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Peripheral blood lymphocytes apoptosis role in rheumatoid arthritis progressing

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Abstract

Rheumatoid arthritis (RA) is an autoimmune, chronic, and genetically linked inflammatory lesion of joint tissues that is accompanied by extra-articular systemic pathologies. The disease progression leads to joints immobilization, and eventually, the patient's disability occurs approximately ten years from the first clinical manifestation. RA pathogenesis involves various mechanisms: specific joint-related damage, nonspecific adaptive, and vessel-related pathological changes. Our research aimed to study the role of peripheral blood lymphocyte apoptosis in RA pathogenesis. We have analyzed research data from Google Scholar, PubMed, Web of Science, and Scopus databases to investigate the role of lymphocyte apoptosis in RA progression. Clinical manifestations in RA are caused by autoreactive T- and B-lymphocyte activity supported by humoral and cellular immune factors activity. Disease pathogenesis is caused by an imbalance in the process of programmed cell death (apoptosis): a proportion of immune cells are rapidly destroyed. In contrast, apoptosis is inhibited in the other classes of immune cells. High infiltration of the joint by autoreactive sensitized lymphocytes worsens the patient's condition. Apoptosis inhibition is especially noticeable in the early stages of RA and correlates with the concentration of the anti-apoptotic molecule Bcl-2 in the synovia. Activating the apoptotic destruction of lymphocytes (by drug action) allows a positive therapeutic effect and sustained remission. However, it should be noted that genetic factors play a significant role in the onset, progression and drug response of RA. In addition, environmental and behavioral factors can activate RA progression and influence treatment efficacy.

Key words: apoptosis, rheumatoid arthritis, lymphocytes, joint, blood serum, genetic factors, pathogenesis, treatment

Introduction

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease. It is diagnosed in over a percent of the world's population [1]. RA is one of the most common autoimmune diseases [2] and is characterised by the development of inflammation, synovitis, articular cartilage and bone damage. Its progression leads to disability and immobilisation of the patient. The effectiveness of RA treatment is around 40-70% and depends on individual patient characteristics [1,3]. However, musculoskeletal damage is not the only manifestation of RA. A chronic disease flowing can be accompanied by skin lesions (20% of patients), eye lesions (10%), gastrointestinal tract damage (hardly ever primary, more often due to drug treatment), lungs (usually asymptomatic - 50%, and 10% of patients have clinical manifestations), vascular, and cardiovascular system lesions (about 50% of patients) [4-6]. Kidney and nervous systems lesions are diagnosed as solitary, and their reasons become because of small vessel lesions (vasculitis), which lead the organ dysfunction

development such as glomerulonephritis, nephropathy, dementias, ischaemic neuropathies, and myelopathies [4,5].

RA is most commonly diagnosed at 52±15 years but can also occur in children (juvenile RA) [7]. Genetic, epigenetic and environmental factors, as well as the development of oxidative stress, must be identified as triggers for the onset and progression of RA. These factors activate cellular and molecular mechanisms associated with the progression of RA pathogenesis. Thus, the progression of joint damage is determined (Figure 1) [8,9].

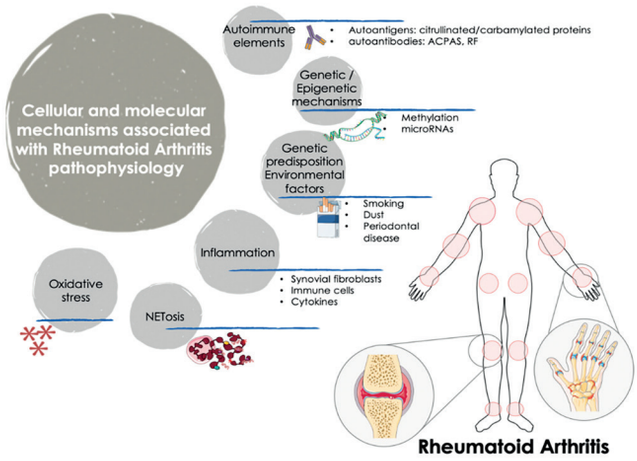

Figure 1 - Triggers for the RA pathogenesis development (according to Lopez-Pedrera et al.): inflectional, inflammation, genetic, environmental, and metabolite together with the points of the most joint damage [9].

