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Genetic and epigenetic alterations in human cancers

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In carcinogenesis, tumor cells acquire certain cancer hallmarks based on the changes at various molecular levels. This review discusses abnormalities in cancer cells at the genetic and epigenetic levels. Genetic alterations are considered in the example of seven cancers, including lung, breast, prostate, colorectal, renal, cervical, and ovary cancers. Genetic changes disrupt the functioning of both oncogenes and tumor suppressor genes and occur as deletions, amplifications, chromosomal aberrations and chromosomal loci, thousands of somatic mutations and the appearance of oncogenic fusion transcripts *etc.* Epigenetic aberrations are also multifaceted. These include hypermethylation and hypomethylation of gene promoters, histone modifications, changes in non-coding RNA expression profiles *etc.* Genetic and epigenetic disorders are tumor-specific and common for many cancer types. The development of modern large-scale methods for detecting genetic and epigenetic alterations makes it possible to detect simultaneously these aberrations and molecular profiles of different cancer types. Many of these alterations could be the targets for cancer diagnosis and the development of effective treatments.

Keywords: carcinogenesis, oncogenes, tumor suppressor genes, deletions, amplification, LOH, somatic and germline mutations, promoter methylation, noncoding RNA, NGS

Introduction

Human malignant neoplasms are a diverse group of diseases with numerous genetic abnormalities in cells that become cancerous. Their appearance in combination with systemic changes at the level of the body leads to the appearance and progression of tumors [1].

The malignant epithelial tumors (cancers) account for more than 90 % of all malignances, which are often diagnosed at late stages, and treatment of patients is expensive and sometimes ineffective with a low 5-year survival rate [2, 3].

In the process of malignant transformation and progression of malignant neoplasms, tumor cells acquire certain cancer hallmarks accompanied by changes at the molecular level of organization (genetic, epigenetic, transcriptomic, proteomic, metabolomic, *etc.*) [4–6].

These alterations are both tumor-specific and general, inherent in many types of epithelial tumors [7]. The main carcinogenic characteristics are acquired by the tumor cells due to certain mechanisms in a different order of genetic and epigenetic disorders [4, 5]. It is this variety of molecular aberrations that causes problems in the diagnosis, treatment and prognosis of the disease. In recent years, thanks to the development of modern methods of molecular biological research (next generation sequencing (NGS), microarrays, FISH analysis), many alterations associated with the development of tumors have been identified [8, 9]. These include chromosomal rearrangements, deletions, amplifications of chromosomes, chromosome loci and genes, the emergence of oncogenic fusion transcripts, thousands of somatic mutations in genes, hypermethylation and hypomethylation of gene promoters, histone modifications, and changes in non-coding RNA expression profiles [10–12]. Additionally, many changes in carcinogenesis are also inherent in mitochondrial DNA [13]. All these disorders affect gene expression, which leads to pathological changes in tissues and provokes the acquisition of malignant properties by cells [4, 6]. According to current knowledge, hundreds of genes are involved in carcinogenesis [14]. On account of their properties to activate or inhibit tumor growth, they are conventionally divided into oncogenes and tumor suppressor genes [15].

Genetic and epigenetic alterations in tumor-associated cellular pathways and genes. Oncogenes and tumor suppressor genes

The carcinogenesis of epithelial tumors has the following stages of development: tumor initiation, promotion, progression, and metastasis [16]. It is not known for certain which changes are highly specific to each stage, but it is known that genetic, epigenetic, and abnormal expression of many genes and proteins is observed throughout all stages of the disease. In recent years, thanks to the development of modern methods of molecular biological research (microarrays, FISH analysis, NGS), a lot of molecular disorders at DNA, RNA, protein levels, associated with the development of tumors, have been identified [8, 9, 10].

All these alterations affect gene expression, which leads to pathological changes in the functioning of cellular processes and cellular metabolism and provokes the acquisition of oncogenic properties by cells [4, 5]. According to current knowledge, hundreds of genes are involved in carcinogenesis [14]. Both oncogenes and suppressor genes, belong to certain cell signaling pathways involved in carcinogenesis [17]. Among the tumor-associated cellular pathways, the following should be noted as very important: p53, Rb, TGF-B, VEGF, HIF1, PI3K-Akt, Jak-STAT, mTOR, cAMP, MAPK, PPAR, Notch, Wnt-b-catenin, Hedgehog, extracellular matrix interaction and adhesion pathways, apoptosis, androgen and estrogen receptor pathways, prostaglandins, cytokine receptors, calcium signaling pathway, and others [18–22]. These pathways intersect, forming a complex biological network of interactions. Additionally, the combination of activated on-

cogenic pathways and inactivated tumor suppressor genes will differ in each type of tumor, as well as in individual tumors [23, 24].

