REVIEW ARTICLE

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Individual and molecular risk factors for the development of rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis is a chronic autoimmune disease of the joints of unknown etiopathogenesis. It affects between ~0.5 and 1% of the total population and occurs 2–3 times more often in women than in men. Several antibodies have been identified in the serum of patients with RA, including rheumatoid factors (RF), anti-citrullinated protein antibodies (ACPA) and anti-carbamylated protein antibodies. These autoantibodies can form immune complexes in the joints, leading to inflammation and damage to the articular cartilage. A characteristic symptom of advanced RA is persistent inflammation of the synovium, which usually affects peripheral joints in a symmetrical way. The exact aetiology of RA is unclear,it is known to be a multifactor disease in which a complex interplay between the host and the environment determines the overall risk of being susceptible to the disease, as well as its persistence and severity. Below we present the RA risk factors including main individual risk factors as hormonal factors, hereditery factors, epigenetic factors as well as the risk of concomitant environmental factors of RA as diet, cigarettes and alcohol abuse. Environmental contaminants, socio-economic factors and molecular mechanisms of RA known so far.

KEY WORDS: rheumatoid arthritis, RA, molecular risk factors, individual risk factors

Wiad Lek. 2024;77(9):2013-2025. 10.36740/WLek/193976 DOI

INTRODUCTION

DEFINITION AND EPIDEMIOLOGY OF RA

Rheumatoid arthritis is a chronic autoimmune disease of the joints of unknown etiopathogenesis. It affects between ~0.5 and 1% of the total population and occurs 2–3 times more often in women than in men. Several antibodies have been identified in the serum of patients with RA, including rheumatoid factors (RF), anti-citrullinated protein antibodies (ACPA) and anti-carbamylated protein antibodies. These autoantibodies can form immune complexes in the joints, leading to inflammation and damage to the articular cartilage. Depending on the presence of RF and ACPA in the serum of patients with RA, the disease can take one of the following two forms: seropositive RA, which is the most common and is characterized by the presence of RF and/or ACPA, or seronegative RA, which is characterized by the absence of both RF and ACPA [1].

A characteristic symptom of advanced RA is persistent inflammation of the synovium, which usually affects peripheral joints in a symmetrical way [2, 3].

Although the exact aetiology of RA is unclear, it is known to be a multifactor disease in which a complex interplay between the host and the environment determines the overall risk of being susceptible to the disease, as well as its persistence and severity. The risk factors for the development of RA can be broadly defined as host-related and environment-related. Host-related factors associated with the development of RA can be further divided into genetic, epigenetic, hormonal, reproductive and neuroendocrine factors and co-existing host-related factors. In contrast, environment-related risk factors include smoking and other airborne exposures; microflora and infectious agents; diet and socio-economic factors.

Based on many years of observation of patients with rheumatoid arthritis, it can be concluded that early diagnosis and initiation of treatment with disease-modifying antirheumatic drugs (DMARD) are of great prognostic importance and lead to quick remission of the disease and definitely improve treatment outcomes for patients with RA [4-6].

AIM

This review is an attempt to present the issue of individual and molecular risk factors for the development of rheumatoid arthritis in the light of available domestic and foreign literature.

REVIEW AND DISCUSSION

MAIN INDIVIDUAL RISK FACTORS FOR RA

An epidemiological correlation has also been noted between an increased future risk of developing RA and apparently unrelated comorbidities. The population of patients already diagnosed with RA are more likely to develop other comorbidities, however, they differ in terms of the risk of their occurrence. The three most common comorbidities in RA include anxiety disorders (62.1%, 95% CI: 43.6%; 80,6%), hypertension (37.7%, 95% CI: 29,2%; 46,2%) and depression (32.1%, 95% CI: 21.6%; 42.7%) [7].

It seems that there is a particular link between psychiatric disorders and RA. The co-existing posttraumatic stress disorder increases the risk of RA both in men and in women . This is thought to be due to the disruption of neuroendocrine-immunological mechanisms caused by chronic stress . Studies on the co-existence of RA with other diseases have shown that depression is one of the factors increasing the risk of developing RA. Depression increases this risk by 28-68% [8-10], whereas the use of antidepressants in patients with depression may protect against the development of RA. This may be related to systemic inflammatory mechanisms. Co-occurrence of RA with other rheumatic diseases (such as psoriatic arthritis), gastrointestinal diseases (such as inflammatory bowel disease) or dermatological diseases (such as alopecia areata, vitiligo) supports the hypothesis that these diseases have an immunological aetiology. There is an interesting inversely proportional relationship between schizophrenia and the development of RA. The epidemiological data, after having been re-verified in two updated meta-analyses, confirmed a significant protective effect of schizophrenia on the development of RA (OR 0,48–0,65) [11, 12].

There are many controversies concerning the relationship between atopy and allergic diseases and the risk of developing RA. High-quality cohort studies suggest a positive relationship between atopy and RA. A positive correlation has also been found between acute and chronic diseases of the upper and lower respiratory tract and an increased risk of seropositive and seronegative RA.

