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Pharmacogenetic Aspects of Drug Resistance in Rheumatoid Arthritis

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Abstract

Glucocorticoids are essential steroid hormones involved in the regulation of adaptation to stress, carbohydrate, protein, fat, calcium and bone metabolism, immune function, growth and behavior regulation. To date, more than 15 different GR mutations have been identified that cause glucocorticoid resistance. This review provides information on the nature of the genes responsible for pharmacoresistance in patients with rheumatoid arthritis to glucocorticoids.

Keywords: glucocorticoid resistance, rheumatoid arthritis, MDR gene.

Glucocorticoid hormones have been used to treat various diseases, including rheumatoid arthritis, for almost 70 years. During this period, a lot of facts have been accumulated indicating the presence of resistance or insensitivity to hormones in patients. Distinguish between primary resistance, due to genetic factors, and secondary, which developed after some time in the course of treatment with a glucocorticoid drug. In primary resistance, genetic factors play a major role.

The glucocorticoid hormone (GH) receptor is a ligand-dependent transcription factor that regulates the expression of hundreds of genes. In the absence of the hormone, GH is retained in the cytoplasm of the cell in a complex with several molecular chaperones, and after binding to the hormone, it is released from this complex and passes into the cell nucleus, where it interacts with specific regions of DNA (GREs - glucocorticoid responsive elements) of HA target genes, which leads to to the activation or repression of these genes. Since GR is central to the mechanism of glucocorticoid regulation, changes in the level of its expression were initially considered as the most likely cause of the development of glucocorticoid resistance.

Glucocorticoid receptors belong to the superfamily of nuclear receptors and are largely represented in podocytes. The GCCR gene encoding glucocorticoid receptors is located on chromosome 5, in the 5q31-32 region and includes 10 exons, among which exons 2-9 encode a protein, and exon 1, along with the 5'-untranslated region, plays an important role in the specific gene expression GCCR. It is now well known that different variants of splicing and modifications lead to the formation of different polypeptides, and therefore the glucocorticoid receptor NR3C1 has several isoforms such as GRα, GRβ, GRγ, GRA and GRP, of which the latter two are believed to be related with steroid resistance. Each of the isoforms of glucocorticoid receptors has a specific function and may influence the sensitivity to steroid therapy. Thus, mRNA of glucocorticoid receptors has eight translation initiation sites, as a result of which eight GRα isoforms (GRαA, B, C1-3, and D1-3) are isolated. Moreover, GRα is the

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only known receptor that binds to glucocorticosteroids through a multi-protein complex (HSP90, hsp70, FKBPs, Sur-40 and p23) in the cell cytoplasm, which helps the receptor to maintain a high affinity for glucocorticosteroids. Of no less importance is the ability of GRα to interfere with genes that produce proinflammatory factors, especially the nuclear (nuclear) factor NF-κβ and the transcription factor AP-1 [1,3].

The role of GRβ is also described, which differs from GRα in the presence of a tail of 50 amino acids, which prevents this receptor from binding glucocorticosteroids.

roids. The predominance of isoforms of GRβ receptors as a result of their overexpression can lead to disruption of the GRα / GRβ balance, which ultimately leads to the formation of hormone resistance in patients with nephrotic syndrome [1,3].

An essential mechanism of insensitivity to antirheumatoid drugs may be the activation of the release system of the chemotherapy drug from the cell due to the activation of the MDR gene (Multidrug Resistance). The MDR1 gene belongs to the MDR family, located on chromosome 7. The MDR family includes 2 human genes MDR 1 and MDR 2, but only MDR1 is related to MDR. The gene's transcriptional activity increases in response to a wide variety of stimuli, including the effects of chemotherapy drugs. This gene encodes a specific glycoprotein-P (Pgp), which plays the role of a pump that ejects many foreign substances from the cell, including drugs. The important role of Pgp in the development of drug resistance is well known in oncology [2].

In rheumatology, this concept has not yet received application, despite the widespread use of anticancer drugs as basic therapy. The activity of Pgp determines the resistance of cells to many antibiotics, plant alkaloids, taxanes, etc. Pgp is a large transmembrane protein with a molecular weight of 170 kDa, consisting of 2 identical parts, each of which includes six hydrophilic regions. Pgp is expressed in different tissues of the body in different ways - from very low (epidermal cells) to high (adrenal cortex cells, intestinal mucosa) levels. Different degrees of expression also apply to the cells of the hematopoietic system. As the cells of the myeloid series mature, the expression of this protein gradually decreases. On lymphocytes, Pgp expression is minimal. In RA, consideration of resistance to basic drugs from the standpoint of MDR development was proposed in 1995 by R. C. Jorgensen et al., Who found increased expression of Pgp by synovial cells, which was associated with the use of more than three basic drugs in previous therapy. In peripheral blood (PC), Pgp expression was found predominantly on Thl lymphocytes. In further studies of Pgp in this disease, it was shown that increased Pgp expression was observed in the group of patients refractory to basic therapy (BT), as well as in the group of patients who received prednisolone for a long time [3,4].

The pathogenetic involvement of Pgp in RA remains largely unexplored. It is known that Pgp is normally expressed on some cells that are actively involved in the immune response in RA, such as macrophages and natural killer (NK) cells. It can be assumed that this glycoprotein also performs some physiological functions, in particular, ensuring the cytotoxicity of NK cells through the secretion of granzyme and perforin molecules [2,5].

The molecular basis of glucocorticoid resistance syndrome is associated with mutations in the hGR gene, which leads to a decrease in its expression, altered ligand affinity, decreased ability to bind to DNA, or increased expression of transcription factors that compete with hGRfor this binding [10]. To date, about 16 mutations have been recorded, mostly heterozygous and partial, since historically it has been argued that complete resistance to glucocorticoids is in-

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compatible with extrauterine life. However, one case has been reported with a mutation that completely inactivates hGR [5,6,7].

Glucocorticoids are essential steroid hormones involved in the regulation of adaptation to stress, carbohydrate, protein, fat, calcium and bone metabolism, immune function, growth and behavior regulation. They act through the glucocorticoid receptor (GR). The gene for the glucocorticoid receptor (GR, NR3C1) is located on chromosome 5q31 and contains 9 exons. The protein-coding part starts from the second exon. The receptor is composed of distinct domains, including an N-terminal domain (NTD), a central DNA-binding domain, and a C-terminal ligand binding domain (LBD). In the absence of a ligand, GR is located in the cytoplasm in a multiprotein complex containing heat shock proteins and other chaperones [9]. Upon ligand binding, GR is released from this complex and translocated into the nucleus. In the nucleus, it binds to DNA through specific DNA sequences (GRE - glucocorticoid response element) and regulates the transcription of target genes. The LBD domain contains a ligand-dependent activation function (AF-2), the conformational change of which upon binding of an agonist stabilizes the receptor in an active conformation, facilitating its interaction with coactivators through LXXLL motifs [3,4,5].

To date, more than 15 different GR mutations have been identified that cause glucocorticoid resistance. It has been shown that mutant receptors can have a predominant negative effect on the wild-type receptor or can reduce the affinity of the receptor for the ligand. In addition, improper localization of the mutant receptor, delay or failed translocation into the nucleus, or decreased transcriptional activity due to decreased binding through GRE can lead to glucocorticoid resistance [3,4,5,8].

Thus, in the study of the pharmacogenetic aspects of the hormone resistance of RA, there are many unclear questions that need to be resolved.

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