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ROLE OF EPIGENETIC FACTORS IN ACUTE LEUKEMIA

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Abstract: The article examines historical aspects of epigenetics as an independent branch of biology, as well as issues of post-translational modifications of histones as epigenetic events. The work provides an overview of the main provisions of epigenetics in current articles and abstracts: DNA methylation, acetylation, phosphorylation and sumoylation of histones in the processes of oncological diseases. To date, the influence of so-called interfering RNA on epigenetic processes has attracted great interest. RNA interference (RNAi) can be used to identify epigenetic regulators for potential pharmacological targeting of tumor cells. The work examines the role of small molecules I-BET and JQ1 in the antitumor response. The importance of BET proteins in oncohematological diseases is highlighted separately. Currently, DNA methyltransferase inhibitors (hypomethylating agents) and inhibitors are used in the treatment of some blood system tumors. Histone deacetylases, which represent a new direction - epigenetic therapy.

Keywords: epigenetics, RNAinterference, methylation, deacetylation, acute leukemia.

Epigenetics is a new branch of science at the intersection of genetics and molecular biology, studying physiological and pathophysiological intracellular processes. Epigenetics is defined as heritable changes in gene expression during cell division that occur without any changes in the DNA sequence. Normally, epigenetic regulation is important for processes such as development, self-renewal, differentiation and proliferation of cells. Loss or disturbances of epigenetic regulation are one of the causes of the development of cancer, in particular tumors of the blood system [2]. This process was initially associated with chromosomal translocations, which could result in the formation of fusion proteins [3]. Protein-protein complexes such as MLL or PML-RARA have been implicated as regulators of epigenetic events. Chromosome translocations or other karyotype abnormalities with structural changes in the MLL gene are often observed when fused with genes from other chromosomal regions. More than 30 different MLL fusion genes have been described [3]. Rearrangements of the MLL gene are localized in its constant region and lead to the synthesis of the MLL fusion protein in hematopoietic cells, which causes acute leukemia. The MLL fusion protein is found in both acute myeloid (AML) and lymphoblastic leukemias [4]. In leukemia cells of the PML-RARA transgenic mouse model of acute promyelocytic leukemia (APL), hypermethylation of the CpG dinucleotide (cytosine + phosphate group + guanine) was detected, which correlates with the expression of microRNAs. In addition, the results obtained provide evidence of the involvement of hypermethylation of the 14q32 domain (region) in the pathogenesis of APL [5]. Recent studies of gene expression profiles and next-generation sequencing technology have made it possible to clarify the mutational status of oncohematological diseases. They confirmed that aberrant expression or mutation of regulators of epigenetic processes are consistent pathobiological processes. Epigenetic information is transmitted through post-translational (protein synthesis process) histone modifications (PTMs). These modifications are “recorded” and “removed” by certain enzyme proteins, i.e. epigenetic processes are reversible. The most studied PTMs include processes such as methylation, acetylation, etc.

Promising results of clinical studies in patients with malignant tumors of the hematopoietic system were obtained by influencing the catalytic function of these enzymes using drugs such as DNA methyltransferase inhibitors (hypomethylating agents) and inhibitors histone deacetylases (SAHA, romidepsin). However, there is another class of proteins, the so-called BET proteins. These molecules recognize and bind to PTMs, altering the transcription process. To date, works have been publishedfocusing on the biology of these epigenetic factors (BET proteins) in the development of a wide range of hematological malignancies. The results obtained are encouraging regarding the possibility of inhibiting the function of these proteins, which may represent a new direction in therapy [6].

BET proteins and transcription regulation. Bromodomain and extra-terminal (BET) proteins include the ubiquitously expressed dual bromodomain proteins of the BET family: BRD2, BRD3, and BRD4. Expression of BRDT, as part of the protein (testicular-specific bromodomain), is limited to testicular tissue [7]. These protein complexes are involved in the initiation and elongation of the transcription process. Recently, it has been demonstrated that the limiting factor for the so-called critical early response genes involved in cell survival, stress response, immunity, glucose metabolism and tumor transformation is the severity of elongation [8]. Thus, BET proteins are important positive regulators of transcription.

