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Cells of Patients with Down Syndrome—A Model to Study Mechanisms of Oncogenesis and Hypersensitivity to Genotoxicants and Antimutagenesis

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Abstract—Several molecular and genetic features of cells from Down syndrome patients are considered in comparison to those of healthy donors, as is the possibility of using these cells to study mechanisms of the transformation of normal cells to malignant ones, based on the study of the expression of the genes controlling these processes. The role of microRNAs in the regulation of gene activity is estimated. These investigations make it possible to detect the genes for a hereditary predisposition to oncogenesis. The application of antimutagens-anticancerogens provides a new approach to the prophylaxis of this and other human pathologies. In addition, the data on the hypersensitivity of Down syndrome cells to genotoxicants (radiation and others) and the possibility of correcting these disturbances with antimutagens are presented. A special section is devoted to specific changes in cells typical for Down syndrome and Alzheimer disease; the commonality of several elements of the pathogenesis of these diseases is emphasized. The research on Down syndrome cells in terms of an imbalance in the entire genome under this pathology opens new means for the prophylaxis and treatment of several human pathologies.

Keywords: Down syndrome, Alzheimer disease, oncogenesis, genotoxicants, antimutagenesis, gene expression, microRNA

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INTRODUCTION

Down syndrome is a well known syndrome associated with chromosomal abnormalities (95% associated with trisomy of chromosome 21, the rest are associated with mosaicism or translocations), the frequency of which in the population is 1 : 650 to 1 : 1000 newborn babies and 1 : 150 during conception (*Thompson & Thompson...*, 2001; Granese, 2011; Lane et al., 2014; and others). This syndrome is characterized by mental retardation, facial features, and dysfunction of several organs. The risk of giving birth to a baby with Down syndrome increases with the mother's age: from 0.6 per 1000 newborns in the age group of about 20 years up to 11 in the age group older than 40 years. In Down syndrome patients, the risk of leukemia development is high; its frequency 20 times higher than that in general population. Autoimmune and endocrine diseases, as well as pathologies of various organs, are also typical for this syndrome. Finally, symptoms of premature aging and Alzheimer disease are developed in Down syndrome. Down syndrome was particularly intensively studied beginning with works on the methylene tetrahydrofolate reductase gene (MTHFR)—one of the key enzymes of folate-homocysteine metabolism. It regulates the intracellular metabolism of folate through the conversion of homocysteine into methionine, which is necessary for nucleotide synthesis. Disturbances in the functioning of this process—folate metabolism, the genes of which are located on chromosome 21—are one of the mechanisms that lead to realization of the pathology (Down syndrome). Another key factor in the pathogenesis of this syndrome is the influence of free radicals, which enhance the damageability of DNA, including the gene of superoxide dismutase 1 (SOD1), which is also localized on chromosome 21 and performs an antioxidant function. The mechanism of increased oxidative stress in Down syndrome is also associated with mitochondrial dysfunction, which leads to the development of many pathologies. It should be emphasized that the difference in the frequency of children born with Down syndrome observed in certain geographical regions may be associated with dietary habits, genetic features, or ethnicity. Medical progress has affected the lifespan of patients with Down syndrome. While the average lifespan of Down syndrome patients was 9 years in the 1930s, it has increased to 60 years to date (Shenoy, 2014).

It was shown that the long arm of chromosome 21 comprises 1% of the entire genome and includes about 400 genes, which perform 81 molecular functions (DNA transcription, signaling, transduction, etc.). At the same time, it was proven that genes located on other chromosomes, can also affect the functioning of genes on chromosome 21 (Granese, 2011). However, there are hypotheses that explain the phenotypic variability of children with Down syndrome. The first is associated with increased expression of the chromosome 21 genes, although it was shown that many genes of this chromosome either are normally expressed or possess even decreased expression. It is believed that increased expression of certain chromosome 21 genes reaches a level of 150% as compared with the control. At the same time, there can be a 40-fold difference in individual expression. The second hypothesis links an increase in the activity of several genes with the general decrease in the level of cell homeostasis. An attempt to diagnose Down syndrome according to the expression of several microRNAs of chromosome 21 was made (Kotlabova and Doucha, 2013). An increase in the concentration of extracellular microRNA-99a, -155, and -125b-2 in pregnant women as compared with nonpregnant women was shown. However, no differences in these parameters were found between pregnant women having an euploid fetus and a fetus with Down syndrome.

In this report, we do not consider the huge number of studies on the role of individual genes in the development of the pathology in Down syndrome that were carried out at the organism level, since the data from the literature presented here and our studies were conducted mainly in vitro. For this reason, molecular pathways, including, for example, links between neuronal degeneration and cognitive disorders; disorders of the immune system, which includes inflammation processes; the formation of phenotypic features depending on the nature of certain genes; and the formation of solid tumors will not be discussed. Furthermore, it is difficult to present the data on the molecular mechanism of the development of Down syndrome analog in mice associated with chromosome 16, as well as the data on drosophila, which requires a special review. The phenotype–genotype relationship is studied in mice; the attention is focused on the cholinergic and noradrenergic systems associated with the hippocampus, the functioning of which provides behavioral characteristics of animals. In this report the following issues will be highlighted: (1) molecular and genetic features of Down syndrome; the role of microRNAs in the regulation of gene expression; (2) Down syndrome—a model for the study of hereditary predisposition to oncogenesis; (3) Down syndrome cells—a system for the study of the mechanisms of hypersensitivity to hypotoxicants; (4) the commonality of several molecular genetic pathways in Down syndrome and Alzheimer disease; (5) the use of antimutagens—an approach to the correction of pathologies associated with oncogenesis and hypersensitivity to genotoxicants in Down syndrome; (6) the relationship of genetic polymorphism and pathologies of individual organs in Down syndrome.

MOLECULAR GENETIC FEATURES OF DOWN SYNDROME. THE ROLE OF microRNAs IN THE REGULATION OF GENE EXPRESSION

In the last decade, Down syndrome research was focused on antenatal screening based on the detection of trisomy, or mosaicism, or translocation in chorionic cells or amniotic fluids. Trisomy of chromosome 21 in the long arm includes approximately 400 genes controlling 81 molecular functions (the length of chromosome 21 is about 1% of the entire human genome) (Granese, 2011; Cunto and Berto, 2013 and others). Abnormalities of chromosome 21 may affect many biological processes in different tissues, resulting in multiple defects. Apparently, a single gene or a combination of several genes is responsible for a certain phenotype of this syndrome. At the same time it is known that genes on other chromosomes may affect the functions of the genes of chromosome 21. Discussing the features of gene expression in Down syndrome, the authors come to the conclusion that, if the expression level of the gene is 1.5 times higher in Down syndrome cells than in normal cells, this gene can be considered a candidate for a causal link with certain phenotypic manifestations. Thus, increased expression of the *APP* gene, which is localized on chromosome 21, is accompanied by a defect of neurogenesis, which explains the hypotonia and weakening of motor activity in patients with Down syndrome, in addition to cognitive features. *APP* overexpression is believed to underlie the pathogenesis of Alzheimer disease. A number of chromosome 21 genes are involved in cognitive disorders: *DYRK1A, SIM2, RCAN1, DSCAM, KCNJ*, and others (Lana-Elola et al., 2011).

According to the simplest model, as mentioned above, gene expression in Down syndrome in general is 150% higher than in normal cells (Granese, 2011). However, first, the gene expression level in Down syndrome varies in different tissues and cells; second, some genes are characterized by increased expression, while other genes are not expressed; third, a 40-fold difference in the expression level is observed among different individuals with Down syndrome. This is caused by the difference in the copy number variations of transcription factors (especially nonencoding regions of post-translational regulation), DNA methylation, and the interaction between genes. Overexpression of the amyloid precursor protein of the *APP* gene, which led to the degeneration of cholinergic and noradrenergic neurons, was found (Sanchez et al., 2012). This mechanism apparently underlies degenerative changes in neurons in Down syndrome. As was already mentioned, variations in the copy number may

vary between individuals. Variations in the copy number of the *APP* gene occur in cases of familial Alzheimer disease. It is believed that chromosome 21 genes are involved in transcription; at the same time, they probably function in a general context. A contribution to the gene regulation is made by microRNAs, which belong to the group of small RNAs containing 20–22 nucleotides (Granese, 2011; Liao et al., 2012; Cunto and Berto, 2013; Kiselev et al., 2013; etc.). It is assumed that they can largely inhibit the translation of messenger RNAs (mRNAs). Each microRNA is capable of regulating the expression of hundreds of mRNAs involved in the functioning of the genes of nervous system; genes that control the expression of a number of other genes; genes of the signaling system, cell cycle, and apoptosis. It is assumed that at least five microRNA genes are included in chromosome 21.

The genomes of multicellular organisms contain thousands of genes, the expression of which depends on the cell type, tissue, and developmental stage and is a response to the action of extracellular signals. Different genome-expression profiles are achieved due to the presence of complex intracellular regulatory networks and are driven by transcription factors (TFs) and microRNAs. TFs bind to gene promoters, while mature microRNAs specifically interact with the untranslated region of mRNAs in approximately 30% of protein-coding genes of animals, including TF genes, repressing ribosomal synthesis. It was found that the fraction of the genes encoding TFs increases with increasing organism complexity. For example, TF genes constitute about 5% of the genome of flies and nematodes, and almost 10% of that for mice and humans (Reece-Hoyes et al., 2005; Kummerfeld and Teichmcen, 2006; Wilson, 2008). The number of genes that encode microRNAs apparently correlates with the complexity of the organism (Grimson et al., 2008). The action of TFs and microRNAs is coordinated in regulatory networks and controls gene expression at the level of systems, rather than individual genes (Martinez and Walhout, 2009). Thus, interactions between TFs and target genes, as well as that between the microRNAs and mRNAs of these genes, regulate the transcriptional activity of the genome and determine the global program of gene expression in a living cell.