Genetic alterations in carcinogenesis

Human cancers are known to have multiple somatic genetic alterations caused by point mutations, recombinations, amplifications, and/or deletions. The genes with genetic aberrations include both oncogenes and tumor suppressor genes, that control DNA repair, and the genes that accelerate proliferation and metastasis [25–27].

It is known that during each phase of carcinogenesis, certain genetic alterations occur in cancer cells, both of a common co-neoplastic nature, and organ/tissue-specific changes [28–31].

Human cancers have all known genetic alterations that are classified according to the extent to which DNA has been damaged [11]. First of all, they are divided into two big groups, namely large and small genetic DNA alterations.

Large DNA alterations cover dozens of genes and can change the structure of chromosomes through loss, gain, or rearrangement of chromosomal segments [32]. The reason for these aberrations is chromosomal instability, which can lead to aneuploidy, loss of heterozygosity (LOH), changes in the number of gene copies (copy number variations), structural rearrangements of chromosomes [33]. These damages lead to four types of chromosomal structural aberrations including inversions, deletions, duplications, and translocations of genomic DNA fragments, which include cancer-associated genes, in particular oncogenes and tumor suppressor genes [34]. Chromosomal translocations have a huge oncogenic influence in many cancer types [35, 36]. LOH in carcinogenesis plays an important role in functional inactivation of many tumor suppressor genes. Detection of LOH is one of the methods of its identification on chromosome [37]. It can affect up to 20 % of the genome of cancer cells. LOH targeting could be used for the development of novel anticancer drugs [38]. On the one hand, numerous structural chromosomal aberrations increase chromosomal instability which in turn causes new oncogenic genetic alterations in carcinogenesis [39, 40].

Small DNA alterations usually cover only one gene or intergene space. It could be represented by the most numerous point mutations like single nucleotide variation, as well as fragment damages within the gene and the intergenic region [41, 42]. The point mutations result from single base pair substitutions, insertions, or deletions. There are numerous alterations occurring in carcinogenesis [43, 44] which include both oncogenes and tumor-suppressor genes.

As an example, Table 1 (a–d) shows the most common and known genetic and epigenetic alterations in the seven most common locations of human adenocarcinomas.

Numerous genetic aberrations, as shown in Table 1 a–d, occur during carcinogenesis both at the level of human chromosomes and at the level of genes in genomic DNA. There are genetic changes, which are common for different cancer types and genetic abnormalities that differ within the same type of tumor. Besides, there are specific alterations for a particular type of cancer [45, 46]. For example, in the study of lung cancer the tumor-associated mu-

Table 1. **The most common and typical genetic and epigenetic alterations in a number of malignant epithelial tumors (cancers)**

Table 1a

Cancer localization	A		B		Reference
	Altered chromosomes &	Type of alteration	Gene/Function	Type of gene alteration	
Lung cancer	3p, 4q, 5q, 10q, 13q	Del., loss of part of Chr.short/ long arm	*TP53* (17p13.1) (TSG)	s.m. s.m.	[48–56]
			EGFR (7p11.2) (OG)	ampl.	
			MYC (8q24.21) (OG)	ampl., s.m.	
			KRAS (12p12.1) (OG)	ampl., s.m.	
			ERBB2 (HER2) (17q12) (OG)	ampl., s.m.	
	7q, 8p, 11p, 12p, 14q	ampl.	PIK3CA(3q26) (OG)	del.	
			FHIT (3p14.2) (TSG)	del., phm	
			RASSF1 (3p21.3) (TSG)	del., phm	
			SEMA3B (3p21.3) (TSG)	del., phm	
			EML4-ALK (OG)	fusion	
Breast cancer	1p, 1q, 3p, 6q, 8p, 11q, 13q, 16q, 17p, 17q	Del., ampl., LOH	*HRAS* (11p15.5), (OG)	s.m.	[57–64]
			KRAS (12p12.1), (OG)	s.m.	
			NRAS (1p13.2) (OG)	s.m.	
			TP53 (17p13.1) (TSG)	s.m.	
			ERBB2 (HER2) (17q12) (OG)	ampl.	
			CCND1 (11q13.3) (OG)	ampl.	
			FGFR1 (8p11.23) (OG)	ampl.	
			BRCA1 (17q21.31) (TSG)	g.m.	
			BRCA2 (13q13.1) (TSG)	g.m.	
			PTEN (10q23.31)(TSG)	g.m./s.m., lgcn	
			CDH1 (16q22.1) (TSG)	g.m./ s.m., LOH	