Other identified risk factors for RA include autoimmune diseases, such as Hashimoto's thyroiditis and Graves' disease, type 1 diabetes 1, alopecia areata, vitiligo , inflammatory bowel disease , multiple sclerosis. Long-term cohort studies suggest that sleep disorders (including obstructive sleep apnoea) and other sleep disorders not related to apnoea represent additional risk factors for RA [13-15]. Recent studies have shown the aforementioned oral mucosal immunity, together with oral and/or intestinal dysbiosis and chronic infections have been closely implicated in the etiology and pathogenesis of RA. The results of a prospective observational study by American and Canadian scientists indicate a high incidence of overweight and obesity (up to 69% in the population of patients with early RA (disease duration <3 years). The conducted study showed that increased body weight is a factor independent of other variables. risk of poorer response to treatment (taking into account demographic factors, smoking, duration of arthritis, baseline disease activity). It turns out that these people are less likely to achieve lasting remission compared to patients with a normal body mass index [48]. They are strongly associated with additional environmental factors, such as smoking tobacco and exposure to occupational dust, which affect the condition of the mucosa. An additional risk factor has been shown to be immunoglobulin IgA, as an early factor in the development of the disease.

HORMONAL FACTORS

Due to the fact that the risk of RA in women is about 2-3 times higher than in men, and also due to the more severe and aggressive progression of the disease with a high inflammatory activity and a high degree of disability [16], it can be assumed that there is a direct relationship between hormonal factors and susceptibility to RA. This is also confirmed by observations that in pregnant women there are frequent remissions of the disease, whereas the second peak in the incidence of RA in women occurs during menopause, which supports the hypothesis that hormonal factors play a significant role in the progression of RA. A decrease in estrogen and/or progesterone levels in the postpartum period and menopause predisposes to an increased incidence of RA. However, there are many controversies concerning the role of hormonal factors in the etiopathogenesis of this disease. In general, estrogens are considered pro-inflammatory, unlike progesterone and androgens, which have an anti-inflammatory effect and whose levels are reduced in men and women with RA. Nonetheless, it is worth noting that the effect of estrogens is more complex, as they may also have anti-inflammatory action in many cells and tissues. The assessment of the role of estrogens as pro-inflammatory or anti-inflammatory factors must also take into account many other factors, such as their concentration in the serum and tissues, dominant cell types and estrogen receptors, as well as the stage of life. Despite controversies, multicentre studies suggest that breastfeeding may protect against RA. The number of births, age during the first period, age during the first pregnancy, the use of oral

contraceptives and hormone replacement therapy play a significant role too. A cohort study published in Oxford Rheumatology (August 2024) showed that oral contraceptives use was associated with a decreased risk of RA in users. In contrast menopausal hormone therapy use was associated with an increased risk of RA. Age at menarche >14 years is associated with a greater RA risk compared with menarche at 13. Based on reports, it is suspected that the earlier the 1st pregnancy, is connected with the lower the risk of RA.

Therefore, it is believed that a sudden drop in estrogen levels during early menopause, the postmenopausal period , the postpartum period and the use of anti-estrogenic agents (such as selective estrogen receptive modulators and aromatase inhibitors) can be identified as risk factors for RA.

RA is also associated with disorders in the neuroendocrine system. It is thought that cortisol and adrenal androgens have anti-inflammatory effects and that their deficiency may trigger activation of an inflammatory process in the synovium. There is also a correlation between hormonal balance disorders and changes in the sympathetic and sensory systems, which likewise contribute to the development of RA. Any disturbances of the sympathetic system have an effect on the progression of RA, due to the shift of sympathetic signalling from anti-inflammatory beta and A2 receptors to inflammatory alpha and A1 receptors.

Another important endocrine mediator with immunomodulatory properties is vitamin D. Research in recent years has shown that there is a close relationship between vitamin D and the immune system. Vitamin D produces an anti-inflammatory effect due to its influence on macrophages, dendritic cells and FLS lymphocytes (which have a vitamin D receptor), indicating that it may potentially protect against RA [17, 18]. Nonetheless, the true role of vitamin D as a factor protecting against RA remains unclear. A large randomized controlled trial (RCT) failed to demonstrate a preventive effect of daily supplementation of calcium and vitamin D on the risk of RA. Instead, more robust evidence confirms the association between vitamin D deficiency and a poorer prognosis in patients with RA, which manifests itself with increased activity of the disease, impaired functions and poorer health-related quality of life [. Another interesting aspect is the relationship between exposures to UVB radiation and the risk of developing RA, suggesting that people who get more sunshine are less likely to develop RA. Research is ongoing to confirm the role of vitamin D as a protective factor. There are reports that there is a relationship between vitamin D deficiency and the occurrence of neuropathic pain. The possible pathomechanism of the phenomenon includes the neuroactive and indirectly neuroprotective effect of vitamin D, as well as its influence on the expression of nerve growth factor genes. Vitamin D deficiency may affect the nervous system, causing non-specific musculoskeletal pain [49].

More and more studies suggest that obesity is another risk factor for the development of RA . A number of meta-analyses have shown a positive association between obesity and RA, as well as an impact of the body mass index (BMI) on the risk of RA. There is some evidence indicating that this association is stronger in women and in seronegative patients (although it remains an open research question). As regards the existing relationship between obesity and RA, it should be assumed that metabolic and endocrine mechanisms play a significant role here. Increased secretion of pro-inflammatory cytokines and adipokines by adipocytes, as well as disorders of sex hormone metabolism due to excessive transformation in the adipose tissue, may increase the production of estrogens catalysed by the aromatase enzyme.