It was found that genes encoding microRNA-99a, -125b-2, -155, -802 and let7c are located in human chromosome 21. It was shown that an increase in the expression of these microRNAs in the brain and the heart of Down syndrome patients, which leads to a change in the expression of their target genes, is observed. The introduction of antimicroRNAs leads to normalization of target gene functioning (Kuhn et al., 2010). An increase in these microRNAs is also detected in other cells in Down syndrome patients (Sethupathy et al., 2007). It was shown in children with Down syndrome suffering from leukemia that the expression of microRNA-125b-2 is increased by almost 30 times (Klusmann et al., 2010). The conducted integrative transcriptome analysis enabled the authors to conclude that an increase in microRNA-125b results in the inhibition of tumor suppressors such as *ST18* (suppression of tumorigenicity 18). Abnormal expression of *CREB1* may also lead to changes in the transcriptional activity of *P53* (Giebler et al., 2000). Due to the fact that the key role in cellular homeostasis maintenance belongs to the *P53* gene, which is localized on chromosome 17; special attention is paid to this gene as a target of microRNAs, the majority of which are included in homeostasis maintenance, cell cycle regulation, and apoptosis. It was shown that microRNA-1246 is a regulator of *P53* and its analogs, *P63* and *P73*, which are involved in the development of the central nervous and immune systems and are suppressors of *DYRK1A* (dual specificity tyrosine phosphorylation-regulated kinase 1A) expression—a Down syndrome-associated kinase that inactivates *NFAT* (Liao and Zhou, 2012). Another representative, microRNA-34a, which is localized on chromosome 1p36.23, also affects *P53*, controlling *P73*, which determines the development of the nervous system and synaptogenesis. It is assumed that microRNA-34a, as well as the P73 inductor, acts as an activator of transcription in central nervous system via the *DYRK1A–NFAT* pathway.

It is assumed that the Down syndrome critical region (DSCR) is responsible for various phenotypical and pathological manifestations in Down syndrome. This region is divided into DCR-1 and DCR-2 (Cunto and Berto, 2013). The genes in these regions play a key role in embryonic development, cell proliferation, differentiation, angiogenesis, and apoptosis. *DYRK1A*, which encodes tyrosine phosphorylation-regulated kinase 1A (which is able to phosphorylate tyrosine and threonine), is the most studied among the DSCR-region genes. This gene is expressed primarily in the cortex, hippocampus, and cerebellum. It is associated with proliferation, neurogenesis, differentiation of neurons, synaptic plasticity, and cell death. It is believed that increased expression of this gene in the brain causes neurodegenerative phenotype in Down syndrome. *DYRK1A* phosphorylates *TAU*. This gene promotes a modification that results in neurofibrillary degeneration, which is the cause of neuronal cell death and dementia of the Alzheimer type. In this regard, a *DYRK1A* inhibitor—a polyphenol compound isolated from green tea leaves—may reduce the expression of the gene (Guedj et al., 2009). Another key gene controlling the CNS phenotype in Down syndrome is the *TTC3* gene, which is expressed at the highest level in several CNS regions (Cunto and Berto, 2013). This gene also participates in maintaining of the cytoskeleton regulator RhoA, which is involved in various programs of cognitive disorders. It was shown that *TTC3* not only affects processes in neurons but also participates in the activation of a specific pathway that turns off the cytoskeleton regulator RhoA. RhoA-kinase and Lim-kinase

are involved in all differentiation programs and various aspects of cognitive disorders.

It should be emphasized that normal functioning of the neural pathways depends on the balance of activating and inhibitory factors, which are disturbed in Down syndrome (Castillo et al., 2011). The possible functioning of allelic sequences localized in the critical region of chromosome 21 constantly varies in Down syndrome, which is associated with the discovery of functions of new microRNAs, methylation features of various genes, and RNA–RNA interactions based on links with microRNAs.

DNA methylation, which has an epigenetic nature, plays a role in gene expression and, therefore, in the processes of mammal development. The relationship between the regulation of gene expression was established by methylation of DNA and microRNA. Methylation is carried out by the family of DNA methyltransferases. It was shown that not only overexpression of the chromosome 21 genes is involved in the implementation of Down syndrome phenotype; a certain contribution is also made by generalized dysregulation of other genes (Shenoy, 2014). Thus, the fact that a number of chromosome 21 genes, as well as an imbalance of genes located on other chromosomes, contribute to the development of the pathology in Down syndrome is important.

DOWN SYNDROME—A MODEL TO STUDY GENETIC PREDISPOSITION TO ONCOGENESIS

Cancer pathologies are diseases characterized by genetic predisposition. There are so-called cancer families (Mohrenweiser and Jones, 1998; Walsh and King, 2007): if one of the parents suffers from cancer, the probability of the disease in children is three times higher than the risk of the disease in the population characterized by the absence of this pathology in the family. The risk increases significantly if both parents died from cancer. The role of heredity in cancer pathology was proven many years ago in monozygotic twins (*Human...*, 1977). It is known that certain hereditary diseases are accompanied by the development of cancer pathologies, the frequency of which sometimes reaches 100% (Turner syndrome, Klinefelter syndrome, xeroderma pigmentosum, ataxia telangiectasia, etc.). Furthermore, hereditary malignant tumors, which include retinoblastoma, familial adenomatous colon polyposis, Li–Fraumen syndrome ,and others, are known (Zaridze, 2004, 2008 and others). Hereditary retinoblastoma is up to 40% of all cases of this disease, while the total incidence is 3.5 per 1 million children. The cause of Li–Fraumen syndrome is an inherited mutation in one allele of the *P53* gene. In this case, there is an increased risk of early tumor development of various localization.

Mutagens (radiation, chemicals, viruses) are also a cause of cancer pathology, especially in persons with hypersensitivity to any influence, i.e. the role of heredity in this case is also obvious. Individuals clearly differ in their ability to repair DNA damage induced by carcinogens in cigarette smoke, excessive alcohol consumption, and endogenous sources of oxidants (Khlifi et al., 2012). The *ERCC2* gene localized on chromosome 19 belongs to highly polymorphic genes. The association of polymorphic *ERCC2* (Lys751Gln) Gln/Gln-genotype with head and neck carcinomas was found. *ERCC2* encodes DNA helicase, which is a component of the NER repair pathway, which normally controls damage induced, in particular, by benzopyrene. Thus, it is believed that patients with this type of cancer are more sensitive to carcinogens due to their less efficient DNA repair. Viruses are able to inhibit DNA repair. For example, it was shown that chicken leukemia virus inhibited repair of UV-induced DNA damage in birds, whereas repair functioned normally in nonleukemic chickens at the level of that in mammals. The same regularity was observed for leukemia virus isolated from humans: it also inhibited DNA repair, which become more intense during the process of normal cell transformation into malignant ones (Dubinin and Zasukhina, 1975).

Oncogenic viruses such as DNA containing viruses (human papillomaviruses HPV16, HPV18 and others, adenoviruses Ad12, Ad18 and others), as well as RNA containing viruses (human leukemia viruses HTLV1; hepatitis C virus, HCV), modify the proliferation pathways of the cells, triggering an uncontrolled pathway of cell division (Kiselev et al., 2013). Thus, tumor suppressors *P53* and *RB* are targets of a number of viral genes. Pathways associated with interleukin 6, telomerase, and nuclear factor NF-κB are also targets of oncogenic viruses. Consequently, inhibition of the tumor suppressors *P53* and *RB* is a necessary step for cell transformation. The authors emphasize that viruses may be either direct carcinogens in cases when the viral genome contains genes that have oncogenic potential or indirect carcinogens (when the genes of the virus are able to interact with genes that control cell proliferation). The latent period between initial infection by an oncovirus and tumor development can be measured in decades. The virus can retain its potential in the cell by integration. Mutations due to endogenous or exogenous influences, as well as rearrangement of chromosomes in the region of viral integration, activation of cell proliferation, or a achange in the immune status, and epigenetic changes (methylation) may activate the virus. For example, the mutation of the *kRAS* gene generates signals of cell division, regardless of the receptor status of the cell. Forty percent of colon tumors are associated with the *kRAS* gene. At the same time, it was shown that tumors with a mutation in this gene are characterized by resistance to treatment with cetuximab or panitumumab. Therefore, testing for mutations in the *kRAS* gene is neces-

sary for the prognosis and adequate treatment of such patients.