BET-proteins in oncohaematological diseases. Dawson et al. put forward a hypothesis about the decisive importance of BET proteins in the formation of a protein-protein complex (MLL fusion protein) [10]. This assumption was based on evidence that MLL fusion proteins function as the SEC/pTEFb complex and create aberrant transcriptional programs that influence the course of acute leukemia [6]. Using new discoveries in proteomics, MA Dawson et al. confirmed the interaction of BET proteins with the SEC/pTEFb complex, as well as with PAFc4 and RNAPolII associated enzyme5, which is another important epigenetic regulator of MLL leukemias [10]. Both reports demonstrated the high efficacy of I-BET and JQ1 in inhibiting MLL leukemia cell lines in vitro, as well as murine models of MLL leukemia, in which animal survival was significantly increased without an obvious increase in toxicity. After the use of both BET inhibitors (I-BET and JQ1), suppression of gene expression was observed - the most important factors in the course of leukemia, such as C-MYC, BCL2 and CDK6. Inhibition of BET by BRD4 further reduced MYC expression and MYC-associated transcription. In addition, BET inhibition has been demonstrated in most MM cell lines, with cell cycle arrest observed in vitro and increased survival in three mouse models of MM. In a study by JA Mertz et al. The use of JQ1 in AML and MM was also confirmed in Burkitt's lymphoma, whose cell lines and animal tumors were highly sensitive to BET inhibition [9]. At the same time, the effect of JQ1 was studied in a number of breast and cervical cancer cell lines, which in most cases were resistant to BET inhibition, despite a decrease in MYC expression.

Thus, BET inhibition can be considered as a promising therapeutic direction for a number of tumors of hematopoietic and lymphoid tissues [6]. The potential for influencing tumorigenesis, including through effects on C-MYC, BCL2, C-MYB and other important mediators of pathobiological processes, can be explained at least by inhibition of BET. It should be noted that a number of issues remain unresolved. Are there other malignant tumors of the blood system that are sensitive to BET inhibitors? What is the reason for the rather narrow spectrum of effectiveness of epigenetic agents? What are the differences in sensitivity to antitumor treatment of oncohematological diseases and solid tumors? These questions require answers, but by now we can talk about the effectiveness of some drugs aimed at epigenetic mechanisms.

DNA modification. Every cell in the body is under “epigenetic control.” One of the main epigenetic processes of gene expression suppression is DNA methylation (attachment of a CH3 group) to cytosine. Following the cytosine there may be a phosphate group and guanine (CpG dinucleotide). Regions with an increased content of CpG dinucleotides are found mainly in the promoter regions of genes. The methylation reaction is catalyzed by DNA methyltransferases (DNMTs), which are a group of enzymes. To carry out gene transcription, the interaction of transcription factors and RNA polymerase with the promoter

of this gene is necessary. Methylation of CpG dinucleotides prevents the action of transcription factors and further reading of information from DNA, including from tumor suppression genes, which is observed in a number of cancers, such as AML.

In 2010, it was discovered that non-amorphous mutations in the IDH1 and IDH2 genes cause DNA hypermethylation and impair hematopoietic cell differentiation. IDH mutations lead to inhibition of DNA and histone demethylation. The work of CB Thompson showed that cell cultures of primary AML with mutations in the IDH1/2 and TET2 genes are characterized by the same epigenetic profile, expressed in global hypermethylation (hypermethylation of the promoter regions of a large number of genes) [9]. According to the author, AML with IDH1/2 and TET2 mutations can be considered as a separate biological variant of leukemia associated with epigenetic regulation of gene expression. When CpG dinucleotides are in a methylated state, they have the ability to interact with methylcytosine binding proteins (MBPs). The 5 proteins involved in DNA methylation in mammals are the most studied: MeCP2, MBD1, MBD2, MBD3 and MBD4. MBPs are able to inhibit transcription and increase the content of histone deacetylase, which leads to deacetylation (removal of the CH3OH group) of histones. As a result, chromatin condensation occurs, which reduces the access of transcription factors2 to certain genes, including tumor suppression genes, for example TP53, Rb, ER.

Thus, epigenetic changes include a variety of mechanisms: changes in DNA methylation, post-translational modifications of histones, chromatin remodeling, expression of non-protein-coding RNAs (microRNAs, small interfering RNAi, etc.) [8]. The prospects for research are enormous, since the 21st century is the century not so much of genetics as of epigenetics—the study of the regulation of gene expression [10]. There is no doubt that in the future antitumor drugs will be developed that will target other, not yet studied, epigenetic processes in addition to those discussed in this review.

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