Although it can be hypothesized that the known systemic, metabolic and immunological effects of obesity (especially of visceral obesity) may predispose to autoimmune diseases, including RA , conflicting research findings indicate that further research is needed to understand the role of obesity in the development of RA, all the more so because weight loss may be an effective prophylactic intervention in people with an increased risk [19]. People with elevated cholesterol levels and disturbed lipid metabolism are much more likely to suffer from rheumatoid arthritis. Therefore, it can be presumed that the use of statins may have a role in protecting against the occurrence of RA. Possibly, this effect is caused by the lowering of lipid levels in the blood and the anti-inflammatory action of statins. However, the role of statins in the context of RA has not been fully understood, as studies on this issue have not as yet provided a clear answer.

HEREDITARY FACTORS

Hereditary factors play a significant role in the risk of developing rheumatoid arthritis (RA), which is confirmed by research involving families and twins. The risk of developing of RA in the identical twin of a patient with RA amounts to 9–15%, which is as much as four times higher than in the case of dizygotic twins and considerably much higher than in the general population [relative risk (RR) of [19-22, 25–35]. Similarly, the relative risk in first-degree relatives ranges from 2 to 5, which is comparable in men and women . In addition, the risk of RA increases 1.5–3-fold in offspring of parents

suffering from other immune-related inflammatory diseases, such as systemic lupus erythematous, Sjögren's syndrome, ankylosing spondylitis or Hashimoto's thyroiditis. Multicentre studies have shown that the contribution of genetic factors to the development of the disease amounts to 50–65% [23]. Recent studies suggest that this contribution is much higher in patients with seropositive RA (50%) than in patients with seronegative RA (20%) [24].

At present, over 100 loci are thought to be associated with an increased risk of RA in various ethnic populations. The major histocompatibility complex (MHC) locus was the first to be identified and remains the most studied region, accounting for approximately one-third of the genetic susceptibility to the disease [25]. In most populations, certain human leucocyte antigen (HLA) loci, such as HLA-DRB1, are strongly associated with RA. The risk varies depending on allele and ancestry, and is higher in the case of HLA-DRB1*0101/*0401*/0404 in Caucasians, in the case of HLA-DRB1*0405/*0901 in Asians and in the case of HLA-DRB1*1402* in native American Indians [26, 27].

An extremely important discovery was the identification of a sequence of five amino acids (QKRAA, QRRAA, RRRAA) in positions 70-74 of the third hyper-variability region of the third DRß1 chain, encoded by the HLA-DRB1 gene. This sequence was highly conserved in RA risk alleles and was therefore given the name of the shared epitome (SE). The SE hypothesis has played a key role in understanding the aetiology of RA. The presence of SE is more strongly associated with seropositive RA than with seronegative RA. In addition, it is associated with more severe progression of the disease , extra-articular symptoms and radiographic damage.

Subsequent studies extended the SE hypothesis by establishing that much of the MHC region-related risk of RA is associated with six amino acids in four HLA molecules: HLA-DRB1, HLA-B, HLA-DPB1 and HLA-A .However, only 30% of the genetic risk of RA comes from the MHC region. Therefore, a lot of effort has been invested to examine genes other than HLA. One of the best-studied non-genetic HLA variants which are associated with the function of immune cells is the single nucleotide polymorphism (SNP; R620W) in the PTPN22 gene, encoding a protein tyrosine phosphatase involved in antigen receptor signalling in B and T cells. This SNP has been widely replicated and remains the second strongest genetic risk factor for RA, with an OR just below 2. SNP R620W has only been associated with seropositive RA. Evidence in support of this observation comes from studies which indicate that it also increases the citrullination of peptides.

Interestingly, SNP R620W is absent in East Asian (e.g. Japanese) populations, which instead have common genetic variants in PADI4, the gene encoding peptidyl-arginine deiminase (PAD, peptide citrullination enzyme), associated with an increased risk of RA (OR 1,31 per copy allele). Other loci and genes involved in inflammatory pathways which are slightly less important in the etiopathogenesis of RA include CTLA4 , STAT4 , TNFAIP3, TRAF1-C5, IL2/21 , CD40, IL2RA/IL2RB IL6R, CCL21 (lymphocyte chemokine) and many other loci and genes. In the case of RA, new genes come under scrutiny and are being studied in other fields, such as oncology. For example, the human tumour suppressor gene RNASET2 has been found to be linked with the development of RA in Asian populations. This gene encodes T2 ribonuclease - an enzyme involved in the development of cancer. It has recently been found that this gene regulates the innate immune response (e.g. macrophage function), which is important for the development of RA [55, 56].

Importantly, in addition to susceptibility to the disease, some genes other than HLA have been found to be linked with the severity of the disease and with the differences between the seropositive and seronegative RA.

EPIGENETIC FACTORS

In recent year, more and more attention has been paid to the role of epigenetic factors in the development of RA. Epigenetic mechanisms give rise to hereditary changes in gene expression without requiring changes in the sequence of the deoxyribonucleic acid (DNA) [28, 29]. In addition, epigenetic modifications can be triggered by various external factors, such as drugs, smoke or diet, therefore they may constitute a link between genetic and environmental interactions. The key epigenetic changes include DNA methylation, histone modifications and non-coding RNAs, all of which have been proven to predispose to RA. Recent epigenomic studies have revealed differences in gene methylation in blood samples of patients with RA. The studies suggest the existence of two areas within the HLA locus (containing 9 genes) or in their close vicinity (1 gene), which suggests that the genetic risk of RA may be associated with this region and may be partially dependent on the methylation of DNA.