Carcinogenic substances can be neutralized or removed from the organism by detoxification enzymes. Carcinogenic effects may be the result of interaction between metabolic processes, leading to the activation or detoxification of carcinogens; they may also be the associated with individual ability of the organism to repair induced DNA damage (Mohrenweiser and Jones, 1998; Zaridze, 2004, 2008; Zasukhina, 2011; etc.). Loss of expression of the suppressor gene or aberrant expression of the oncogene is also accompanied by cancer development. We identified differences in the expression of a number of genes in Down syndrome patients as compared to healthy donors (Zasukhina et al., 2013b). The expression levels of suppressor genes of tumor growth in blood cells of Down syndrome patients (31 patients) was significantly suppressed as compared with those in control cells (40 donors) (*P53*, *ARF*, *NPM1*), while expression of the oncogene (*kRAS*) was increased by 4.7 times. These parameters indicate a high predisposition to oncogenesis in Down syndrome, which is of particular importance for prognosis of the disease development and leukemia prevention by drugs, including anticarcinogens.

A huge contribution to the implementation of oncotransformation is made by long-term stress factors, accompanied by the emergence of free radical processes, which may also lead to cardiovascular diseases and other pathologies. If we consider that up to 100 thousand apurinic and apyrimidinic sites are spontaneously formed in the cell during the day, resulting in 20 to 40 thousand single-strand breaks, it becomes clear that the weakening of cellular protective systems is accompanied by the manifestation of primary damage and mutational events and, consequently, the development of the pathological process (Zasukhina, 2011; etc.).

As was mentioned above, Down syndrome refers to diseases characterized by a high degree of susceptibility to leukemia, the number of which exceeds by 20 times the general populational level of this pathology (*Thompson & Thompson*..., 2001; Lane et al., 2014; etc.), i.e., this syndrome can be attributed to diseases with a high degree of genetic predisposition to cancer pathology. Accordingly, it can serve as an excellent model for, first, the study of genes controlling oncogenesis in a comparative aspect (patients with Down syndrome/healthy donors), and second, the search for drugs that are tropic to target genes of oncogenesis and capable of modifying the expression the genes controlling cellular homeostasis and processes of normal cell transformation into a malignant one. The role of the *P53* gene family in the development of leukemia in Down syndrome via microRNA-1246 and, accordingly, a new pathway in the development of leukemia was recently revealed: *P53*—microRNA-1246—*DYRK1A*—*NFAT* (Liao and Zhou, 2012). MicroRNA-34, which has the *P53* gene controlling cellular homeostasis, cell proliferation, and apoptosis, was previously shown to play a role as a target. A number of microRNAs associated with *P53* were also registered: microRNA-149, which is oncogenic regulator, microRNA-192, -194, -215, whose functions are associated with cell cycle, and others. It turned out that *P53* inhibits *DYRK1A* expression via microRNA-1246, suggesting that this gene plays a major role in tumorigenesis. The product of the gene *DYRK1A*, being a serine-threonine protein kinase, phosphorylates caspase-9 and inhibits the ability of the cells to undergo apoptosis by activating antiapoptotic protein WDR68. The authors believe that the pathway *P53*—microRNA-1246—*DYRK1A* is responsible not only for the antioncogenic function of the *P53* gene family but also for Down syndrome-associated leukemias (Liao et al., 2012). Extremely interesting data were obtained by a group of researchers who found that about 100 of the studied thousands of different genes are more active in Down syndrome, and they all are under the control of *PRC2* (Lane et al., 2014). Loss of *PRC2* causes B cells to divide and proliferate before they mature, and that is the main feature of leukemia. One hundred genes are responsible for the explosion of the activity of cell growth and division. It turned out that the extra copy of the *HMGN1* gene is important for *PRC2* switching off and the ability to increase cell proliferation. Therefore, we can assume that *PRC2* switching off may have an antileukemic effect. In this regard, it may be promising to use an inhibitor of histone demethylase as a specific drug.

It should be emphasized that the localization of the studied genes controlling cellular homeostasis and tumorigenesis is related to different chromosomes: *Nras*—1p13, *Myc*—8q24, *KRas2*—12p12.1, *TP53*—17p13.1 (Zaridze, 2008). At the same time, it is known that the regulation of gene expression is performed by microRNAs, the number of which exceeds 2000 in human cells. Each miRNA is involved in the activation of hundreds of genes encoding proteins. In this regard, we evaluated the expression of microRNAs having suppressor or oncogenic properties of the corresponding genes, along with the expression of genes encoding proteins.

The methylation process, which makes a great contribution to oncogenesis, is involved in gene regulation. For this reason, methylation and demethylation of DNA and microRNA are of great importance in the process of carcinogenesis (Hodyrev et al., 2012; Kiselev et al., 2013; Rykov et al., 2013; etc.). Expressed hypomethylation is often observed in cancer simultaneously with hypermethylation of specific genes, such as suppressor genes (Granese, 2011). It is very important to note that a change in folate metabolism caused by diet may affect DNA methylation; a correlation between folate deficiency and increased risk of many cancers has been noted. The gene encoding the carrier of folate level reduction is localized on chromosome 21.

Increased expression of the *DYRK1A* gene due to trisomy of chromosome 21 varies in intensity in different tissues and depends on the time of cell differentiation and proliferation (Liu et al., 2014). The authors showed that *DYRK1A* expression in Down syndrome is reduced in the bone marrow of adult patients with acute myeloid leukemia (AML), a typical cancer for this syndrome, as compared with the norm. This gene was observed to have increased expression during proliferation of the cells of AML line when the cells were in G0/G1 phase, which is associated with a change in the regulation of the *Myc* oncogene. The experimental data of the authors suggest that *DYRK1A* is a potential suppressor in AML.

MicroRNAs are involved in the development of a number of cancers: a general decrease in the microRNA level is often observed under oncological diseases (Yin et al., 2013). At the same time, a particular role belongs to the methylation of CpG-islands and their promoter regions (Rykov et al., 2013). The authors found a correlation between th methylation frequency of the microRNA-125b and microRNA-137 genes and the metastasis parameters in lung tumors.

Aberrant expression and a change in TF function plays an important role in tumor development (Ying et al., 2011). For example, it was found that microRNA-193a performs a regulatory role in adenocarcinoma: it induces increased expression of *YY1* (multifunctional TF), which controls the processes of development and differentiation. Increased expression of *YY1* was observed in various types of cancer. In another microRNA example, miRNA-130b expression was significantly reduced in malignant cells; patients with higher levels of microRNA-130b lived longer (Dong et al., 2013). Levels of microRNA-143 and -145 were reduced in different tumors, which consequently affected the functioning of *TP53* (Pagliuca et al., 2013). It was demonstrated that activation of the *P53* pathway increased the levels of microRNA-143 and -145 via transcription. Thus, it was found that a significant role in the mechanism of oncogenesis belongs to microRNAs, the expression level of which affects target genes by suppressing or enhancing their activity that ultimately affects growth or inhibition of the tumor.

Frequent leukemia development is typical for Down syndrome. MicroRNAs are a key mechanism for oncogene activation. Suppression of microRNA-193a methylation during genesis of myeloid leukemia was shown to play a role in Down syndrome (Gao et al., 2011). MicroRNA-193a incorporated into the CpG-island and suppressed hypermethylation of the promoter and in acute myeloid leukemia but had no effect on normal bone marrow cells. These data indicate the major role of microRNA-193a, which is repressed by methylation, and the possibility to regulate this process for therapeutic purposes. In light of the high incidence of leukemia development in Down syndrome, the data on the involvement of certain genes and their combinations in the process of carcinogenesis, the regulation of gene activity by microRNAs and the possibility to activate or suppress them by inhibitors, it can be assumed that Down syndrome is an excellent model for studying genetic predisposition to cancer diseases.

CELLS OF DOWN SYNDROME PATIENTS—A SYSTEM TO STUDY MECHANISMS OF HYPERSENSITIVITY TO GENOTOXICANTS

The cells of Down syndrome patients, like the cells of ataxia telangiectasia and progeria, exhibit increased sensitivity to ionizing radiation and radiomimetics as compared with the cells of healthy individuals (Chudina, 1968; Gadhia et al., 1988; Khandogina, 2010; etc.). In our work we investigated genetic polymorphism in a number of allelic variants in the cells of Down syndrome patients (46 persons) as compared to cells from healthy donors (62 persons). The set of studied genes consisted of a number of allelic variants of detoxification genes (*GSTM1*, *GSTP1*, *CYP1A1*) and other genes (*MTHFR, P53*, *XPD*(*312*), *XRCC1*(*399*) and others). Thus, the *GSTM1*(0/0) genotype, which determines the function of the corresponding protein, is more often encountered in the cells of Down syndrome patients than in cells from healthy donors. Statistically significant differences were obtained for the *XPD*(*312*) gene encoding a protein with normal activity, which was detected less frequently in Down syndrome patients than in the group of healthy donors. The presence of mutations in the seventh exon (codons 246–250) of the *P53* gene was noted in the cells of most Down syndrome patients in the absence of such mutations in cells from healthy donors (Kuzmina et al., 2009).

