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PROTECTIVE EFFECTS OF SULFORAPHANE ON THE ALCOHOL-INDUCED TOXICITY AND ENDOPLASMIC RETICULUM STRESS IN C57BL/6 MICE

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Abstract: Objective It is known that alcoholic liver disease (ALD) caused by the acute and chronic exposure to alcohol is one of the chronic liver diseases with the high mortality. Sulforaphane (SFN), rich in various cruciferous vegetables, has been widely studied as a chemo-preventive agent. In this study, we focused on the protective effects of SFN on alcohol-induced toxicity and mechanisms.Methods Male C57BL/6 mice were orally administrated with SFN (0, 12, 40, 80 mg/ kg.bw) for 14 days. At the 13th day, mice were challenged with alcohol (5g/kg.bw) every 12 h for 3 times. Results SFN markedly reversed the alcohol induced decrease of antioxidant capacity through enhancing GSH, GSH-Px, GST redox system. And the protective actions are related with activating Nrf2 and inactivating NF-κB. SFN attenuated the triglyceride (TG) and cholesterol (CHOL) contents which is possibly mediated by down-regulating sterol regulatory element-binding protein-1 (SREBP-1c). In addition, SFN weakened the stimulation of the chaperone GRP78, and its downstream sensory receptor ATF-6, triggered by acute alcohol intake. Conclusion The results suggest that antioxygenation is involved in the protective effects of Sulforaphane on the alcohol-induced toxicity. The current findings indicated that SFN weakened the liver toxicity triggered by alcohol through enhancing antioxidant capacity and reducing the endoplasmic reticulum stress.

Keywords: sulforaphane; alcoholic liver disease; endoplasmic reticulum stress

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PERSONIFIED MEDICINE – MEDICINE OF THE 21ST CENTURY

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In April 1953, the journal «Nature» published an article by James Watson and Francis Crick, “The Molecular Structure of Nucleic Acids, the Structure of Deoxyribonucleic Acid” (1). It is with this publication that the emergence of a new biological science - molecular biology - the science of the molecular foundations of life, is connected. mechanisms of storage, reproduction, transfer and realization of genetic information, structure and functions of molecules of biopolymers - nucleic acids and proteins (2). The paper proposed a three-dimensional spatial model of a DNA molecule in the form of a double helix. From the model follows the principle of matrix synthesis, i.e. syntheses, in which information about the structure of the synthesized molecule is encoded in the structure of the molecule-matrix. The mRNA molecule is synthesized on the matrix of the DNA molecule, which in turn is the matrix for the protein-synthesized polypeptide chain synthesized on the ribosomes. Thanks to this discovery and the suggested direction of reading the genetic information of RNA DNA, the protein, called the central dogma of molecular biology, was universally recognized. Molecular biology uses its own methods of research - genetic engineering, cloning of cells and organisms, artificial expression and knockout of genes. In the 20th century, molecular biology achieved tremendous results, explaining the molecular foundations of the most important manifestations of vital activity-the storage and transfer of genetic information, immunity, cellular respiration, apoptosis, and others, and the molecular mechanisms of the origin of the most important human diseases.

The term “molecular illness” was first used in 1949. Linus Polling applied to sickle cell anemia, a disease caused by a point mutation accompanied by the replacement of negatively charged glutamic acid in the 6th position of the hemoglobin β chain with a hydrophobic amino acid valine and leading to a sharp decrease in the solubility of hemoglobin, precipitation, change in the shape of erythrocytes and restriction The ability of cells to carry oxygen (3).