Recent findings have demonstrated that there are two distinct groups of patients with RA, which are characterized by specific methylome and transcriptome signatures in the hip, knee, and MCP (metacarpophalangeal) joints. This discovery explains the differences in disease severity in various joints. Another mechanism of epigenetic regulation are non-coding RNAs, including microRNAs (miRNA, approximately 22 nucleotides) and long non-coding RNAs (lncRNA, over 200 nucleotides).

Both types have been analysed for their role in susceptibility to RA, its severity and effectiveness of treatment. MiRNA-155, miRNA-146a, miRNA-223 and miRNA-124a have proved to be crucial for the pathogenesis of RA. Specific gene targets of these miRNAs have been identified, confirming their significance in the development of that disease [28].

The presence of citrullinated histones is considered an early factor triggering the production of autoantibodies and considered an important element of the pathogenesis of RA. Gene expression can also be modified by the process of histone phosphorylation. This applies especially to histone. The so-called citrullinated peptides (containing the amino acid citrulline) are target antigens of the autoimmune reaction, which results in the production of antibodies directed against them. Citrulline is not a typical amino acid, it is produced after the protein synthesis stage by modifying the amino acid arginine. This conversion, known as citrullination, is catalyzed by enzymes from the peptidyl arginine deaminase (PAD) family. This process affects the characterization of important protein parameters, such as net charge, conformation and antigenicity. Citrullination takes place in healthy tissues, but is also thought to be part of or a result of general inflammatory processes. An increased amount of citrullinated proteins was also observed in synovial fluid. Amino acid modification results in the creation of completely new epitopes. The patients' immune system then reacts with the newly created epitopes, producing ACPA (anti-citrullinated protein antibodies). This immune response, rather than the presence of citrullinated proteins itself, is characteristic of RA.

THE ROLE OF CONCOMITANT ENVIRONMENTAL FACTORS OF RA DEVELOPMENT

Multicentre studies have confirmed the significant impact of the environment on the development of RA. Environmental factors can be divided into several main categories, which have been described as the main determinants of RA and which depend on the diet, the use of stimulants such as alcohol and smoking, as well as socio-economic factors.

DIET

The epidemiological relationship between diet-related factors and RA is still widely studied. It can be concluded that diet-related changes in the intestinal microbiome has an effect on the risk of development of RA [30, 31]. It has been demonstrated that autoimmunity is strongly influenced by nutrition . Multicentre trials have shown that the Mediterranean diet based on the daily consumption of extra virgin olive oil, fish and omega-3 fatty acids protects against the development and clinical symptoms of RA. High consumption of sodium and red meat, which is typical for the Western diet, is associated with an increased risk of polyarthritis or RA. In addition, the above diet is associated with an increased risk of obesity, which is considered a significant health risk, especially in terms of the potential risk of developing RA. A diet rich in dietary fibre and reduced consumption of carbohydrates may improve the composition of the intestinal microflora in patients with RA. There have also been reports that the consumption of coffee may protect against RA, however, a Mendelian randomization analysis does not confirm a causal relationship between the consumption of coffee and the development of RA. Large prospective trials confirm that the Mediterranean diet and the use of products such as fruit and vegetables rich in vitamin C and antioxidants reduce the risk of developing RA. The Mediterranean diet which is especially rich in fruit, vegetables, olive oil and fish protects against the occurrence of RA. The studies confirming this fact are still ongoing.

CIGARETTES AND ALCOHOL

There is a close association between several harmful airborne factors and the development of RA. One of them is smoking cigarettes. Smoking accounts for 20-15% of the total risk of RA and for up to 35% of the risk of RA with a positive ACPA result [32, 33]. There is a clear relationship between the number of cigarettes smoked and the response of the body [32-34]. It has been shown that cessation of smoking gradually reduces the risk of developing RA and that after 20-30 years it returns to the level found in never-smokers . In addition, there is an association between passive exposure to cigarette smoke in the prenatal period, in childhood and in adulthood [33] and the occurrence of RA. Epidemiological studies have shed light on the pathogenesis of RA, demonstrating that smoking is responsible for the citrullination of proteins in situ (i.e. ACPA) and the ultimate development of RA [50, 51].

It has been proven that it is the cigarette smoke, and not tobacco or nicotine, which appears to have a key role in the development of RA, causing chronic inflammation of the respiratory tract. The positive correlation between exposure to cigarette smoke and the occurrence of RA is associated with a significant effect of smoking on immune responses, increased oxidative stress of the body, disruption of apoptosis and provocation of inflammatory processes. This in turn

causes citrullination and epigenetic changes, such as methylation of DNA. It has been shown that there is a gene-environment interaction between smoking and the HLA-DRB1 SE genotype. There is evidence of an association between cigarette smoking and the incidence of RA, as well as the severity of the clinical progression of RA and response to DMARDS drugs.

Low to moderate consumption of alcohol is associated with a reduced risk of RA, particularly in a dose-, time and gender-dependent manner. This association is more pronounced in the case of ACPA-positive RA. There are reports of a synergistic effect of alcohol and tobacco smoking, where the positive association between smoking and the occurrence of RA decreased with increasing consumption of alcohol. There have been reports of a three-way interaction between alcohol, smoking tobacco and HLA-DRB1-SE as regards the risk of developing ACPA-positive RA.