We found changes in the expression of genes that control cell homeostasis in Down syndrome patients (Zasukhina et al., 2013b). The expression of several tumor suppressor genes was decreased (*P53*—5 times, *ARF*—2 times, etc.), whereas the gene expression of the protooncogene (*kRAS*) was increased significantly (4.7 times) as compared with the corresponding values in healthy donor cells. A hallmark of the cells of Down syndrome patients is the lack of formation of adaptive response (AR), which develops when the cells are exposed to a small dose of radiation or a chemical mutagen, followed by exposure to a large dose of radiation or a high dose of a chemical mutagen (after 4–5 h). The development of cell resistance to genotoxicants is expressed in the reduction of the number of chromosomal aberrations, micronuclei, and enhancement of cell survival. At the same time, AR has a nonspecific nature, i.e., preliminary exposure of the cells causes resistance to chemical mutagens and vice versa. We (Vasileva et al., 2009) showed that pretreatment of cells from Down syndrome patients with low doses of

cadmium chloride was not accompanied by the formation of AO under subsequent action of high doses of the mutagen in contrast to control cells, i.e., the system that provides the protection of the cells from high doses of exogenous influence is absent in the cells of Down syndrome patients. It was shown that one of the proteins, which is formed under these conditions in normal cells, was not formed in the cells of Down syndrome patients. The increased sensitivity of cells from Down syndrome patients to genotoxic stress recently was studied in the aspect of involvement of certain genes (Micali et al., 2010). It turned out that the *PREP1* gene, a transcription factor localized on chromosome 21, which regulates the size of various organs, as well as most of developmental pathways, showed increased expression in the cells of Down syndrome patients. The excess of the Prep1 protein increased sensitivity to genotoxic stress, while apoptosis directly correlated with the level of this protein. It should be added that the neurodegenerative and immune defects in Down syndrome correlate with an increased level of apoptosis, which, in turn, is associated with increased expression of proapoptotic tumor suppressor *P53*, a direct transcriptional target of *PREP1.* This is accompanied by increased expression of *PREP1* and reduced level of apoptosis. Consequently, the balance of *PREP1* plays an essential role in apoptotic homeostasis, and its absence or increase in its amount lead to induction of apoptosis, and it was shown that increased expression of this protein leads to genotoxic-induced, but not spontaneous, apoptosis. Genotoxic-induced apoptosis is *P53*-dependent, and increased expression of *PREP1* increases the *P53* level. Consequently, in Down syndrome, in contrast to the norm, there is an increase in the *PREP1* level and, accordingly, an increase in apoptosis. The apoptotic response to genotoxic stress directly correlates with the level of *PREP1*, which is certainly included in the phenotype in Down syndrome. The authors used etoposide and UV irradiation as genotoxicants. Both genotoxicants caused increased (as compared to normal cells) level of apoptosis in the cells of patients with Down syndrome, which correlates with increased levels of caspase-3 in Down syndrome as compared to the control.

Therefore, the cells of Down syndrome patients have an increased sensitivity to genotoxicants, which is implemented due to a change in the structure of polymorphic variants and gene expression, ultimately determining the phenotypic characteristics of the syndrome.

COMMONALITY OF SEVERAL MOLECULAR GENETIC PATHWAYS IN DOWN SYNDROME AND ALZHEIMER DISEASE

It is known that most or even all Down syndrome patients develop a complex of initial symptoms of Alzheimer disease before the age of 40 years (Ryoo et al., 2007, 2008; Sanchez et al., 2012; Cunto and Berto, 2013; etc.). Increased production of amyloid beta, which leads to the formation of amyloid plaques, was shows in cerebral tissue both in Down syndrome and Alzheimer disease. One of the mechanism of overexpression of this protein is associated with increased expression levels of the *APP* gene, which encodes protein precursor and is localized on chromosome 21. An increased number of copies of the *APP* gene is observed during the development of Alzheimer disease symptoms in patients with Down syndrome. *APP* overexpression affects the differentiation of neurons and glias in this syndrome. Moreover, it is believed that the product of the *DYRK1A* gene also is a major candidate of those determining the symptoms of this disease. The authors suggest that *DYRK1A* overexpression through phosphorylation of *APP* affects *APP* processing, which may underlie the development of early symptoms of Alzheimer disease in Down syndrome. Consequently, the regulation of increased amyloid beta production is performed by increasing the concentration of the *DYRK1A* gene product in the brain of Down syndrome patients. One pathological sign of Alzheimer disease is the presence of neurofibrillary tangles consisting of hyperphosphorylated *TAU* (*TAU* in the Thr212 position is phosphorylated by *DYRK1A*), i.e., the physiological role of *DYRK1A* in *TAU* hyperphosphorylation confirms that extracopying of this gene contributes to the manifestation of early signs of Alzheimer syndrome.

The practical significance is that women who gave birth to a baby with Down syndrome at a young age have an increased level of lymphocytes with micronuclei (Migliore et al., 2009). This fact is often accompanied by folate metabolizing gene polymorphism. The *MTHFR* gene is localized on chromosome 21 and catalyzes NADPH-dependent conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which participates in the transformation process of homocysteine to methionine, a donor in methylation processes (Liu et al., 2010). Two major polymorphic loci of the *MTHFR* gene were described: A1298C and C677T. A low activity level of *MTHFRS677T* variant is associated with hypomethylation of DNA, which is accompanied by genomic instability and may affect the activity of tumor suppressor genes and oncogenes (Miyaki, 2010). Polymorphism of the *MTHFR* gene was studied in terms of predisposition to oncological diseases, as well as to Alzheimer disease (Schjeide et al., 2009). These authors believe that, in mothers who gave birth to a baby with Down syndrome at a young age, the risk of development of Alzheimer disease significantly increases, which also confirms the relationship between Down syndrome and Alzheimer disease.

In conclusion it may be noted that Down syndrome and Alzheimer disease share common links in the pathogenesis of the pathologies—the genes involved in these pathological processes—and, consequently, the treatment of these diseases may have common approaches.

ANTIMUTAGENE APPLICATION—AN APPROACH FOR PATHOLOGY CORRECTION IN DOWN SYNDROME

Antimutagens, most of which have anticarcinogenic, protective, and adaptogenic properties, can be divided into natural and synthetic. Natural antimutagens include extracts of various plants, their components, cytokines, including interferons, and vitamin preparations. Plant extracts contain polyphenols, flavonoids, vitamins, and carotenoids. They provide multifactorial activities, having radioprotective properties, as well as the ability to intercept free radicals, reduce apoptosis, modify the cell cycle, and the potential of the mitochondrial complex. One mechanism of antimutagen action, the effect of which is aimed at weakening the action of damaging agents and increasing the organism's resistance to genotoxicants, is the antioxidant activity. This is associated with the fact that the effect of radiation and chemical mutagens causes the development of oxidative stress, when genes and proteins are exposed to free radical attack (Durnev, 2001; Zasukhina, 2005, 2011; and others). It should be emphasized that the effects of extracts of some plants have a diverse nature; for example, extracts of ginseng, magnolia, and others possess not only antioxidant properties but also the ability to produce cytokine, to activate repair and apoptosis, and, at the level of the organism, to stabilize the immune status.

As far back as 1970s, we discovered a new property of interferons—antimutagenic activity—and described the mechanism of its action: the ability to reduce the level of structural changes of chromosomes up to 70–80% (chromosome aberrations, sister chromatid exchanges) induced by fast neutrons, radiation, UV rays, 4-nitro-quinolin-1-oxide, N-nitro-N-nitrosoguanidine, and heavy metals (compounds of Cd, Mo, Co) (Zasukhina, 2011). It was shown in human cells treated with interferon that the activation of an error-free DNA repair pathway occurs. It is important to note that the antimutagenic activity of interferon is realized at low doses of this preparation (30–50 IU/mL), whereas its anticarcinogenic activity in humans was identified only with huge concentrations (10000 IU and higher). We used the antimutagenic property of interferon for the treatment of patients with xeroderma pigmentosum, in which the UV repair pathway of DNA damage is inhibited (Zasukhina, 2005). It was shown that daily injections of interferon (50 IU/mL) in patients with this disease led to the restoration of inhibited DNA repair and improvement of the state of patients. Thus, it was shown that the application of antimutagens may contribute to the activation of repair and, accordingly, be used as a therapeutic drug that increases the resistance of the cells to exogenous influence, as well as to industrial hazards that reduce the function of protective mechanisms of human cells.

Certain targets—genes or ways of genetic material realization—have recently become a focus of studies on the effects of antimutagens. Thus, some ginsenosides (isolated from ginseng roots) inhibited the gene expression of matrix metalloproteinases (MMPs), enhanced apoptosis with increasing enzymatic activity of kinases, and increased the gene transcription of SOD and catalase (Arushanyan, 2009). Meso-zeaxanthin, being a carotenoid, possessed a high antioxidant activity and the ability to increase gene activity of SOD, catalase, glutathione peroxidase, which was reduced in mice exposed to radiation (Firdous and Sindhu, 2013). L-carnitine, another herbal preparation, was also effective as a radioprotector in irradiated rats (Acpolat et al., 2013). An effective radioprotector having the same set of activities and containing flavonoids and polyphenolic compounds is silymarin, which is extracted from *Silybum marianum* (Adhikari et al., 2013).

Since the *P53* gene and microRNAs play an important role in the processes of tumorigenesis, these loci are used as targets when therapeutic and prophylactic drugs are used. Several authors proposed an approach for reactivation of the mutant *P53* gene (Wassman et al., 2013). As is well known, half of all human tumors are associated with mutation in the *P53* gene. For this reason, the authors proposed to use compounds that act in the packet between domains *L1* and *S3* of *P53*, causing reactivation of mutational changes, for potential cancer therapy.