A part of researchers associates RA with genetic factors today. Tilloeva gives data about the carriage of DRB1*0401 and DRB1*0404 complexes associated with RA development: in 50-61% and 27-37% of cases, respectively [7]. Catrina et al. declare that RA autoantigens are not tissue or organ-specific. They mark RA autoantigens as innate stimuli broad collection of post-translational modified proteins (citrullinated proteins) [10]. Almutairi K. et al. state that the global prevalence of RA (1980-2019 analysis) is 460 per 100,000. Although this pathology prevalence is heterogeneous, it may vary depending on the geographical, racial, and environmental features of a current region [11], as well as lifestyle (diet, labor type, and physical activity intensity) [8]. Rural residents are more susceptible to RA onset and progression (about 70% of diagnosed cases are fixed in Uzbekistan). Women are more predisposed to this pathology: it is recorded twice as often in this gender [2]. According to Tilloeva, the rate in women is 5.1% [7]. This disease also has a high incidence (3.5%) in first-degree relatives. We can note the connection between the RA diagnosis process and the economic state in the region: better state wealth level gives citizens an availability to have detection programs and self-ability to be checked for RA [11]. However, the link between RA pathogenesis and the humoral and cellular factors' activity in the immune system remains undisputed [8]. There is evidence that there is a close link between dysregulation of immune cell apoptosis, leading to an increase in synovial fibroblasts, inflammatory cells and cytokines, and the progression of disease signs in RA. In patients with different types of pain, such as chronic and neuropathic pain, this may be the cause of increased central hypersensitivity [12].

The aim of our study was to investigate the role of peripheral blood lymphocyte apoptosis in rheumatoid arthritis pathogenesis.

Material and methods

The current research was conducted by analysing literature sources Google Scholar, PubMed, Web of Science and Scopus databases to investigate the role of lymphocyte apoptosis in the pathogenesis of RA. Data from Kazakhstani and international clinical trial reports, analytical reviews and meta-analyses were included in our study. In this regard, the search and analysis used such keyword combinations as "rheumatoid arthritis", "rheumatoid arthritis pathogenesis", "rheumatoid arthritis prevalence", "lymphocyte apoptosis in rheumatoid arthritis", "autoreactive T-lymphocytes", "leukocytes in rheumatoid arthritis", "rheumatoid arthritis treatment". Short messages and advertisements have been excluded from the analysis.

Results and discussion

RA pathogenesis and the apoptosis role in it

Apoptosis is a programmed, controlled, specialised cell death. It is characterised by structural and functional changes in the cell's self structure. This process culminates in macrophages' phagocytosis of the destroyed cell (apoptotic cells). Apoptosis plays a significant role in inflammation development or its termination. But in the case of RA development, this process has changed. So, complex intercommunication of inflammatory and joint-damaging processes progress [13,14].

Typical, apoptosis starts with the activation of membrane "death receptors" (FasR, TNFR1, CARI, DR3, DR4, DR5), which in turn activate the Bcl-2 protein group inducing the apoptosis process and simultaneously inhibit the apoptosis antagonist protein Bcl-2 (Bak). Further, caspases (cysteine-dependent endoproteases) are involved in the process. They act as inducers and effectors of apoptosis and as pro-inflammatory components. Also, they trigger several enzymatic processes that accompany cell death and activate Ca /Mg2+2+ -dependent endonucleases (CPAN/DFF40) [13,15,16].

The early RA stages are characterised by the development of inflammation-induced synovial tissue hyperplasia with further invasion of cartilage and bone tissue, leading to the destruction of these joint structural components [17]. Synovial fibroblast-like synoviocytes (FLS) are activated and exhibit tumour-like behaviour [18]. Joint synovial tissue hyperplasia becomes due to an imbalance between the proliferation and apoptosis of fibroblasts (less subject to apoptosis) and synovial macrophages [17]. At the RA later stages, apoptosis increases with a predominance of hypertrophic joint fibroblast and chondroblast destruction [15]. In the early stages, large numbers of T cells infiltrate the synovial membrane along with synovial hyperplasia. T-lymphocytes interact with other immunocytes, such as dendritic cells, tissue macrophages, and synoviocytes, thereby releasing many inflammatory mediators. T-lymphocytes interact with other immunocytes, such as dendritic cells, tissue macrophages, and synoviocytes, releasing many inflammatory mediators. The inflammatory mediators' predominance of anti-inflammatory mediators contributes to chronic process development. Bcl-2 protein's high concentration in the joint provokes the proliferation of autoimmune T-lymphocytes [12,19]. Bcl-2 protein high concentration in the joint causes the proliferation of autoimmune T-lymphocytes [19]. Thus, the number of B-lymphocytes, whose primary function is to produce antibodies (autoreactivity proteins against RA) and inhibit memory B-cells apoptosis, is increased. Autoantibodies stimulate T-lymphocytes proliferation and release interleukins (IL-10), activating factors that promote apoptosis (caspases) and tumour necrosis factor (TNF). This process triggers abnormal T-cell autoreactivity that contributes to the exacerbation of RA symptoms [20].