ENVIRONMENTAL CONTAMINANTS

The first identified contaminant is silica, especially in people working in mining and construction. The relationship between silica pollution and the occurrence of RA is associated with an increase in the titre of IL-1alpha, IL-1-beta, IL-2,IL-4, IL-6 i IL-10, as well as TNF-alpha, which indicates that exposure to silica stimulates the immune system and triggers an inflammatory reaction [35]. In addition, textile dust and inorganic dusts such as asbestos and cement, have been found to be risk factors for RA. Other pollutants contributing to the development of the disease also include particulate matter, ozone, carbon monoxide, nitrogen dioxide, sulphur dioxide and lead . In this case, the lungs are an organ that initiates autoimmunity, playing a significant pathophysiological role. Damage to the respiratory tract caused by exposure to the above substances leads to systemic inflammation, increased oxidative stress and epigenetic modifications. Air pollution increases the likelihood of developing RA. Fine PM2.5 particles are most closely associated with ACPA titres. It is interesting to note that there is a relationship between air pollution and the severity and exacerbation of RA, as exposure to high levels of air pollutants has been found to be associated with increased CRP levels and a higher risk of exacerbation of the disease.

SOCIO-ECONOMIC FACTORS

A lower socio-economic status appears to increase the risk of RA, although it is probably more strongly linked with a poor prognosis concerning the progression of the disease. It has been demonstrated that a lower educational level is independently associated with RA, in particular with the seropositive form. A low educational level of parents of children in the household as well as other poor socioeconomic status indicators in early stages of life have also been found to be associated with more severe RA in adults, further supporting positive epidemiological observations [38]. Studies suggest that socioeconomic deficit may be an identifiable risk factor for RA, possibly resulting from unmeasured environmental exposure connected with, among other things, infections or low-quality diet.

It is also worth noting that a low socio-economic status may be more common in people performing physical work, which is associated with an increased incidence of RA too. This relationship is also seen in the case of the father's profession and may be attributable to various factors. Physical workers are often exposed to the adverse effects of the earlier-described harmful inhaled substances such as textile dusts, inorganic dusts, silica and other earlier-mentioned substances, which are important risk factors for RA. Interestingly, it has been shown that long-term physical work is associated with an increased risk of both seropositive and seronegative RA, with interaction with HLA-SE in the former case . Other occupational factors such as stress, conflicts at work and shift work have also been found to increase the risk of RA.

MOLECULAR MECHANISMS OF RA DEVELOPMENT ASSOCIATED WITH ERAD RESPONSE TO UNFOLDED PROTEINS

Most secretory and transmembrane proteins fold and mature in the endoplasmic reticulum (ER). The flux of proteins entering the ER is dynamic and regulated. Adapting to this load requires quality control mechanisms that monitor the levels of unfolded proteins and prevent their accumulation due to the risk of aggregation [3]. To prevent the accumulation of abnormally folded proteins in the ER, proteins that fail quality control are retranslocated to the cytosol, where they are ubiquitinated. Abnormal and potentially toxic proteins are eliminated by proteasomes through the ER-associated degradation (ERAD) mechanism. The ERAD process involves the recognition of substrates in the ER membrane, their translocation to the cytosol, ubiquitination and delivery to the proteasome for degradation. Therefore, a wide range of misfolded proteins require a rapid and highly processable control mechanism. When these quality control mechanisms are compromised or when cells are subjected to a stress that alters the physiology of the secretory pathway, such as viral infection or in response to disease [9, 10], the balance between

folded and unfolded proteins in the ER is upset, leading to the accumulation of misfolded proteins, a condition termed ER stress.

Endoplasmic reticulum ER-associated degradation and the reaction of unfolded proteins are two key quality control mechanisms in the cell. ER-associated degradation is responsible for transferring misfolded proteins in the ER to cytosolic proteasomal degradation, while unfolded protein response (UPR) is activated in response to accumulation of misfolded proteins . When the balance between folded and unfolded proteins in the ER is upset, resulting in the toxic accumulation of misfolded proteins, chronic ER stress begins to dominate the abnormal cell function.

Eukaryotic cells then respond to ER stress and accumulation of unfolded proteins in the endoplasmic reticulum by activating the misfolded protein response - UPR [39]. One of the transmitters of the UPR in mammals is the PERK kinase, which, following ER stress, causes attenuation or global inhibition of protein synthesis via phosphorylation of the eIF2α factor. However, there is a group of genes termed the ER-adaptosome, which is induced in the transcription process under chronic ER stress. Eukaryotic cells with developed ER induce different translating mRNAs than normal cells. Therefore, it has been suggested that UPR-related risk factors may impair adaptation to chronic stress, increasing the risk of rheumatoid arthritis.

In addition to its key role in cell growth and function, UPR modulates the risk of diseases such as diabetes, hepatic steatosis, inflammatory bowel disease, cancer and others. The role of ER stress in rheumatoid arthritis has been suggested many times. Nowadays, the involvement of the UPR in RA patients is identified as an important contribution to both disease initiation, progression and response to treatment [40, 41]. Thus, how adaptation to chronic ER stress is modulated in rheumatoid arthritis cells and whether the lack of adaptation can be exploited in the treatment of patients with rheumatoid arthritis should be the subject of future studies to determine the response pathway of unfolded proteins as a modulator of rheumatoid arthritis initiation, progression and therapy (Table 1).