MicroRNAs may also be used as targets for expression normalization and their effect on target genes. We used all trans retinol acid (ATRA) for correction of the process. ATRA was effective towards microRNA let7c in acute myeloid leukemia (Pelosi et al., 2013) and also towards microRNA-340 in neuroblastoma (Das et al., 2010, 2013). The role of methylation and demethylation of genes and microRNAs was shown. Analysis of the ATRA action in neuroblastoma cells revealed that 82 demethylated genes showed a more than twofold increase in the expression level, while 13 hypermethylated genes were characterized by reduced expression levels. Consequently, demethylation and the re-expression of genes enhance transduction, including the *NOS1* gene responsible for differentiation of neurons. Overexpression of microRNA-152, which has *DNMT1* as a target, promoted differentiation processes, i.e. it demonstrated the plasticity of dynamics of epigenetic changes in the processes of tumor cell differentiation. The addition of retinoic acid to the growth medium of glioblastoma tumor-initiating stem cells was accompanied by a morphological change in neurons inducing growth arrest (G1/G0 to S transition), a decrease in the expression of cyclin D, and increased *P27* expression (Ying et al., 2011). In addition, a multidirectional change was observed in the expression of approximately 350 genes, the activity of which was changed 48 h after exposure. These data

identify the mechanism by which retinoic acid can be regarded as a drug for the treatment of glioblastomas.

It should be emphasized that a change in the metabolism of certain vitamins is associated with various human diseases, including cancers. Thus, changes in the level of pyridoxal-5-phosphate (bioactive form of vitamin B_6) are associated with cancer (Galluzzi et al., 2013). This vitamin is involved in the metabolism of homocysteine, histamine, serotonin, dopamine, and other products of the metabolism at the level of the cell and organism. It was shown that increased amounts of circulating B_6 (due to B_6 containing food intake) correlate with a reduced number of neoplasia incidence. Therefore, B_6 deficiency causes immunosuppression associated with cancer, which is accompanied by tumor suppression and, accordingly, disturbance of DNA repair, genomic instability, and tumor development.

Neuronal plasticity (in the mouse model of Down syndrome) was also shown by the action of epigallocatechin-3-gallate (EGCG), a polyphenolic compound isolated from green tea leaves (Xie et al., 2008). This drug modulated a number of biochemical pathways, including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase, p35 kinase, and several other kinases. One of the targets of EGCG action was the *DYRK1A* gene localized on chromosome 21, the expression of which is increased in Down syndrome. However, the effect of EGCG was clearly depended on the concentration of the compound, which is an inhibitor of the activity of this gene (Guedj et al., 2009).

Returning to the studies on retinol, it can be stated that microRNAs that regulate the expression of genes controlling the process of carcinogenesis (both in leukemia and solid tumors) also become a target of retinol action. We would like to emphasize that we successfully used retinol previously as an antimutagen in human cells defective in repair (Vasileva et al., 2008). It is known that most antimutagens also possess anticarcinogenic properties. For this reason, retinol, as a drug that affects the expression of certain genes, is promising also as an anticarcinogen. We showed in human cells defective in the ability to repair DNA damage induced by radiation and cadmium salts (Ehlers-Danlo syndrome, homocystinuria, progeria) pretreated with retinol that cell viability was increased by up to 50%, while it was increased in cells from healthy donors by up to 70% or higher. In terms of Cd-induced breaks, DNA protection of retinol-treated cells reached 80% in these syndromes. In the cells of Down syndrome patients pretreated with retinol, the coefficient of protection from cadmium salts in terms of survival reached 80%, exceeding that of cells from healthy donors (about 60%). If Cd-induced DNA breaks are used as a criterion of retinol activity, the coefficient of protection for cells treated with retinol in Down syndrome reached 70%, and it was 50% for cells from healthy donors (Zasukhina et al., 2009). It can be added that the level of protection was not associated with polymorphic features of a number of studied genes (*GSTM1, GSTT1, GSTP1, MTHFR, XPD*(*312*), *XPD*(*751*), *XRCC1* and others). At the same time, it should be stated that in patients with null genotypes (*GSTM1, GSTT1*), which constantly eat vegetables (cruciferous), the risk of cancer development was decreased by 57% (Seou et al., 2002). It was demonstrated that these plant products have a high content isothiocyanate, which is known as an anticarcinogen inducing enzymes of phase II detoxification.

We investigated the lymphocytes of 31 Down syndrome patients (the control contained 40 healthy donors) in terms of gene expression (real time PCR); they control cellular homeostasis, including tumor suppressor genes: *P53* and others, oncogenes: *kRAS* and others (Zasukhina et al., 2013b). Multidirectionality of these parameters in Down syndrome and in the control group was revealed. For example, the expression level of the oncogene *kRAS* in Down syndrome was 4.7 times higher than in the control, and a decrease by 5.1 times was observed for the *P53* gene. Expression of the *SOD3* gene was increased by 3.6 times in Down syndrome cells, which corresponded to the numerous literature data on the increased level of oxidative stress and, accordingly, the SOD enzyme in this syndrome (Cunto and Berto, 2013). Composite phytoadaptogen was tested as a corrector in mice of the CBA line, which are predisposed to the development of hepatocarcinomas, according to expression parameter of leukocyte integrins and cytokines IL-6 and IL-10 (Bocharova et al., 2014). It was shown that this preparation plays a certain role in the antitumor control.

A pronounced protective effect under cadmium chloride exposure was described in cells of Down syndrome patients treated with crown compound ($C_{18}H_{26}N_2O_7$), synthesized in the Photochemistry Center, Russian Academy of Sciences (Vasilyeva et al., 2009). The coefficient of cell protection reached 40% in terms of both cadmium-induced DNA breaks and cell survival. It should be emphasized that the antimutagenic properties of the crown compound under gamma irradiation, as well as cadmium chloride exposure, were described previously in cells from healthy donors and cells of patients characterized by repair defects of induced DNA damages (Zasukhina et al., 2002). Crown compounds are described in the literature as potential anticancer drugs, the toxic properties of which do not exceed those of aspirin (Kralj et al., 2008). Aminothiols were also used as a radioprotectors (Copp et al., 2013). The authors synthesized 17 new nucleophilic polyamines, some of which turned out to be effective radioprotectors. Purine compounds (caffeine, inosine-5-monophosphate, etc.), showing radioprotective properties increased mouse survival to 50%

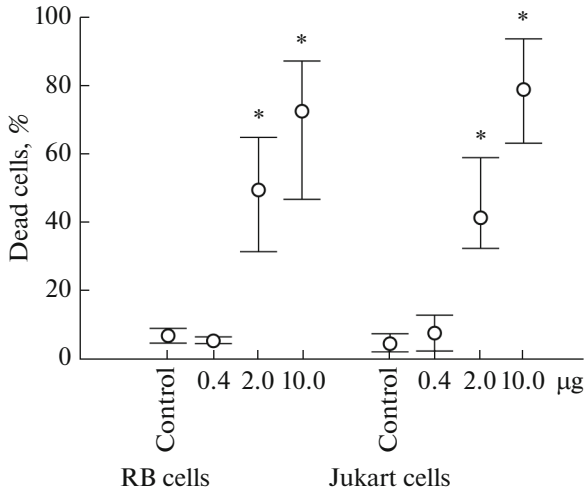


Fig. 1. Survival of RD and Jukart cells treated with thionine Ns-W2, isolated from seeds of black cumin depending on the concentration of the drug (0.4–10 μg).

after radiation exposure (Popova et al., 2014). The authors consider these compounds to be preventive and therapeutic agents for reducing the risk of radiation induced pathologies. Some authors believe that the radioprotective effect can be enhanced by a combination of several drugs that have a synergistic effect.