Peripheral blood cell apoptosis in RA: its role and significance

Apoptosis is a general biological mechanism responsible within the immune system for eliminating activated lymphocytes that have fulfilled their function to prevent autoimmune reactions. Defects in the process of programmed peripheral lymphocyte death can cause tolerance disorders and chronic inflammation [13-17].

RA is an autoimmune disease, as evidenced by increased levels of immunoglobulins in the blood serum. And the increase in the concentration of rheumatoid factor (RF) in the blood, as well as lymphocytes sensitised to the structural components of the connective tissue, is essential [21]. The pathogenesis of the disease is determined by the state of the synovial macrophages, fibroblasts and lymphocytes. Thus, the progression of joint tissue hyperplasia in RA is diagnosed by the accumulation of synovial macrophages and fibroblasts. These cells provoke the progression of inflammation and destruction of the joints due to the release of cytokines, interleukins and proteases that initiate the inflammatory process [22]. RA progression is accompanied by increasing of the T-lymphocytes, especially CD4+ cells that concentrate on their surface activating antigens such as IA+ cells (class 2 proteins of the major histocompatibility complex), receptors for interleukins (IL-2 in particular), and TFR+ (transferrin) cells [21]. The high expansion of autoreactive T-lymphocytes into the affected joint is also noteworthy. They attack the synovial cease and destroy them. A high amount of inflammatory mediators are released, and significantly fewer anti-inflammatory mediators are produced [11]. Chronicity of the process becomes the consequence of the predominance of inflammatory mediators in the progression of the pathogenetic chain of the disease [13,22]. The degree of infiltration by lymphocytes, macrophages and FLS in the joint correlates with increased expression of the anti-apoptotic factor Bcl-2 in the synovium [23] and the increased expansion of autoimmune T lymphocytes into the affected joints due to both the tumour-like behaviour of FLS and inhibition of apoptosis by blood T cells [24].

Activated autoimmune rheumatoid-induced T-lymphocyte (B7-H1) stimulates the proliferation and apoptosis of blood lymphocytes [25]. Dong et al. (2003) report that B7-H1 boosts CD4+ T-cell proliferation and secretes interleukin IL-10, activating apoptosis-inducing ligands, caspase-3, and TNF. These processes cause abnormal T-cell responses in RA progression and exacerbate disease symptoms [24].

Peripheral blood lymphocytes (autoreactive T-lymphocytes) apoptosis in AR is activated by the CD44 protein triggering Fas ligand (FasL) on the surface of autoreactive T-cells. FasL activates Mg^{2+}/Ca^{2+}-conjugated cytokines associated with IP3 receptors. This mechanism triggers actin cytoskeleton rearrangements which induce T-lymphocyte death [13]. But there is also an undefined relationship between synovium and leukocyte survival. Zaichko et al. report that the "mortality" of T-lymphocytes in the joint cavity is lower compared to the same cells outside the joint environment (synovium) [23]. According to their study, Goltsev et al. confirm the connection between T-lymphocytes and survival in synovium. Although the characteristics of lymphocytes infiltrating the joint suggest that they are 'doomed' to the process of apoptosis (high Fas-receptor expression coupled with low Bcl-2 (an anti-apoptotic factor) activity), they are not involved in this process. The reasons for this situation are unclear, especially considering that neutrophils in the same patients undergo apoptosis in masse [21].