The starting point for the emergence of new directions of medicine, for example gene therapy, therapeutic cloning, which allows to receive stem cells by genetic engineering methods and use them as medicines, was the implementation of the international scientific project “Human Genome” (1989-2002). The project was aimed at complete DNA sequencing of Homo sapiens ie. establishment of a sequence of 3.2 109 pairs of nucleotides in a DNA molecule. The project was conceived in the mid-80s of the 20th century and began to be implemented since 1990. Initially, the scientists believed that the project would take a whole century to complete, then, taking into account the unprecedented methodological progress, the project was planned to be completed by 2005, but in fact the main goals were achieved by mid-2001. And the organizers of the project reported on its more than successful implementation. The implementation of the project provided detailed information on the structure, organization and functioning of human DNA, contributed to the development of new effective technologies in the field of molecular biology, the creation of international electronic databases of genes and proteins open for free access, led to the emergence of a new triad of biological sciences - genomics, proteomics and bioinformatics , Had immense significance for biology, medicine and the international community as a whole and each individual, opened up new per-

spectives willows to understand the causes of the origin of many diseases and develop new ways of treating them (4)

Today abroad, the term “molecular medicine” passes from the sphere of science to the sphere of practical public health. The medicine of the near future is a personified medicine, based on the characteristics of the genome of a particular individual, predisposing to the occurrence of a disease in him (5). Scientists began to see the cause of the disease in characteristic disorders of the genome and proteome (the totality of all proteins of the cell and the organism as a whole), which are manifested in the violation of the structure of a particular gene and the appearance of proteins with altered properties, called “biological markers” of the disease. To prevent disease or timely treatment, it is necessary to identify the underlying defects in the genome and proteome (biological markers of the disease) as early as possible with the help of molecular diagnostics representing the result of introducing into the clinical laboratory diagnostics methods of PCR and macromolecular blotting. The analysis of biological markers by molecular biology methods will allow to assess the risk of developing the disease, monitor its course, draw conclusions about the prognosis, and select medicines based on the sensitivity or insensitivity of the affected gene or protein to them. These genes and proteins are targets for fundamentally new drugs, created with the help of one of the directions of bioinformatics - computer design of drugs, which significantly shortens the terms of the first stage of drug development and its cost. You do not need to synthesize anything. All that is needed is already in electronic databases, including more than 6 million low-molecular-weight compounds. It is necessary to identify the target (gene, protein molecule) and assess the ability of the compound from the database to interact with the receptor. Then, high-performance screening, used throughout the world for pharmacological purposes and allowing simultaneous analysis of several thousand different compounds in parallel mode. Found in this way, the basic structures already in the next stage by their chemical modification become the final drug. Computer design of medicines uses methods of computational chemistry to create, improve the efficiency and study the mechanism of action of drugs. The main goal is to predict whether a given molecule will bind to a target molecule and, if so, how strong the binding will be. There are two types of computer design of drugs - structural design and design based on the properties of the ligand (6). At first, the selection of candidates for the role of a new drug is based on the ability to recognize the known three-dimensional structure of the receptor protein (drug target), established experimentally by Rg-structural analysis, NMR spectroscopy, electron cryomicroscopy. The second search for candidates that maximally match the characteristics of the “pharmacophore” “- a set of characteristics of the compound (three-dimensional structure, features of the electronic structure, etc.), which should have a candidate for the role of a drug for optimal drug receptor recognition and expression of biological effects.

Computer design can be used at any stage of the drug development: identification of the target for the drug using virtual-screening (structure-or ligand-based design), optimization of the affinity and selectivity of the ligand to the target (hit-to-lead optimization), optimization of other pharmaceutical Properties of the drug with preservation of high affinity. This approach underlies targeted therapy - a new direction in the treatment of malignant tumors.

The first drug, created with the help of computer design, is the inhibitor of carbonic anhydrase dorzolamide, registered in 1995. Another vivid example of the effectiveness of the use of computer design was the creation by Novartis (Switzerland) of Imatinib (Glivec), a new generation tyrosine kinase inhibitor. The drug has proved to be an effective tool in the treatment of myeloleukemia and a number of tumors (7). Difference of the drug from its predecessors is the ability to differentially affect malignantly transformed cells and not to affect normal rapidly dividing cells. At the Department of Chemistry of the Amurskaya GMA, bioinformatics methods were used to develop a new preparation of a serine protease inhibitor based on a soybean trypsin inhibitor (8-10). The use of in silico methods has made it possible to reveal a certain proximity of the primary structures of soybean and pancreatic trypsin inhibitors (aprotinin, the active principle of the pharmaceutical preparation Gordoks and Contrikal) and to predict the ability of the plant inhibitor to influence hemostasis processes (8,9), which was experimentally confirmed in in vitro experiments (10). Currently, the department of bioinformatics methods are used for the comparative analysis of plant and animal protease inhibitors (11), as well as characteristics and TRP-receptors (12).