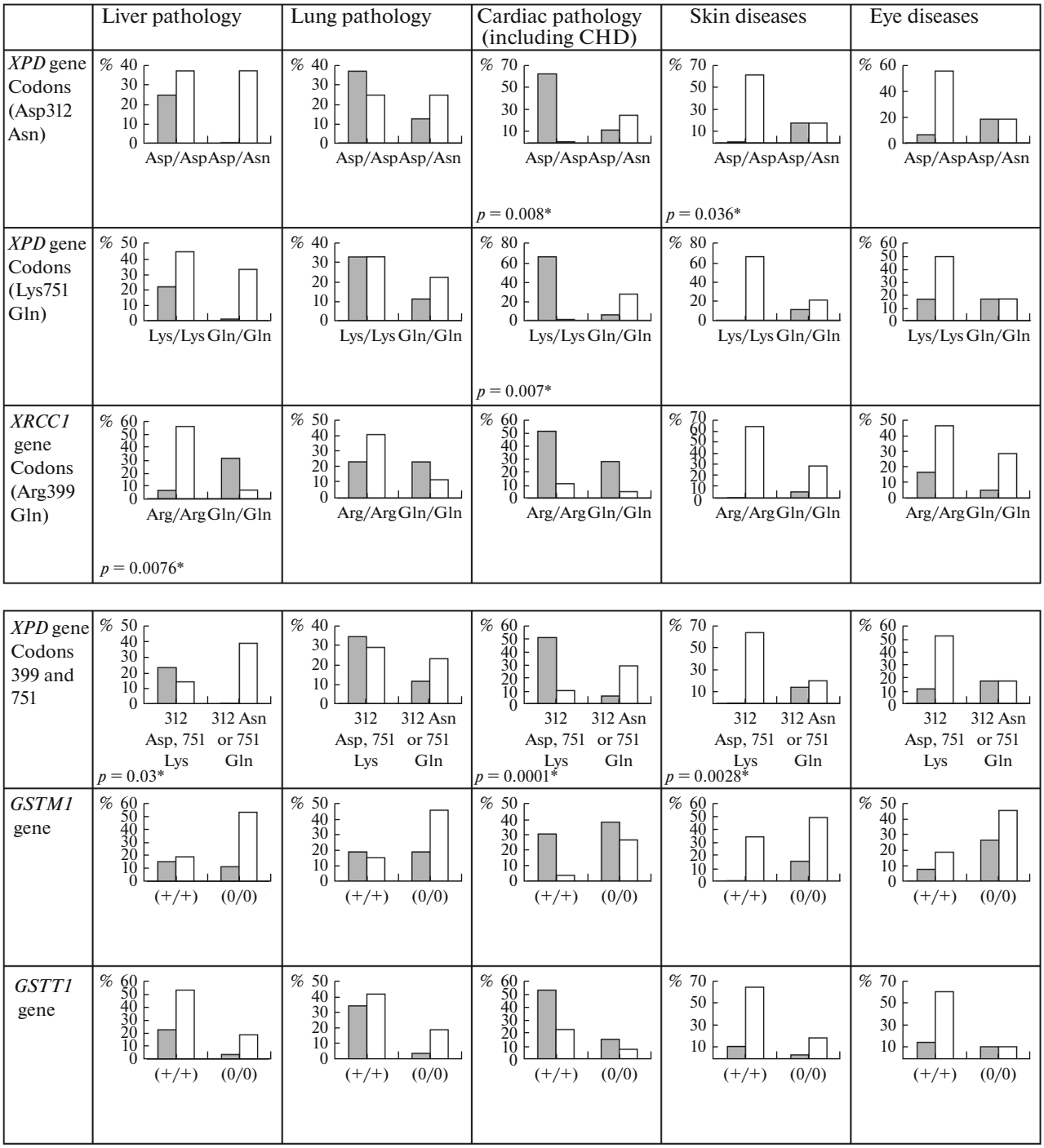
A new approach to the radioprotection involves glyburide (hypoglycemic agent) as a radioprotector, which effectively reduced radiation induced cell death in several lines of normal and malignant cells (Jiang et al., 2009). The authors identified 116 candidate genes that may play a role in glioblastoma cell protection. For the screening of corresponding drugs that could be radioprotectors, the authors used a library of 16500 short interfering RNA (SIGNA). Genes with products including kinases, different receptors, phosphatases, proteases, and ion tubules were targets.

To study possible antimutagenic activities, we tested peptides derived from wheat seedlings (*Tritium kiharae*), black cumin (*Nigella sativa*) and the crown compound (Odintsova et al., 2011; Zasukhina et al., 2012a). It was shown that the coefficient of human cell protection treated with cadmium chloride and pretreated with wheat peptide reached 88%, while the coefficient of protection in the experiments with extract of wheat seedlings did not exceed 70%. Wheat peptide possessed higher antioxidant activity than the original seedling extract, which was one of the main mechanisms of the effectiveness of its actions (Zasukhina et al., 2013a). We also investigated the activity of the peptide isolated from black cumin; its extracts were found to have anticarcinogenic properties in vivo (Linjawi et al., 2013) and in vitro (Elkady, 2012). Thus, it was shown under the action of DMBA (carcinogen inducing rat breast cancer) that thymoquinone, or black cumin oil, reduced the level of activity of certain tumor markers and induced the expression of genes *BRCA1*, *BRCA2* and *P53*, which indicated an anticarcinogenic activity of the drug. We conducted a comparative study on the influence of thionine from black cumin, beta-purothionine from wheat, and the crown compound in RD cells (rhabdomyosarcoma) and human blood cells (Mikhailov et al., 2015). All three antimutagens in RD cells—a decrease in the expression of several genes (*MMP* family, etc.) were shown to be effective; this was not observed in blood cells. In RD cells and Jukart (human lymphoblastoid T cells) treated with thionine from black cumin, up to 80% of dead cells were marked (Fig. 1). Therefore, the cytotoxic effect and suppression of the expression of genes controlling oncogenesis indicate a pronounced anticarcinogenic properties of thionine from black cumin. One can assume that data on retinol, a polyphenol compound from green tea, as well as peptides extracted from plants, which affect oncogenes or their complexes, open up new methods for the prevention and treatment of human pathologies.

LINK BETWEEN GENETIC POLYMORPHISM AND PATHOLOGY OF INDIVIDUAL ORGANS IN DOWN SYNDROME

Children with Down syndrome are characterized by a delay of mental and physical development. Many children have problems with the position of the head, standing, pronouncing their first words and phrases, and other features (Schjeide et al., 2009; Cunto and Berto, 2013; etc.). At the same time, the majority of patients have gastrointestinal disorders, cataracts, and astigmatism. Fourty-four percent of children with Down syndrome have problems with the cardiovascular system (Shenoy, 2014). In this case the association of heart diseases may be connected not only with chromosome 21 but also with genes not in chromosome 21 that, for example, control collagen α-chains (located on chromosomes 6 and 3). The risk of thyroid dysfunction and muscle hypotonia is increased in Down syndrome.

For this reason, we attempted to identify the possible link between the features of genetic polymorphism and pathologies of several organs (heart, liver, eyes and others) in Down syndrome (Fig. 2). A correlation between certain polymorphic genes and pathologies of heart, liver was revealed (Zasukhina et al., 2012b). Thus, the presence of the association between combinations of allelic variants of *XPD Asp312Asp* and *Lys751Lys* genotypes and heart pathology was found in patients with Down syndrome. In the studied group (31 patients) a correlation between *XRCC Gln399Gln* genotypes, combined with *XPD Asp312Asp* and liver pathology, was also revealed. There were no significant differences between these genes (detoxification and others) and skin and eye pathologies. The data on



p—Significance of the data on genotypes of patients with a certain type of pathology; (■) pathology is present, (□) pathology is absent.

Fig. 2. Study of the relationship of several genotypes with the pathology of individual organs in Down syndrome patients.

the detection of the link between polymorphic variants and a certain pathology make it possible already at birth to pay attention to the examination of certain systems in which the risk of pathologies is sufficiently high. This will allow preventive correction of the possibility of the disease development. This approach, which is widely discussed in the literature, is used in cognitive anomalies in which the expression of genes involved in the pathology is increased; certain compounds, the effect of which comes down to inhibition

of the corresponding pathological processes and, accordingly, improvement of behavioral reactions, were tested in the mouse model (Sanchez et al., 2012).

CONCLUSIONS

A large amount of information about the role of individual genes or their complexes in the development of tumors, metastasis, disease prognosis, and approaches to prevention and treatment, as well as the issue of human sensitivity to mutagens and use of antimutagen-anticarcinogens, has been accumulated. From our point of view, the identification of a hereditary predisposition to oncological diseases and, accordingly, the development of drugs that impede this process is of particular importance in the aspect of prevention of human pathologies. The process of transforming normal cells into malignant ones is primarily associated with stress influences (oxidative stress, genotoxicants, and others). In this respect, a special role is played by the intensity of induced DNA damage repair, which may be inhibited in a number of hereditary diseases; under *de novo* mutation in genes that control cell homeostasis; or as a result of chronic exposure to genotoxicants or viruses, some of which inhibit DNA repair.

In research on hereditary predisposition to a pathology, particularly to oncogenesis (as one of the causes of cancer—hypersensitivity to genotoxicants), population studies with analysis of family features, as well as environmental influence, are needed. However, the study of syndromes characterized by a high predisposition to the pathology, particularly, to oncotransformation, does not require a huge number of people and can be one of the approaches to the identification of corresponding genes and their use as targets for preventive interventions that impede the development of cancer pathology via drugs with anticarcinogenic properties. From this point of view, Down syndrome is an excellent model, since its high predisposition to the development of leukemia enables the study of both the molecular genetic characteristics of this pathology and the use of antioxidants-anticarcinogens-antimutagens as a new approach for the prevention of this type of malignant transformation. Antimutagens-anticarcinogens can be used to enhance human resistance to genotoxicants: to correct the hypersensitivity of some individuals, including under certain hereditary diseases or chronic influence of adverse environmental factors (industrial hazards, increased background of radioactivity in the regions due to accidents, etc.) on humans.

In this regard, we attempted to summarize the literature data and our own research in order to attract attention to Down syndrome as a model to study associated phenomena: hereditary predisposition to oncogenesis, hypersensitivity to genotoxicants; and the search for and use of antimutagens-anticarcinogens for the correction of genetic dysfunctions. The relationship of Alzheimer disease and Down syndrome is of particular importance, both to discover common mechanisms of cognitive and somatic dysfunction and possible prospects for the prevention and treatment of these pathologies.

REFERENCES

Acpolat, M., Gulle, K., Topcu-Tarladacalisit, J., et al., Protection by L-carnitine against radiation-induced ileal mucosal injury in the rat, *Int. J. Rad. Biol.*, 2013, vol. 89, no. 9, pp. 732–740.

Adhikari, M., Dhaker, A., Adhikari, J., et al., In vitro studies on radioprotective efficacy of silymarin against γ-radiation, *Int. J. Rad. Biol.*, 2013, vol. 89, no. 3, pp. 200–211.

Arushanyan, E.B., Systemic and cellular mechanisms of antitumor activity of herbal adaptogens, *Vopr. Onkol.*, 2009, vol. 55, no. 1, pp. 15–23.