Table 1b

Cancer localization	A		B		Reference
	Altered chromosomes &	Type of alteration	Gene/Function	Type of gene alteration	
Prostate cancer	2p, 3q, 7q, 8q, 9q, 17q, 20q, Xq	ampl. of parts of Chr. cancer-assoc. SNP	*AR* (Xq12) (OG)	s.m.	[65–71]
			BRCA2 (13q13.1) (TSG)	g.m.	
			CDKN1B (12p13.1) (TSG)	del., LOH	
			EZH2 (7q36.1) (OG)	ampl.	
	2q, 5q, 6q, 8p, 10q, 12p, 13q, 16q, 17p, 17q, 18q, 21q, 22q	del. of parts of Chr, hyperploid., aneusomy,	*KLK3 (PSA)* (19q13.33) (OG)	SNP	
			GSTP1 (11q13.2) (TSG)	s.m., phm,	
	7, 17				
	21q22	numerous rearrang. TL-TMPRSS2/ ERG — the most frequent	*MYC* (8q24.21) (OG)	ampl.	
			NKX3.1 (8p21.2)(TSG)	del., s.m., phm, LOH	
			TP53 (17p13.1) (TSG)	g.m./s.m.	
			PTEN (10q23.31)	LOH, s.m.	
			TMPRSS2-ERG (OG)	fusion	

Cancer localization	A		B		Reference
	Altered chromosomes &	Type of alteration	Gene/Function	Type of gene alteration	
Colorectal cancer	1p, 5q 15q, 18q, 17p, 17q 7q, 8p t(5;10) (q22;q25), inv(5) (q22q31.3)	aneuploidy, loss of Chr. parts, rearrang. loss of Chr. parts, TL	*APC* (5q22.2), (TSG) *BRAF* (7q34), (OG) *CTNNB1* (3p22.1), (OG) *EGFR* (7p11.2) (OG) *KRAS* (12p12.1), (OG) *MLH1* (3p22.2), (TSG) *PIK3CA* (3q26.32), (OG) *PTEN* (10q23.31) (TSG) *TP53* (17p13.1) (TSG/OG mutant) *AKT1* (14q32.33),(OG) *SOX9* (17q24.3) (TSG/OG)	g.m./s.m., LOH s.m. s.m. s.m. s.m. g.m./s.m., s.m. LOH, s.m. s.m. s.m. s.m.	[72–77]

Table 1c

Cancer localization	A		B		Reference
	Altered chromosomes &	Type of alteration	Gene/Function	Type of gene alteration	
Renal cancer	3p (3p12-14, 3p21, 3p25) 7, 5 (5q22-qter), 8, 10, 12, 18, 20 Y, 8p, 9p, 13q, 14q	Del., LOH, TL, Trisomy Loss of Chr. parts, LOH	*VHL* (3p25.3) (TSG) *FHIT* (3p14.2) (TSG) *RASSF1* (3p21.31) (TSG) *MET* (7q31.2) (OG) *PTEN* (10q23.31) (TSG) HIF-1α (TSG) HIF-2α (OG) *MTOR* (OG), *PIK3CA* (OG) *PBRM1* (TSG)	s.m., LOH, phm s.m., LOH, TL. s.m., LOH, TL, phm g.m./ s.m., TL s.m., del., TL del., s.m. s.m., ampl. TL, ampl. s.m. ampl. s.m. s.m., del.	[56, 78–81]
Cervical cancer	3, 11, 17 4p16, 4q21-35 5p 6p21.3-p25	LOH LOH ampl. Loss of Chr. parts	HPV E2 (OG) *TP53* (17p13.1) (TSG) *FHIT* (3p14.2) (TSG) *RASSF1* (3p21.31) (TSG) *PIK3CA* (3q26.32), (OG) *FGF12* (3q28-q29), (OG) *CDH1* (16q22.1) (TSG) *RB1* (13q14.2) (TSG) *CDKN2A* (9p21.3) (TSG) *PTEN* (10q23.31) (TSG)	Integration s.m. del. phm s.m., ampl. s.m., ampl. s.m., phm s.m., phm s.m., del., phm s.m., phm	[82-89]