PERK KINASE-DEPENDENT ADAPTIVE CELLULAR RESPONSE PATHWAY UPR

Eukaryotic cells respond to ER stress by activating a signaling pathway called the unfolded protein response - UPR. The UPR is a collection of signaling pathways that can prevent the effects of ER stress by integrating the control of mRNA translation with the regulation of gene transcription. When, ER stress persists despite activation of these feedback responses, the UPR will initiate apoptosis [42]. In mammalian cells, the UPR consists of three main branches: inositol-requiring enzyme-1 **(**IRE1), protein kinase like endoplasmic reticulum kinase (PERK) and activating transcription factor 6 (ATF6), each of which is activated as a factor in the level of misfolded proteins and consequently activates the corresponding signaling cascades. As a consequence of induced ER stress, the trans-membrane factor ATF6 moves from the ER to the Golgi apparatus, where it is cleaved in a manner that releases the N-terminal domain of ATF6 (ATF6(N)). ATF6(N) moves into the nucleus and acts as a transcription factor. PERK is activated by oligomerization, and once activated, phosphorylates the translation initiation factor eIF2α (eIF2α). This reduces translation initiation, leading to a global decrease in protein synthesis. Paradoxically, eIF2α phosphorylation increases the synthesis of selected transcripts, some of which contain short overlapping open reading frames in their 5'UTR, such as ATF4, a transcription factor that coordinates the transcription of genes that determine cell fate after ER stress. The third UPR factor, IRE1, is both a kinase and an endonuclease. When activated, it digests the transcription factor XBP1 (XBP1) mRNA, removing a 26-nucleotide intron. This non-canonical splicing causes a shift in the reading frame, yielding a spliced form of XBP1 (XBP1s). XBP1s is a very potent transcription factor that consistently induces ER expansion (Fig. 1) [10].

An analysis of the Kyoto Encyclopedia of Genes and Genomes (KEGG) database showed that the group of genes under expression during chronic ER stress is enriched with those that encode proteins involved in ER function, including genes listed for the PERK-dependent UPR [43]. ER adaptosome genes (including 35 ER protein processing pathway genes) are known targets of UPR-induced transcription factors, including ATF6, which exhibits protective functions during chronic ER stress. One of these factors is a transmembrane glycoprotein termed wolframine, which is a regulator of ER calcium levels and plays a key role in cell homeostasis. Since ATF4 induction requires PERK activation and is essential for maximal ATF6 induction, it has been suggested that sustained PERK activity during chronic ER stress is crucial to this process. Recent scientific reports indicate that endoplasmic reticulum stress is an important etiological factor in various human diseases, including conditions associated with the development of inflammation. In particular, the study of the PERK cell signaling pathway has promising potential for understanding the pathological mechanisms involved in rheumatoid arthritis. Therefore, current ongoing studies aim to use mRNA expression (UPR genes) as molecular

Tab. 1. Genes of unfolded proteins response (UPR) pathway involved in development of rheumatoid arthritis

Gene	Function
PERK	protein kinase like endoplasmic reticulum kinase
ATF6	activating transcription factor 6
ATF6(N)	N-terminal domain of ATF6
eIF2α	translation initiation factor 2α
XBP1	X-box binding protein 1
ATF4	activating transcription factor 4
BAX	proapoptotic Bcl-2 associated X-protein
BCL-2	antiapoptotic B-cell CLL/lymphoma 2 protein
eIF2B	translation initiation factor 2B
eIF3	transcription initiation factor 3
eIF4	transcription initiation factor 4
NRF2	nuclear erythroid related factor 2