Bocharova, O.A., Bocharov, E.V., Karpova, R.V., Il'enko, V.A., Kazeev, I.V., and Baryshnikov, A.Yu., Integrins LFA-1 and Mac-1 and cytokines IL-6 and IL-10 in high-cancer mice under the influence of phytoadaptogen, *Bull. Exp. Biol. Med.*, 2014, vol. 157, no. 2, pp. 258–260.

Castillo, P., Chiu, C., and Caroll, R., Long-term plasticity at inhibitory synapses, *Curr. Opin. Neurobiol.*, 2011, vol. 21, pp. 328–338.

Chudina, A.P., Study of the radiosensitivity of human chromosomes in norm and Down syndrome, *Genetika*, 1968, vol. 4, no. 6, pp. 99–111.

Copp, R., Peebles, D., Souf, C., et al., Radioprotective efficacy and toxicity of a new family of aminothiol analogs, *Int. J. Rad. Biol.*, 2013, vol. 89, no. 7, pp. 485–492.

Cunto, F. and Berto, G., *Down Syndrome*, New York: InTech, 2013.

Das, S., Bryan, K., Buckley, P., et al., Modulation of neuroblastoma disease pathogenesis by an extensive network of epigenetically regulated microRNAs, *Oncogene*, 2013, vol. 32, pp. 2927–2936.

Das, S., Foley, N., Bryan, K., et al., MicroRNA mediates DNA demethylation events triggered by retinoic acid during neuroblastoma cell differentiation, *Cancer Res.*, 2010, vol. 70, no. 20, pp. 7874–7881.

Dong, P., Karaayvaz, M., Jia, N., et al., Mutant p53 gainof-function induces epithelial-mesenchymal transition through modulation of the mir130b-2EB1 axic, *Oncogene*, 2013, vol. 32, pp. 3286–3295.

Drachev, I.S., Legeza, V.I., and Turlakov, Yu.S., Prospective use of selenium compounds as radiation protectors, *Radiobiol. Radioekol.*, 2013, no. 5, pp. 475–480.

Dubinin, N.P. and Zasukhina, G.D., *Reparativnye mekhanizmy kletok i virusy* (Reparative Mechanisms of the Cells and Viruses), Moscow: Nauka, 1975.

Durnev, A.D., Modification of mutation in the human cells, *Vestn. Ross. Akad. Med. Nauk*, 2001, no. 10, pp. 70–76.

Elkady, A., Crude extract of *Nigella sativa* inhibits proliferation and induced apoptosis in human cervical carcinoma Hela cells, *Afr. J. Biotechnol.*, 2012, vol. 11, pp. 12710–12720.

Firdous, A., Sindhu, E., Ramnath, V., et al., Amelioration of radiation-induced demages in mice by carotenoid meso-zeaxanthin, *Int. J. Rad. Biol.*, 2013, vol. 89, no. 3, pp. 171–181.

Galluzzi, L., Vasselli, E., Michels, J., et al., Effect of vitamin B oncogenesis, tumor progression and therapeutic responses, *Oncogene*, 2013, vol. 32, pp. 4995–5004.

Gao, X., Lin, J., Li, Y., et al., MicroRNA-193a represses c-kit expression and functions as a methylation-sileneed tumor suppressor in acute myeloid leukemia, *Oncogene*, 2011, vol. 30, pp. 3416–3428.

Gadhia, P., Gadhia, M., and Zankl, H., Effect of bleomycin on Down's syndrome lymphocytes in culture, *Mutat. Res.*, 1988, vol. 207, pp. 153–158.

Giebler, H., Lemasson, I., and Nyborg, J., P53 Recruitment of CREB binding protein mediated through phosphorylated CREB: a novel pathway of tumor suppressor regulation, *Mol. Cell Biol.*, 2000, vol. 20, no. 13, pp. 4849–4858.

Granese, B., Molecular bases of Down syndrome: differential gene expression and pathway dysregulation associated with trisomy 21, *PhD Thesis*, Napoli: Univ. of Naples, 2011, pp. 1–113.

Grimson, A., Srivastava, M., and Fahey, B., Early origins and evolution of microRNAs and Piwi-interacting RNAs in animals, *Nature*, 2008, vol. 455, pp. 1193–1197.

Guedj, F., Sebrie, C., Rivals, I., et al., Green tea polyphenols rescue of brain defects induced by overexpression of DYRK1A, *PLoS One*, 2009, vol. 4, no. 2, pp. 4606–4610.

Hattori, M., Fujiama, A., Taylor, T., et al., The DNA sequence of human chromosome 21, *Nature*, 2000, vol. 405, pp. 311–319.

Human Biology. An Introduction to Human Evolution, Variation, Growth, and Adaptability, Harrison, W.A., Weiner, J.S., Tanner, J.M., and Barnicot, N.A., Eds., Oxford: Oxford Univ. Press, 1977, 2nd ed.

Jiang, J., McDonald, P., Dixon, T., et al., Synthetic protection short interfering RNA screen reveals glyburide a novel radioprotector, *Rad. Res.*, 2009, vol. 172, pp. 414–422.

Khandogina, E.N., Study of genetic control of radiosensitivity, *Russ. J. Genet.*, 2010, vol. 46, no. 3, pp. 257–264.

Khlifi, R., Rebai, A., and Hamza-Chaffai, A., Polymorphism in human DNA repair genes and head squamous cell carcinoma, *J. Genet.*, 2012, vol. 91, no. 3, pp. 375–383.

Khodyrev, D.S., Pronina, I.V., Rykov, S.V., Beresneva, E.V., Freedman, M.V., Loginov, V.I., Braga, E.A., and Kazubskaya, T.P., Involvement of methylation of group of miRNA genes in regulation of expression of RAR-beta2 and NKIRAS1 target genes in lung cancer, *Mol. Biol.*, 2012, vol. 46, no. 5, pp. 693–704.

Kiselev, F.L., Imyanitov, E.N., Kiseleva, N.P., et al., *Molekulyarnaya onkologiya* (Molecular Oncology), Moscow: GEOS, 2013.

Klusmann, J., Li, Z., Bohmer, K., et al., miR-125b-2 is a potential oncomiR on human chromosome 21 in megakaryoblastic leukemia, *Genes Dev.*, 2010, vol. 24, no. 5, pp. 478–490.

Kralj, M., Tusek-Bozic, L., and Erkanes, L., Biomedical potentials of crown ethers: prospective antitumor agents, *Chem. Med. Chem.*, 2008, vol. 3, pp. 1478–1492.

Kotlabova, K., Doucha, J., Chudova, D., et al., Extracellular chromosome 21-derived microRNA's in euploid and aneuploid pregnancies, *Ind. J. Med. Res.*, 2013, vol. 138, pp. 935–943.

Kummerfeld, S. and Teichmcen, S., DBD: a transcription factor prediction database, *Nucleic Acids Res.*, 2006, vol. 34, pp. 74–81.

Kuhn, D.E., Nuovo, G.J., Terry, A.V., et al., Chromosome 21-derived microRNAs provide an etiological basis for aberrant protein expression in human Down syndrome brains, *J. Biol. Chem.*, 2010, vol. 285, no. 2, pp. 1529–1543.

Kuz'mina, N.S., Ushenkova, L.I., Zasukhina, G.D., et al., Gene polymorphism in patients with Down syndrome, *Zh. Nevropatol. Psikhiatr. im. S.S. Korsakova*, 2009, vol. 109, no. 4, pp. 50–54.

Lana-Elola, E., Watson-Scales, S., Fisher, E., et al., Down syndrome: searching for the genetic culprits, *Dis. Model. Mech.*, 2011, vol. 4, pp. 586–595.

Lane, A., Chapny, B., Lin, C., et al., Triplication of a 21q22 region contributes to B cell transformation through HMGN1 overexpression and loss of histone H3Lys27 trimethylation, *Nat. Genet.*, 2014, vol. 10, pp. 2949–2957.

Le, M., Shyh-Chang, N., Xie, H., et al., MicroRNA-125b is a novel negative regulator of p53, *Genes Dev.*, 2009, vol. 23, no. 7, pp. 862–876.

Liao, J., Zhou, X., Zhang, Yu., and Lu, H., A new link of the p53 family with cancer and Down syndrome, *Cell Cycle*, 2012, vol. 11, pp. 2624–2630.

Linjawi, S., Khali, W., Hassanane, M., et al., Evaluation of the protective effect of Nigella sativa extract and its primary active component thymoquinone against DMBA-induced breast cancer in female rats, *Arch. Med. Sci.*, 2013, vol. 33, pp. 329–339.

Liu, A., Menson, S., Colson, N., et al., Analysis of the MTHFR C 677T variant with migraine phenotipes, *BMC Res. Notes*, 2010, vol. 213, no. 3, pp. 1–6.

Liu, Q., Liu, N., Zang, S., et al., Tumor suppressor DYRK1A effects on proliferation and chemoresistance of AML cells by down-regulation *c-Myc*, *PLoS One*, 2014, vol. 9, no. 6, pp. 1–8.

Martinez, N.J. and Walhout, A.J.M., The interplay between transcription factors and microRNAs in genome-scale regulatory networks, *BioEssays*, 2009, vol. 31, no. 4, pp. 435–445.

Migliore, L., Migheli, F., and Coppede, F., Susceptibility to aneuploidy in young mothers of Down syndrome children, *Sci. World J.*, 2009, vol. 9, pp. 1052–1060.

