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გამოწმები შეიქმნება შესახებ გრამატიკული ხანგრძლივობის გამოკვლევა.

Dubivska SS, Omelchenko-Seliukova AV, Lazyrskyi VO, Viedienieva Ry. STUDY OF THE PROCESSES OF LIPID PEROXIDATION, THE STATE OF THE ANTIOXIDANT SYSTEM IN PATIENTS WITH POLYTRAUMA AND ALCOHOL ANAMNESIS. 118-124


Ahmad Mohammed SMADI, Salam Bani Hani, Abedalmajeed SHAJRAWI, Marwa Alhalabi. COMPLIANCE AND CHALLENGES OF TRANSMISSION BASED PRECAUTION PRACTICES AMONG NURSES IN JORDANIAN HOSPITALS DURING THE NOVEL COVID-19: A DESCRIPTIVE STUDY. 132-137

Georgi Tchernev. THE NITROSAMINE CONTAMINATION IN BETA BLOCKERS (BISOPROLOL/ METOPROLOL), ACE INHIBITORS (LISINOPRIL/ PERINDOPRIL), THIAZIDES DIURETICS (HCT), CALCIUM CHANNEL BLOCKERS (AMLODIPINE/ FELODIPINE), SARTANS (Candesartan) AND THE SUBSEQUENT SKIN CANCER DEVELOPMENT AND PROGRESSION: APOCALYPSE NOW. 138-145

MOLECULAR EFFECTS OF RESVERATROL IN THE TREATMENT OF AUTOIMMUNE DISEASES


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Abstract.
The article represents the molecular effect of resveratrol on the course and progression of autoimmune processes. It has been shown that resveratrol in a low dose inhibits the formation and activity of some B-lymphocytes subpopulations. On the one hand, this leads to the use of resveratrol in the treatment of autoimmune diseases. On the other hand, it activates antitumor immunity. However, there are several problems that prevent the widespread use of resveratrol nowadays. In particular, its poor water solubility, bioavailability, and dosage. In order to place resveratrol as a cutting-edge molecule in medicine, additional multicenter and placebo-controlled trials have to be carried out.

Key words. Resveratrol, immunity, B-lymphocytes, autoimmune diseases, tumors, antitumor effect, decreased production of autoantibodies.

Resveratrol.

Effects and field of use:
There are many experimental studies highlighting the regulatory mechanisms and immunomodulating role of resveratrol both in vivo and in vitro. These data show the promising role of resveratrol in the prevention and treatment of a wide range of chronic diseases, including cardiovascular, inflammatory, metabolic, neurological, and dermatological diseases, as well as various infectious diseases. Over the last few years emerged more evidence that it has strong chemosensitizing effects in various forms of cancer. These studies present that resveratrol modulates many cellular and molecular mediators of the inflammatory response. However, several studies report that resveratrol can also act as an antagonist of biologically active substances involved in the inflammatory and immune response.

Structural interactions of resveratrol and B-lymphocytes.
B cells are characterized by their ability to produce antibodies. In addition, they secrete cytokines. B cells have separate subpopulations that perform both regulatory and pathogenic functions. Regulatory B cells (Breg) are a rare subpopulation of B cells (less than 10% of the total number of B cells in circulation) with regulatory/suppressor functions and play important role in the mechanisms of peripheral tolerance. Their regulatory activity is usually mediated through the production of IL-10. Less than 20% of these cells from various subpopulations after stimulation remain producers of IL-10. Inflammation strongly promotes the development and differentiation of Bregs. Breg activation requires a combination of different molecules, including TLR, CD40, B-cell receptor, CD80, CD86, and cytokines. Based on activation pathways, three different types of Breg cells have been characterized: innate Breg cells requiring signaling through innate receptors such as TLR; immature Breg cells requiring CD40 stimulation; antigen-specific Breg cells requiring both B-cell receptor and CD40 signaling. Bregs prevent inflammation by inhibiting Th1 cells activation, maintenance of Treg cells populations, and Th17 proliferation and differentiation. Although IL-10 is a key molecule in the inhibition of Breg inflammation, recent studies have shown that certain Breg subgroups perform their inhibitory function through additional factors. There are data showing that cancer metastasis requires the involvement of regulatory immune cells such as FoxP3+, CD4+, Tregs, and TGFβ-expressing tBregs. Tregs and tBregs must be monitored to effectively prevent lung metastases. A series of experiments showed that low and noncytotoxic doses of resveratrol prevent the progression of B16 melanoma and 4T1.2 breast cancer cells, eliminating lung metastases by inactivating tBreg. This results in blocking the ability of tBregs to convert FoxP3+ Tregs – a process that requires TGFβ expression. Moreover, low, and non-cytotoxic doses of resveratrol suppress the formation and function of tBreg by inactivating Stat3. This inactivation of Stat3 into tBregs probably causes the inhibition of expression of TGFβ, a downstream target of Stat3 [1-16].