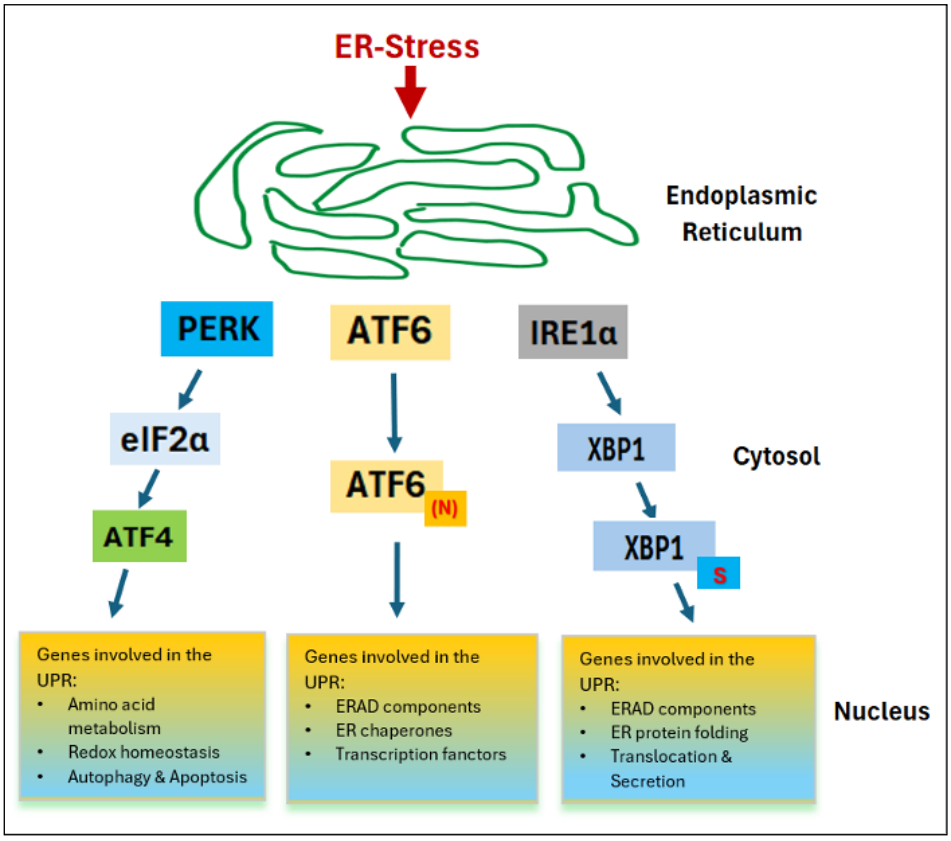

Fig. 1. Pathway of unfolded proteins response (UPR) to ER-stress, key components: protein kinase like endoplasmic reticulum kinase (PERK); activating transcription factor 6 (ATF6); N-terminal domain of ATF6 (ATF6(N)); translation initiation factor eIF2α (eIF2α); transcription factor XBP1 (XBP1); mRNA of XBP1 after removing a 26-nucleotide intron (XPB1s); activating transcription factor 4 (ATF4).

markers to determine global changes in the translation of chronic ER stress-specific factors in patients with rheumatoid arthritis.

UPR GENE EXPRESSION PROFILING AS A RISK MODULATOR IN RA PATIENTS

A major gene involved in the pathogenesis of RA is the PERK gene, which is involved in the unfolded protein response UPR pathway. Studies have shown that PERK gene expression is elevated in RA patients, leading to increased activation of the UPR pathway. This chronic ER stress may contribute to the development and progression of RA by inducing inflammatory cells to release cytokines, further perpetuating the inflammatory response. Given the role of PERK in the pathogenesis of RA, researchers have investigated the use of PERK inhibitors as a potential strategy for targeted molecular therapy. PERK inhibition has been shown to reduce inflammatory cytokine production and reduce joint inflammation in animal models of RA . Moreover, increased expression of autophagy-related genes, including Beclin-1, has been observed in RA patients,

suggesting a potential link between ER stress, mediated by PERK, and autophagy in the pathogenesis of this disease [44]. Additionally, administration of GRP78/BiP, a protein involved in the UPR pathway, has been shown to have potential therapeutic benefits in RA. However, further studies are needed to fully understand the complex relationship between PERK gene expression and RA pathogenesis.

It has also been shown that phosphorylation of eukaryotic initiation factor 2 (p-eIF2) may be a critical factor in the regulation of protein synthesis and may play a key role in the inflammatory response. In RA, *p-eIF2* gene expression has been shown to be involved in the inflammatory and proliferative processes of the disease [46]. Studies have shown that *p-eIF2* gene expression is increased in RA synovial membrane fibroblasts, which are cells lining the joints and contribute to inflammation and joint tissue degradation. Several studies have been conducted on the correlation between RA and *p-eIF2* gene expression. One study showed that RA patients exhibit differential expression of genes encoding cytokine/chemokine-dependent immunity compared to healthy individuals. Takigawa et al. study showed that the ATF6 factor protein, which regulates *p-eIF2* gene expression, simultaneously increases the expression of genes associated with inflammatory response in RA [58].

Another gene that has been identified as involved in the development and progression of RA is transcription factor 4 [45]. ATF4 is a transcription factor that is involved in regulating the cellular response to stress and maintaining cellular homeostasis. It is maintained constitutively at low concentrations, but can be rapidly induced to high levels under stress conditions. The findings have provided insight into the relationship between *ATF4* gene expression and the development of RA. A study by Krabben et al. analyzed gene expression in RA and found that *ATF4* was induced to high levels in the synovial membrane. These findings suggest that ATF4 may be involved in the pathogenesis of RA and may serve as a potential molecular marker of the disease [57].

Although the exact cause of the development of RA is unknown, genetic and environmental factors are thought to play an important role in the development of the disease. Accordingly, recent studies have focused on the role of apoptosis as a mechanism of programmed cell death in the pathogenesis of RA, and the *BAX* gene has emerged as a potential predisposing factor for increased disease risk. *BAX* is a proapoptotic gene that may play a key role in regulating cell death in a wide variety of autoimmune diseases [53, 54]. The aim of another study was to analyze the expression of apoptosis-related proteins in the synovial membrane of patients with rheumatoid arthritis. Consequently, they showed that the level of a potential gas pedal of apoptosis, which is BAX, was higher in healthy controls than in RA patients [59].

It appears that this characteristic imbalance in apoptosis-related proteins may contribute to the survival of autoreactive lymphocytes, leading to chronic inflammation in the synovial membrane. A study by Hilbers et al. examined the expression of the anti-apoptotic gene *BCL-2* in peripheral blood, synovial fluid lymphocytes and synovial tissues of RA patients [46]. The results indicated that *BCL-2* expression was not increased in lymphocytes or synovial tissues from RA patients. Instead, reduced *BCL-2* expression was observed, suggesting that impaired apoptosis may contribute to the pathogenesis of RA [46]. However, another study found that interleukin-17 increased *BCL-2* expression in synoviocytes in RA, suggesting a potential role for *BCL-2* in the inflammatory response in RA. Overall, the role of *BCL-2* gene expression in RA remains unclear and requires further research to fully understand its potential impact on the disease. To summarize previous studies, endoplasmic reticulum-associated ERAD degradation and the response to unfolded UPR proteins are two key mechanisms for controlling translation quality in the cell. Therefore, it has been suggested that *BCL-2* is involved in the regulation of ERAD protein synthesis, while *BAX* gene activity may be associated with UPR activation in response to the accumulation of misfolded proteins during chronic inflammation in RA patients.