Micali, N., Longobardi, E., Lotti, G., et al., Down syndrome fibroblasts and mouse Prep1-overexpressing cells display increased sensitivity to genotoxic stress, *Nucleic Acid Res.*, 2010, vol. 38, no. 1, pp. 3595–3604.

Mikhailov, V.F., Shishkina, A.A., Vasilyeva, I.M., Shulenina, L.V., Raeva, N.F., Rogozhin, E.A., Startsev, M.I., Zasukhina, G.D., Gromov, S.P., and Alfimov, M.V., Comparative analysis of natural and synthetic antimutagens as regulators of gene expression in human cells under exposure to ionizing radiation, *Russ. J. Genet.*, 2015, vol. 51, no. 2, pp. 130–137.

Miyaki, K., Genetic polymorphisms in homocysteine metabolism and response to folate intake: a comprehensive strategy to elucidate useful genetic information, *J. Epidemiol.*, 2010, vol. 20, no. 4, pp. 266–270.

Mohrenweiser, H. and Jones, J., Variation in DNA repair is a factor in cancer susceptibility: a paradigm for the promises and perils of individual and population risk estimation? *Mutat. Res.*, 1998, vol. 400, pp. 15–24.

Odintsova, T.I., Vassilieva, I.M., Korostyleva, T.V., Utkina, L.L., Slavokhotova, A.A., Shiyan, A.N., Pukhalskii, V.A., Zasukhina, G.D., and Rogozhin, E.A., Antimutagenic activity of wheat β-purothionin Tk-AMP-BP, *Russ. J. Genet.*, 2011, vol. 47, no. 9, pp. 1128–1131.

Pagliuca, A., Valvo, C., Martino, S., et al., Analysis of the combined action of miR143 and miR145 on oncogenic pathways in colorutal cells reveals a coordinate program of gene repression, *Oncogene*, 2013, vol. 32, pp. 4806–4813.

Pelosi, A., Careccia, S., Lulli, V., et al., MiRNA lrt 7a promotes granulocytic differentiation in acute myeloid leukemia, *Oncogene*, 2013, vol. 32, pp. 3648–3654.

Popova, N.R., Gudkov, S.V., and Bruskov, V.I., Natural purine compound as a radiation-protective agent, *Radiobiol. Radioekol.*, 2014, vol. 54, no. 1, pp. 38–49.

Reece-Hoyes, J., Deplancke, B., Shingles, J., et al., A compendium of *C. elegans* regulatory transcription factors: a resource for mapping transcription regulatory networks, *Genome Biol.*, 2005, vol. 6, p. 110.

Rykov, S.V., Khodyrev, D.S., Pronina, I.V., Kazubskaya, T.P., Loginov, V.I., and Braga, E.A., Novel miRNA genes methylated in lung tumors, *Russ. J. Genet.*, 2013, vol. 49, no. 7, pp. 782–786.

Ryoo, S., Cho, H., Lee, Y., et al., Dual-specificity tyrosine (Y)-phosphorylation regulated kinase 1A-mediated phosphorylation of amyloid precursor protein: evidence for a functional link between Down syndrome and Alzheimer disease, *J. Neurochem.*, 2008, vol. 104, pp. 1333–1344.

Ryoo, S., Jeong, H., Radnaabazar, C., et al., DYRK1A-mediated hyperphosphorylation of Tau: a functional link between Down syndrome and Alzheimer's disease, *J. Biol. Chem.*, 2007, vol. 282, no. 48, pp. 34850–34857.

Sanchez, M., Heyn, S., Das, D., et al., Neurobiological elements of cognitive dysfunction in Down syndrome: exploring the role of APP, *Biol. Phys.*, 2012, vol. 71, pp. 403–409.

Schjeide, B., McQueen, M., Mullin, K., et al., Assessment of Alzheimer's disease case-control association using family-based method, *Neurogenetics*, 2009, vol. 10, no. 1, pp. 19–25.

Seow, A., Guan, J., Sun, C., et al., Dietary isothiocyanates, GST polymorphisms and colorectal cancer risk in the Singapore Chinese Health Study, *Carcinogenesis*, 2002, vol. 23, no. 12, pp. 2055–2059.

Sethupathy, P., Borel, C., Gagnebin, M., et al., Human microRNA-155 on chromosome 21 differentially interacts with its polymorphic target in the *AGTR1* 3' untranslated region: a mechanism for functional single-nucleotide polymorphisms related to phenotypes, *Am. J. Hum. Genet.*, 2007, vol. 81, no. 2, pp. 405–413.

Shenoy, V., Genetics of Down syndrome: recent advances, *Muller J. Med. Sci. Res.*, 2014, vol. 5, no. 1, pp. 1–4.

Thompson & Thompson Genetics in Medicine, Nussbaum, R.L., McInnes, R.R., and Willard, H.F., Eds., Philadelphia, PA: W.B. Saunders, 2001, 6th ed.

Vasilyeva, I.M., Semyachkina, A.N., Semenova, S.S., and Zasukhina, G.D., Protective effect of antimutagens in reparative-defective human cells, *Radiobiol. Radioekol.*, 2008, vol. 48, no. 2, pp. 195–199.

Vasilyeva, I.M., Shagirova, Zh.M., Sinelshikova, T.A., Mavletova, D.A., Kuzmina, N.S., and Zasukhina, G.D., Protection of radiosensitive human cells against the action of heavy metals by antimutagens and adapting factors: association with genetic and protein polymorphisms, *Russ. J. Genet.*, 2009, vol. 45, no. 6, pp. 659–662.

Walsh, T. and King, M., Ten genes for inherited breast cancer, *Cancer Cell*, 2007, vol. 11, pp. 103–111.

Wassman, C., Barino, R., Demir, O., et al., Computational identification of a transiently open L1/S3 pocket for reactivation of mutant P53, *Nat. Comm.*, 2013, vol. 4, pp. 1–7.

Wilson, D.V. Charoensawan, V., Kummerfeld, S., et al., DBD—taxonomically broad transcription factor predictions: new content and functionality, *Nucleic Acids Res.*, 2008, vol. 36, pp. 88–93.

Xie, W., Ramakrishna, N., Wieraszko, N., et al., Promotion of neuronal plasticity by Epigallo-catechin-3-gallate, *Neurochem. Res.*, 2008, vol. 33, pp. 776–783.

Yin, D., Ogawa, S., Kawamata, N., et al., MiR-34a functions as a tumor suppressor modulating EGFR in glioblastoma multiform, *Oncogene*, 2013, vol. 32, pp. 1155–1163.

Ying, M., Wang, S., Sang, Y., et al., Regulation of glioblastoma stem cells by retinol acid: role for Notch pathway inhibition, *Oncogene*, 2011, vol. 30, pp. 3454–3467.

Zaridze, D.G., *Kantserogenez* (Carcinogenesis), Moscow: Meditsina, 2004.

Zaridze, D.G., Molecular epidemiology of cancer, *Biochemistry* (Moscow), 2008, vol. 73, no. 5, pp. 532–542.

Zasukhina, G.D., Mechanisms of human cell protection associated with genetic polymorphism, *Russ. J. Genet.*, 2005, vol. 41, no. 4, pp. 412–424.

Zasukhina, G.D., Mechanisms of human cell resistance to mutagens, *Biol. Bull. Rev.*, 2011, vol. 1, no. 6, pp. 496–508.

Zasukhina, G.D., Kurbatova, L.A., Shagirova, Zh.M., et al., The role of genetic polymorphisms in the pathology of the internal organs in children with Down syndrome, *Ross. Vestn. Perinatol. Pediatr.*, 2012b, vol. 57, no. 3, pp. 71–73.

Zasukhina, G.D., Odintsova, T.I., Shulenina, L.V., Ushenkova, L.N., Mikhailov, V.F., Shagirova, Z.M., Vedernikov, A.N., Gromov, S.P., and Alfimov, M.V., Antimutagens (β-purothionin and crown compound) as modulators of expression of genes involved in carcinogenesis in human cells, *Dokl. Biochem. Biophys.*, 2012a, vol. 446, no. 1, pp. 254–256.

Zasukhina, G.D., Shagirova, Zh.M., Reutova, N.V., et al., Changes of gene expression controlling the cellular homeostasis in patients with Down syndrome, *Tekhol. Zhivykh Sist.*, 2013b, vol. 10, no. 7, pp. 38–44.

Zasukhina, G.D., Vasil'eva, I.M., Durnev, A.D., Gromov, S.P., Fedorova, O.A., and Alfimov, M.V., Antimutagenic activity of crown-containing compounds, *Dokl. Biol. Sci.*, 2002, vol. 384, nos. 1–6, pp. 257–259.

Zasukhina, G.D., Vasilyeva, I.M., Kadnikov, I.A., Voronin, M.V., Odintsova, T.I., Korostileva, T.V., and Pukhalskii, V.A., Antimutagenic activity of wheat polypeptides in human cells exposed to cadmium chloride, *Bull. Exp. Biol. Med.*, 2013a, vol. 155, no. 3, pp. 370–372.

Zasukhina, G.D., Vasilyeva, I.M., Shagirova, G.M., Sinelshchikova, T.A., and Mavletova, D.A., Comparison of the effects of antimutagens and adapting factors in radiation-resistant and sensitive cells related to protein and gene polymorphism, *Tekhol. Zhivykh Sist.*, 2009, vol. 6, no. 1, pp. 3–13.

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