We have established that activating one immunocompetent cell population causes other immunocytes to become activated. Therefore, it is rather difficult to interrupt this chain. Thus, activation of CD4+ T-lymphocytes (which prevail in RA progression) is combined with activation of B-cells, production of pro-inflammatory factors, and autoantibodies to RF. B-lymphocyte apoptosis is inhibited due to a decrease in FasL activity, which induces a process of programmed lymphocyte death. Accordingly, the release of B-cell metabolites supports inflammation, the destruction of joint tissue, the release of inflammatory mediators and T-cell activation [13,19]. And the immune mechanisms' activation process in a patient with RA

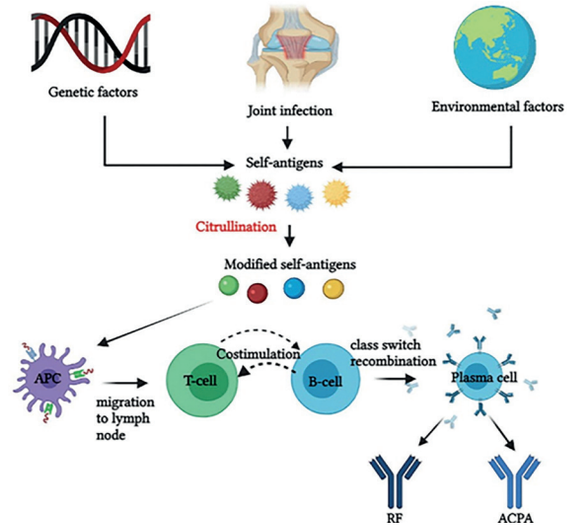

Figure 2 - Mechanism of the RA pathogenesis progression from triggers to the antibodies production by activated B-lymphocytes according to Radu and Bungau (2021) [25].

already occurs in the preclinical period of disease progression (Figure 2). So, the trigger factors (such as genetic, infectional, or environmental) activate the mechanisms of antigens reaction to body-self tissues. And this process is circle-connected to joint damage and the production of autoactivated immunocytes [26,27].

And increasing in serum levels of autoantibodies to RF, in particular - to Anti-citrullinated protein antigens (ACPA) – registered before clinical symptoms appear. Increasing antibody concentration to other post-translationally modified proteins, such as carbamylated proteins, is also detected. It is also established that in the preclinical stage of the disease some biomarkers and changes in autoreactive T-lymphocytes are observed, such as glycosylation of their variable region. This situation is considered highly predictive of future RA progression [26].

RA therapy strategy: principles and mechanisms, the significance of the lymphocyte apoptosis activation

Understanding the pathogenesis of the disease and the mechanism of the immune response is the basis for developing drug therapies to alleviate symptoms and achieve stable remission [28]. Today, an integrated approach to RA therapy is practiced, combining moderate activity, physiotherapy, symptomatic and anti-inflammatory treatment, and modifying traditional and biological anti-rheumatoid drugs [29,30]. It is subordinate to the benefit/risk assessment formula [23]. This approach can achieve remission or control the disease symptoms. But its effectiveness is not 100% guaranteed for the patient. In some cases, neither mono- nor combination therapies can achieve positive outcomes

[17,30]. However, mechanism activation of programmed autoreactive lymphocyte death, followed by the release of anti-inflammatory mediators into the bloodstream, alleviates the symptoms and stops the RA progression [13,31,32]. Genetic and environmental factors can influence therapy efficiency, including prognosis improvement [10,25]. At the same time, lack of timely therapy leads to disability in patients: 80% are diagnosed with joint damage, and 40% become disabled in 10 years [30].

One theory of therapy aimed at relieving symptoms and alleviating the patient's condition is the activation of the p53 molecule, which can affect the tumorigenic nature of cell division (suppression) and activate apoptosis [4,33]. But activating this molecule does not bring a positive therapeutic effect in the early stages of RA. Thus, a high p53 titre (+0.85) is observed in the patients' blood with active clinical RA in the early stages of the disease, which can even be considered a high disease activity predictor. In contrast, activation of the p53 molecule confers a positive therapeutic effect at the later stages of the disease. A direct correlation between apoptotic factor p53 concentration and non-erosive RA (+0.8) can be asserted. In the case of the erosive form, this relationship has been established for the anti-apoptotic molecule Mdm2 (+0.7). Therefore, activation of p53 in the RA early stages leads to worsening symptoms and can only be performed in late-stage patients [4].

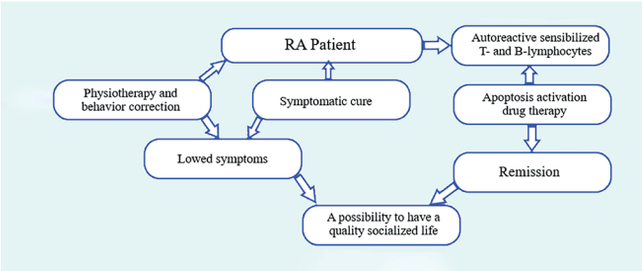

Figure 3 - Current common treatment approach in getting RA remission.

