7,8,9], suggesting a genetic contribution. Similarly, there is a well-established genetic influence on the development of other autoimmune diseases [10]. Presumably, none of the involved genes is necessary or sufficient for the manifestation of diseases, but contributes to the development of the disease. The described features of RA (summarized in Table 1) are common to several multifactorial diseases common in the human population, such as cancer, cardiovascular, psychiatric and autoimmune disorders.

Table 1

Characteristics	Description
Multifactor influence	The contribution of genetic as well as environmental factors to the development of the disease
Phenotypic heterogeneity	Great variety of clinical phenotypes within the syndrome
polygenicity	The influence of many genes that contribute to the disease
Genetic heterogeneity	Different genes or even different alleles for the same gene can contribute to the development of the same phenotype.
Variable onset of the disease	The onset of the disease can vary from person to person, often late in life.

Evidence of hereditary predisposition to RA is the family aggregation of the disease. The first attempts to obtain statistical data on the frequency of RA in families were made in the 1950s. R.M. Stecherm et al. analyzed the family history of 1453 relatives of RA patients from 224 families and revealed the disease in 3.4% of them compared to 0.58% in controls [10]. A.G. Wasmuth, using the analysis of medical records and interviews of 1425 relatives of RA patients, noted a tenfold increase in the prevalence of RA in families compared with the population (2.6% vs. 0.26%).

Results and discussions

When studying the ethnic specificity of associations of individual HLA genotypes/alleles with rheumatoid arthritis, it was found that in Europeans with seropositive RA, the common epitope is predominantly encoded by the HLA-DRB1*04:01, *04:04, 01:01, and 10:01 alleles, while in In East Asians, the SE-coding allele DRB1*04:05 is the most common [12]. In North American Indians and Alaska Natives, the DRB1*14:02 allele manifests itself as a risk factor for severe disease [13]. In African Americans, the frequency of SE-coding alleles is approximately one third compared with people of European origin, nevertheless

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remaining a risk factor for RA. It has recently been established that there are no fundamental differences between the subpopulations of African and European origin in the UK [15]. Associations of RA with the HLA class II region and some other genes have been found in Latin America, which are also characteristic of the population of European and Asian countries [14]. Asian ethnic groups, including those inhabiting Malaysia, also showed an analogy with Europeans, since they lacked the association of a number of alleles of a common epitope with seronegative arthritis [13].

Thus, the HLA locus polymorphism plays a key role in the development of RA in various populations, showing a certain ethnospecificity with respect to disease risk alleles. The association of alleles of this locus with RA also has its own characteristics depending on the seropositive or seronegative status of the patient. Further study of this problem is still relevant both from the point of view of fundamental science and for practical medicine.

In addition to the HLA-DRB1 alleles, the role of the so-called "non-HLA" genes that are not related to the major histocompatibility complex has been identified [8, 32]. Among them: PTPN22, IL23R, PADI4, TRAF1, CTLA4, IRF5, STAT4, FCGR3A, IL6ST, IL2RA, IL2RB, CCL21, CCR6, CD40 and others involved in signal transduction, regulation of the activity of interferons and other components of the immune system, cytokines, chemokines and their receptors that initiate and maintain inflammation.

In some cases, non-HLA gene variants increased the risk of developing RA in different populations, while others, on the contrary, showed ethnic specificity. For example, an association of the T allele of the STAT4 gene (rs7574865) with RA was found in both European and Asian populations (OR [95% CI] = 1.3[1, 195–1, 414], $p < 0.001$; OR [95 % CI] = 1.216[1, 135–1, 303], $p < 0.001$, respectively) [33]. The stratification of patients by ethnicity in the work of R. Elshazli and A. Settin [34] showed that the T allele, CT+TT genotypes of the PTPN22 locus (rs2476601), T allele, and GT+TT genotypes of the STAT4 locus (rs7574865) are statistically significantly associated with RA in individuals of European, Asian, and African ancestry, while the TT genotype of the PTPN22 locus is associated with RA in Europeans, but not in Asians and Africans, and the TT genotype of the STAT4 locus is associated with RA in Europeans and Asians, but not in Africans. No evidence was found in favor of associations of SNPs in the TRAF1/C5, CD40, and CCL21 genes with RA in the Korean population [35]. An association of PTPN22 gene polymorphism with RA was established for European populations, and PADI4 gene polymorphism was found for populations of Asian origin [36]. As for the FCGR loci, although the FCGR3B polymorphism did not change the sensitivity of populations to RA, FCGR2A and FCGR3A showed an association with the disease in Europeans, while remaining neutral in Asians [37]. A meta-analysis of 32 studies, including material from 25,059 patients with RA and 25,466 controls, revealed the effect of the 1858C/T polymorphism at the PTPN22 locus (rs2476601) on the predisposition to RA in Caucasians (OR = 1.612, 95% CI: 1.544–1.683, $p < 0.001$), while in Asians the frequency of the minor allele of this gene was extremely low [38, 39].

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Characteristically, this polymorphic variant is associated with the seropositive subtype of the disease and is less common in RF- or ACCP-negative patients. In the Egyptian population, the 1858C/T variant (rs2476601) was identified in a heterozygous form only in two (out of 100) patients with RA and was not detected at all in the control group [40]. In contrast, an association of the polymorphic variant of the STAT4 gene (rs7574865) with RA was established, and it prevailed in RF- or ACCP-positive patients.

Conclusion

Taking into account the features of RA as a multifactorial disease (first of all, the possibility of heterogeneity, incomplete penetrance, epistasis), it is obvious that independent large-scale studies are needed to identify genes of susceptibility to RA by various methods in homogeneous ethnic groups with subsequent meta-analysis of the obtained results.

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