Table 1d

Cancer localization	A		B		Reference
	Altered chromosomes &	Type of alteration	Gene/Function	Type of gene alteration	
Ovarian cancer	3, 8, 12, 14	Trisomy	*EGFR* (7p11.2) (OG)	ampl., s.m.	[90–96]
			ERBB2 (17q12) (OG),	ampl., s.m.	
	1, 2, 3, 6, 7, 9, 12, 20	ampl.	*KRAS* (12p12.1), (OG)	s.m.	
			MYC (8q24.21) (OG)	s.m., ampl.	
	4, 8, 11, 13, 14, 15, 17, 22	Loss Chr./ del.	*CDKN2A* 9p21.3) (TSG)	s.m., del., phm	
			RB1 (13q14.2) (TSG),	s.m., del.	
			BRCA1 (17q21.31) (TSG)	g.m./ s.m.	
	1p, 1q, 3p, 3q, 6q, 7p, 10q, 11p, 11q, 12q	Rearrang. del., unbalanced TL	*CTNNB1* (3p22.1) (OG)	s.m.	
			CDK12 (17q12) (OG)	s.m.	
			FOXL2 (3q22.3) (TSG/OG)	s.m.	
			GATA4 (8p23.1) (OG)	s.m., phm	
			TP53 (17p13.1) (TSG)	del., s.m.	
			CCNE1 (19q12) (OG)	ampl., phom	

Notes: *A* — chromosomal alterations; *B* — gene alterations; & — data according to https://atlasgeneticsoncology.org; Chr. — chromosome; OG — oncogene; TSG — tumor suppressor gene; ampl. – amplification; del. — deletion; rearrang. — rearrangements; TL — translocation; s.m. — somatic mutation; g.m. — germline mutation; lgcn — loss of gene copy number; LOH — loss of heterozigosity; phm — promoter hypermethylation; phom. — promoter hypomethylation; SNP — single nucleotide polymorphism

tations of the most well-known 10 oncogenic drivers (*KRAS, EGFR, ALK* rearrangements, *ERBB2, BRAF, PIK3CA, MET* amplification, *NRAS, MEK1*, and *AKT1*) in patients of various racial groups were found to differ significantly [47]. This also indicates the population factors that contribute to heterogeneity in the development and progression of tumors.

Lung cancer is characterized by many chromosomal and genomic alterations involving oncogenes (*EGFR, MYC, RAS, PIK3CA, NKX2-1, ALK*) and their pathways, as well as tumor suppressor genes (*TP53, RB1, CDKN2*, 3p gene cluster) [48–52]. Among the most important factors in the growth and proliferation of lung tumors are the ERBB family tyrosine kinase receptors encoded by the epidermal growth factor receptor (*EGFR*, 7p12), *ERBB2* (*HER2/neu*, 17q12), *ERBB3* (12q13) and *ERBB4* (2q33. 3) genes. It has been noted that EGFR protein is overexpressed in most lung carcinomas [49, 53–56].

Activating mutations in the *EGFR* tyrosine kinase domain predominate in the patients with lung cancer of East Asian ethnicity, non-smoking men, and women [50, 53]. Along with these abnormalities, lung cancer is characterized by reorganizations in the form of fusions of gene or their parts. For example, the *EML4-ALK* gene fusion plays an important role in establishing the subtype of lung cancer and is associated with the subtypes of acinar and solid tumors with mucin secretion [54].

For breast cancer, deregulation of the EGFR pathway is associated with other pathways, namely PI3K/PTEN/Akt/mTORC1, which are

also considered as targets for therapeutic action [57, 58]. These pathways are known to play a leading role in oncogenic transformation, apoptosis avoidance, metastasis, and drug resistance. Gene expression of these pathways is disrupted in breast cancer by somatic mutations and amplifications. Among them are *HER2, ESR1, BRCA1, BRCA2, EGFR1, PIK3CA, PTEN, TP53, RB,* which are oncogenes and tumor suppressor genes [57–61]. The impact on these pathways and their genes is being discussed in clinical trials of new small molecule inhibitors [58]. For breast cancer, the classification system based on genomic molecular features of tumors is currently well developed [62]. It can detect basal and luminal subtypes of cancer. Additionally, a special place among breast cancers is occupied by triple-negative tumors [63], which are characterized by the loss of estrogen, progesterone, and HER2 receptors. They are resistant to many drugs and include the following subtypes: basal-like, mesenchymal, luminal with androgen receptor expression, and immuno-enriched [64].