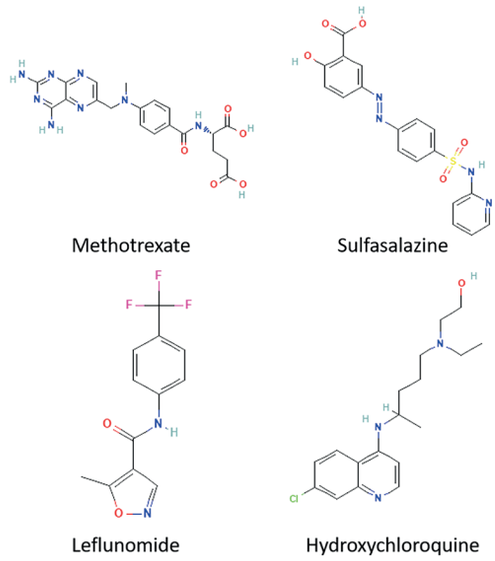

Figure 4 - Molecular structure of the most common disease-modifying anti-rheumatic drugs in the modern clinic practice.

Dedicated research into the treatment of RA has resulted in significant advances in the pharmacotherapy of RA as a chronic disease (Figure 3). This approach reduces symptoms, slows disease progression and may prevent associated complications. The European Alliance of Associations for Rheumatology [34] recommends combining treatment of symptomatic RA with disease-modifying drugs (Figure 4).

Greenblatt et al. (2020) report that a single dose of rituximab can delay the onset of RA symptoms [26]. Rituximab is essentially a chimeric monoclonal antibody. Its action is based on its mechanism of binding to the surface marker of B-lymphocytes CD20. The drug activity extends to mature (plasma) cells as well as to non-activated B-lymphocytes and memory cells. The rituximab effect is to kill target cells by activating cytotoxicity (antibody- and complement-dependent) and apoptosis [29,35]. Greenblatt et al. also hypothesise that abatacept, hydroxychloroquine and methotrexate are effective in RA treatment [26]. There is data about raising the pro-inflammatory cytokines' level due to methotrexate use in the treatment schema. According to research data, this improves the proposed cure's efficiency [36]. López-Rodríguez et al. (2018) provide evidence that the methotrexate treatment efficacy is associated with the polymorphism of the A-allele MTRR-rs1801394 in the patient [37]. It is also related to genetic variants SLC19A1-rs1051266, DHFR-rs836788 and TYMS-rs2244500 [38]. Methotrexate is an antimetabolite, similar in structure to folic acid, and its accumulation in the body provokes an antiproliferative effect by depleting the intracellular folate depot [39]. However, any therapy aimed at relieving symptoms, stabilising the patient's condition and achieving a stable remission should be accompanied by a treatment focused on repairing damaged tissue (mesenchymal stem cell therapy) [30,31].

Conclusion

Programmed cell death (apoptosis) has been extensively studied and is recognised as one of the main pathological mechanisms in RA. Its dysregulation in the pathological process contributes to RA progression and exacerbation of disease symptoms.

An imbalance of autoimmune T- and B-lymphocyte cell death enhances autoimmune and inflammatory reactions. At the same time, massive cell death of macrophages and neutrophils is fixed. Therefore, these processes contribute to the developing pathological responses associated with RA. Additionally, the increased joint structural cells death, like osteoblasts, chondrocytes, and osteoclasts, causes the destruction of articular surfaces and bone. Consequently, the unbalanced death of several cell types works in tandem, forming a vicious circle. Activation of each of its links aggravates the clinical manifestation of the disease. At the same time, genetic and environmental factors influence symptomatology development and the rate of pathology progression (flowing).

Activation of autoreactive leukocyte apoptosis (both T- and B-cells) positively affects the disease's course and prognosis, significantly alleviating the pathology symptoms. So this allows for improving the patient's life quality and delaying his disability.

Prospects for further research

Analysing the literature data, we have to fix the necessity to continue studying the intensity of lymphocyte apoptosis, taking into account the degree of RA activity and the ongoing treatment's effect on the programmed death of lymphocytes. The next planned step would become the guidelines for the RA diagnosis development and personalised therapy for RA patients.

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