TOPOISOMERASE INHIBITORS AND MULTIDRUGS RESISTANCE

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Introduction. The nuclear enzymes topoisomerase inhibitors I and II are critical for DNA function and cell survival and recent studies have identified these enzymes as cellular targets for several clinically active anticancer drugs. Topoisomerase II inhibitors (anthracyclines, epipodophyllotoxins, etc.) are active against several types of tumors. However, treatment with these drugs often results in the development of the multi-drug resistance. Because topoisomerase II-active drugs have several different modes of action, different mechanisms of resistance, including decreased activation and increased detoxification by glutathione-dependent enzymes, have also been implicated.

Aim. The aim of the study was to study the biochemical mechanisms of action of topoisomerase inhibitors and the possibility of drug resistance in the case of their use.

Materials and methods. In order to achieve this goal, an information search was conducted in the materials of scientific articles.

Results and discussion. Topoisomerase II is a target of alkaloid, anthracycline and related antitumor agents. Two types of multiple drug resistance are associated with these enzymes. In classical (typical) multidrug resistance, inhibitors are actively effluxed from cells by P-glycoprotein. In atypical multidrug resistance, topoisomerase II is either reduced in cellular content or mutated to a form that does not interact with inhibitors. Because cytotoxicity of most antineoplastic topoisomerase II inhibitors is directly related to the number of active topoisomerase II molecules, a reduction in this number leads to resistance. In the topoisomerase II mechanism, through which the DNA linking number is altered, DNA double strands are cleaved, and the termini transiently bound covalently (5′) or noncovalently (3′) to the enzyme while a second double strand is passed through the break in the first.

Conclusions. Multidrug resistance results from either 1) decreasing cellular content of the inhibitor by P-glycoprotein (typical) or 2) decreasing cellular content and/or activity of the target, topoisomerase II, as, for example, when its content or activity is modulated downward by decreased expression, deactivation, or by mutations to the topoisomerase II gene, producing an enzyme that reacts poorly with inhibitors (atypical). Mixed types, both typical and atypical, are known. Attempts to abrogate or prevent both typical and atypical multidrug resistance to topoisomerase II inhibitors have been described.

IMMUNOMODULATING PROPERTIES OF VITAMIN D AND DIABETES TYPE 1

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Introduction. Vitamin D (VD) is traditionally classified as a fat-soluble vitamin, while its derivative calcitriol belongs to hormones. Indeed, calciferol is an important nutrient that, after

activation in the body, is involved in the regulation of many processes. Of great interest is its effect on the immune system, incl. the ability to prevent autoimmune diseases. Type 1 diabetes mellitus (T1DM) is a chronic endocrine metabolic disease caused by insulin deficiency due to immune-mediated destruction of pancreatic β-cells, one of the risk factors for which is VD deficiency.

Aim. The aim of this work was to analyze the literature data on the mechanisms of the immunomodulatory effect of VD in preventing the development of type 1 diabetes mellitus.

Materials and methods. Search and analysis of open sources of scientific literature.

Results and discussion. Numerous literature data indicate that over the past decades, ideas about the role of calcitriol have changed. VD takes part not only in the metabolism of calcium and phosphorus, but also in the regulation of proliferation and differentiation of all organs and tissues, it stimulates synthesis of receptors for many hormones (insulin, thyrotropin, glucocorticoids, etc.), regulates the formation of ATP, promotes the coupling of oxidation and phosphorylation, affects the structural and functional activity of cell membranes, weakens adaptive immunity and stimulates innate one, inhibits neoplastic processes, exhibits anti-inflammatory effects, etc.

The established antidiabetic effect of VD is associated with its anti-inflammatory and immunomodulatory properties. The immunomodulatory effect of calcitriol is its ability to modify the transcription of certain genes in the cells of the immune system. From the point of view of autoimmune diseases, the most important role of VD is its ability to suppress acquired immunity and induce immunological tolerance, as well as to induce an anti-inflammatory effect, which together prevents the development of autoimmune pathologies, including T1DM. Calcitriol accelerates the maturation of monocytes into macrophages, but at the same time reduces their ability to present antigens to T cells, decreasing the expression of the surface histocompatibility complex MHC-II (MHC - major histocompatibility complex). It also disrupts the maturation process of dendritic cells, resulting in the formation of tolerogenic dendritic cells without surface MHC molecules, which are thus unable to present antigen. In addition, VD promotes the differentiation of CD4 + T cells into Th2 and regulatory T cells, decreases the production of Th1 and Th17 cells, resulting in a decrease in the Th1 / Th2 ratio, a decrease in the production of pro-inflammatory cytokines and an increase in the release of anti-inflammatory cytokines. Moreover, calcitriol enhances immune tolerance not only by shifting the balance of the body's T-cell response from Th1 to Th2 response, but also by maintaining B-cell homeostasis (prevents B-cell proliferation, differentiation into plasma cells, B-cell formation and production of immunoglobulins, including autoantibodies). In general, these actions prevent Th1/Th2 cell imbalance, reduce the inflammatory response and thus prevent the destruction of pancreatic β-cells.

Conclusions. Thus, literature data indicate that one of the central mechanisms of calcitriol action in preventing the development of T1DM is the ability to inhibit the proliferation of cytotoxic T-lymphocytes and natural killer cells, as well as stimulate the activity of T-suppressors, maintaining the body's resistance to its own antigens.