PERK INHIBITORS IN TARGETED THERAPY AS A NEW TREATMENT STRATEGY FOR RA

Repression of protein translation by PERK kinase in response to chronic ER stress is reversed by an adaptive process that restores cellular homeostasis. Phosphorylation of eIF2α by PERK and other kinases attenuates translation initiation through repression of the multisubunit transcription factor eIF2B. This results in inhibition of the translation initiation complex and leads to global repression of protein synthesis. Since cells cannot survive under long-term repression of translation, homeostatic mechanisms are involved in the gradual restoration of protein synthesis during chronic ER stress. One such mechanism, described in another studdy, is the conversion from classical and efficient CAP-dependent mRNA translation at the 5′ end (7-methylguanosine with a 5′,5′ triphosphate bond) and driven by the eIF4E factor, to a less favorable mechanism that relies on ribosome recruitment by the eIF3 initiation factor. At the same time, this adaptation process is dependent on the continued repression of eIF2B activity.

PERK kinase interacts with its molecular targets in UPR signaling pathways in a cell type- and physiological context-dependent manner, demonstrating significant tissue specificity [47]. For example, PERK has been found to be essential for the progression of melanoma with BRAF mutations, but plays a lesser role in tumors without BRAF mutations . PERK regulates cellular redox through direct phosphorylation and activation of NRF2. PERK interacts with circadian oscillations (so-called clock genes) by inducing miRNA, which inhibits gene expression in a manner that affects Burkitt's lymphoma progression. Not surprisingly, a number of pharmaceutical companies have taken to synthesizing high-affinity PERK inhibitors. Glaxo Smith Kline developed the GSK2606414 (GSK414) inhibitor; Amgen developed the AMG PERK 44 inhibitor; and Eli Lilly developed Ly4. Our laboratory has also developed specific PERK inhibitors for the treatment of neurodegenerative disorders, including glaucoma (referred to as PERKi). The potential for the use of PERK kinase inhibitors in targeted therapy as a new strategy for treating diseases underlying disorders of protein biosynthesis encourages research into different tissue types and combinations with other drugs to evaluate its role as an effective molecular therapeutic target.

Analysis of the transcriptome in model cells subjected to long-term ER stress identified a set of 567 genes that were induced at the transcriptional level and translated into specific proteins known as the ER-adaptosome . Interestingly, 35 of these genes encode proteins that function in the ER as involved in folding, glycosylation, transport and degradation. Since the ER protein processing pathway involves a total of about 141 genes (according to the KEGG database; PATHWAY:ko04141), it should be noted that a relatively large subset of genes specifically in this category were up-regulated during adaptation to chronic ER stress. Consistently, specific mRNAs were upregulated by both changes in translation efficiency (61 genes) and mRNA abundance (105 genes). Therefore, the term ER-adaptosome has been proposed to describe a group of target-induced genes during chronic ER stress.

Although the exact cause of RA is unknown, previous studies have clearly shown that genetic factors play a significant role in the development of the disease. Our original study analyzed the expression of ER protein processing pathway genes in blood samples from patients with rheumatoid arthritis compared to control subjects. Gene expression was analyzed for *PERK, BCL-2, p-eIF2, ATF4* and *BAX*, as well as the endogenous housekeeping gene (*GAPDH*). Referring to the literature data, we found that the expression of ER stress genes (*PERK, BCL-2, p-eIF2, ATF4* and *BAX*) was significantly higher in RA patients than in controls. According to the literature, the disease is more common in women than in men [2]. Interestingly, our study showed that the expression levels of PERK-dependent UPR genes in patients divided by gender were higher compared to controls in both men and women, suggesting that the UPR response to misfolded proteins is a global process involved in the pathogenesis of RA.

CONCLUSIONS

In conclusion, knowledge of epigenetic and molecular factors in the development of RA provides an opportunity to better understand the etiopathogenesis of this disease, as well as the prospect of creating targeted therapy for the treatment of RA in both its early and advanced forms. Literature reports confirm the influence of both individual and molecular factors on the development of RA. The conclusions drawn from the analysis of the above-mentioned literature are consistent with my clinical observation of patients, expressed both by clinical symptoms, an increase in the concentration of inflammatory markers, and the results of imaging tests. Analyzing the cause of RA at the cellular level. The exact cause of RA is not fully understood, but it most likely involves a complex interaction between UPR chronic stress factors (ER-adaptosome), and genetics, as well as environmental factors. As shown, a key function in the regulation of chronic ER stress is played by PERK kinase, which may be a promising molecular target for RA therapy. Although the current findings are promising, further studies are needed to determine the safety and efficacy of PERK kinase inhibitors for the treatment of RA patients.

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CONFLICT OF INTEREST
The Author declare no conflict of interest

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RECEIVED: 05.08.2024
ACCEPTED: 03.10.2024