Future personalized medicine will be based on identifying the characteristics of genomes in individuals, determining the person’s propensity to develop a disease in him. New generation sequencing methods (SPS) have been developed, which allow to quickly and relatively cheaply decipher the genome of a particular individual. Today the cost of sequencing an individual genome is about 1000 dollars. For the wide introduction of the method into practical medicine, the cost of sequencing must be brought to $ 100. The principles of SNP technology are based on the sequencing of DNA chips, using cyclic enzymatic reactions. At the first stage of sequencing, libraries of random DNA sequences are created, which can be stitched together with public adapter sequences. In the second stage, amplicons are created using the PCR method, which will be used as samples. The third stage determines the primary structures of all fragments.

The possibility of sequencing individual genomes introduces an individual approach to the treatment and prevention of human diseases and is the fundamental basis of personified medicine, bringing together two historically established philosophical and methodological concepts of medicine. At the heart of the first, which arose in the extreme antiquity, lies a holistic view of the nature of man - the human body is a single whole. You need to treat not the disease, but the patient. The first to express this idea was the famous Greek physician Hippocrates (13). A holistic view of the nature of the human body and the disease was shared by the coryphaeus of Russian medicine - M.Ya. Mudrov, N.I. Pirogov, etc. M. Ya. Mudrov addressed the students with the words: “You, my friends, will always repeat the same thing more often and louder than the same thing that one should not treat a disease by its name alone, should not treat itself illness, for which we often do not find the name, should not treat the causes of the disease, which are often

not known to us, either sick or surrounding, because they have long since left the patient and can not be eliminated, the patient himself has to be treated, his composition, his organs, his strength. Here is the secret of my treatment, which I bring to you as a gift "(14). A holistic approach underlies traditional Chinese medicine. A Chinese doctor thinks how to restore the health of a person as a whole, and not just how to cure the disease or diseased organs (15).

The second concept, which appeared in Europe in the 19th century and dominates in Western medicine today, rightly paying attention to the idealism of the first, requires finding a material substratum of the disease and ironic over the medicine of the countries of the East. A vivid representative of this concept, Rudolf Virchow, is the founder of cellular (cellular) pathology, in which painful processes are reduced to changes in the vital activity of the smallest parts of the animal organism-cells (16). Virkhov considered an anachronism to raise the question of the general disease of the whole organism and refused the principle of treating the patient, and not the disease, saying "to consider the disease as the suffering of the whole organism and to call for the treatment of healthy organs and systems - absurd!". Traditional eastern medicine today in the West is considered pseudoscience. The development of natural science led in the 19th and 20th centuries to rapid progress in the field of biology, based on the achievements of natural fundamental sciences, and unrecognizably changed medicine. The cause of the disease today is seen not even cell damage, but in molecular defects that arise as a result of the violation of the genetic apparatus of the cell, and the task of medicine is seen in the selection of such drugs that will eliminate the existing molecular defect. In fact, it is proposed to treat not even a disease, but defects of molecules (3,4). At first glance, Western methodology completely dominates in modern medicine and the holistic view of the nature of man and disease is forever forgotten. However, paradoxically this sounds, it is the latest achievements in molecular biology, the decoding of the human genome and the ability to quickly peruse individual genomes can unite two seemingly irreconcilable philosophical concepts of medicine. Yes, the disease has a material substrate. At the heart of the origin of diseases are very specific changes in cells and macromolecules, but it is the unique characteristics of each person that predetermine the possibility of the occurrence of a disease, the effectiveness of a medicine.

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THE PROTEINS OF NERVOUS TISSUE INVOLVED IN NEURODEGENERATIVE DISORDERS. BIOINFORMATIC STUDY

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