This study showed that low doses of resveratrol could be used to induce an antitumor effector and to combat tBreg-mediated tumor escape. It has been found that resveratrol treatment can alleviate lupus nephritis in MRL/lpr mice by activating FcγRIIB, what results in a selective reduction of B cells in spleen and bone marrow. Moreover, plasma cells expressing the highest levels of FcγRIIB were significantly reduced in both spleen and bone marrow in response to resveratrol administration. The depletion of autoreactive plasma cells caused a decrease in the production of autoantibodies, what led to a decrease in the deposition of immune complexes in kidneys. This result has clinical significance because neither antiproliferative agents such as cyclophosphamide nor anti-CD20 monoclonal antibodies such as Rituximab can effectively remove plasma cells from the bone marrow of patients with systemic lupus erythematosus (SLE). Moreover, it was shown that resveratrol induced Sirt1 inhibits B cells proliferation and autoantibody production, improving the course of SLE in a mouse model with constitutive and persistent Th1 cells activation [15,16].

Lupus nephritis is characterized by glomerular and tubulointerstitial inflammation and proliferation of mesangial cells, followed by progressive glomerulosclerosis and interstitial fibrosis between the tubules. Resveratrol significantly reduces glomerular and tubulointerstitial fibrosis and restores glomerular
morphology. In addition, it notably reduces the deposition of immune complexes in the glomeruli. The inhibitory effect of increased FcγRIIB expression on B cells in vivo may allow FcγRIIB to perform a self-regulatory feedback function to control plasma cells number through immunocomplex-dependent apoptosis. This effect is clinically important because reduced expression of surface FcγRIIB on memory B cells is often observed among patients with SLE, what leads to a limited ability to inhibit B cell activation and induce apoptosis. Therefore, the pharmacological regulation of FcγRIIB expression by resveratrol can lead to a significant decrease in the production of autoantibodies. These data indicate that depletion of autoreactive cells in the bone marrow after resveratrol treatment is mainly mediated by an FcγRIIB-dependent apoptotic pathway rather than inhibition of R-dependent B cell receptor (BC) activation [12,14,16]. Other studies have supported the idea that the elimination of autoimmune cells in bone marrow has a major importance in the treatment of patients with SLE. Clinically, upregulation of FcγRIIB in B cells may be beneficial in improving the outcome of SLE patients who manifest suppression of surface FcγRIIB on their memory B cells [7,8,10]. In addition, it was demonstrated that NF-κB is a critical regulator of resveratrol in the upregulation of FcγRIIB expression. Because neither T cells nor NK cells express FcγRIIB, the selective modulation on humoral immunity via FcγRIIB highlights a unique approach to SLE treatment with no influence on other immune functions, thereby circumventing the side effects of systemic immunosuppression induced by current therapeutics.

**Conclusion.**

To sum up, resveratrol has established itself as an effective substance for prevention and treatment of a wide range of diseases, including autoimmune diseases. However, despite the fact that preclinical studies of resveratrol have shown impressive results, many questions about the use of this drug in the clinical practice still remain because of the lack of large randomized, placebo-controlled clinical trials. At the same time, there are many difficulties in the clinical use of resveratrol, such as its poor water solubility, bioavailability, and dosage. Therefore, various strategies are being implemented, which include the development of resveratrol analogues and formulations such as adjuvants, nanoparticles, liposomes, micelles, and phospholipid complexes, to improve its bioavailability. Moreover, several other approaches have been used to increase its bioavailability, which include altering the route of administering resveratrol and blocking the metabolic pathways by co-treatment with other agents. Since resveratrol, being a naturally occurring polyphenol, has several intracellular targets, more data are needed to determine the consequences of interactions or synergistic effects between other polyphenols and vitamins, amino acids and other micronutrients or commonly used drugs. According to the authors, more detailed preclinical and clinical trials are needed to evaluate the efficiency of these new formulations. Therefore, further studies in humans are required to improve its bioavailability and elucidate the mechanisms of action of resveratrol under different physiological conditions in order to make this substance a cutting-edge therapeutic strategy.

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