The typical molecular changes in prostate cancer include genetic inactivation of the *NKX3. 1* and *PTEN* genes, which control epithelial cell differentiation and prevent oncogenic initiation [65, 66]. At the same time, among the oncogenic factors the most characteristic of this type of cancer is the expression of long non-coding RNA *PCA3*, which leads to a suppressive effect of the suppressor gene *PRUNE2*, located on the complementary DNA strand [65, 67, 68]. Furthermore, prostate cancer is characterized by racial differences in genetic alterations [70] and the appearance of numerous oncogenic fusion transcripts [68, 71].

Colorectal cancer is characterized by the following genetic alterations: hereditary and somatic mutations, including changes caused by DNA repair deficiency, as well as genomic changes: chromosomal instability, microsatellite instability, aneuploidy, chromosome loss, chromosomal rearrangements, loss of chromosome parts, deletions of 5q, 15q, 18q, 17p, 17q, which leads to deregulation of WNT, RTK/Ras/MAPK, PI3K, TGF-Beta and P53 signaling pathways [72, 73, 74, 75, 76, 77].

Renal, cervical and ovarian cancers also have certain peculiarities of genetic and epigenetic changes in oncogenes and tumor suppressor genes. The main genetic and epigenetic aberrations are presented in Tables 1c and 1d.

By analyzing the results of NotI-microarrays of human Chromosome 3 in 7 locations of epithelial tumors of different tissue origins, the authors identified 74 genes and/or loci with significant genetic and/or epigenetic disorders. Twenty of them are characteristic of 5-7 tumor types (tumor-specific disorders), and 23 genes and/or loci are tumor-specific [97]. It has been shown that the largest number of individual genetic and/or epigenetic abnormalities was found in prostate tumors, indicating peculiarities of carcinogenesis that are different from other types of epithelial tumors.

The Not-I microarray identified dozens of genes and/or loci with genetic and/or epigenetic abnormalities in tumor samples, indicating the inactivation of a number of tumor suppressor genes and potential tumor suppressor genes on the 3p and 3q arms of human Chromosome 3 in epithelial tumors [56, 82, 98]. Other methods were used to confirm the results. For the genes *ITGA9, LRRC3B, THRB, RBSP3* and *SEMA3B*, the epigenetic inactiva-

tion, namely methylation of gene promoters, was detected. The genes *NKIRAS1, PPM1M, PRICKLE2* and *GPX1* have been found with genetic changes in tumors — hemizygous deletions. For the genes *GORASP1, GNAI2, NKIRAS1, GPX1, GPX3, PPM1M, PRICKLE2, SEMA3B, BHLHE40, BCL6* and *ITGA9* genetic and/or epigenetic alterations have correlated with decreased relative gene expression in epithelial tumors [97, 99, 100].

It is known that different types of tumors, as well as individual tumors, have their own patterns of somatic mutations [25, 101] and genetic aberrations, which are realized in the phenomenon of heterogeneity within tumors, between tumors and different tumor types [102, 103]. Among somatic mutations, there are so-called driver or causative mutations [104] and passenger mutations. They are the result of the carcinogenic process on the one hand, and on the other hand, the factors that enhance and deepen the aggressive properties of tumors [105] and occur throughout the entire process of carcinogenesis [106]. It is not yet possible to accurately define and distinguish between these two types, but there are the approaches that have already detected a number of driver mutations and genes in carcinogenesis, most of them based on computational and interactive approaches to analyzing databases of genetic alterations according to large-scale cancer studies [107, 108].

The functions of driver genes in carcinogenesis are experimentally verified using many expressing systems, among which the replication-incompetent retroviral and lentiviral expression systems occupy an important place [109, 110].

Genetic alterations, including deletions, amplifications, rearrangements, somatic mutations, can be caused by both exogenous (ultraviolet light, nicotine, carcinogens) [111, 112] and endogenous factors of an organism, such as deamination (spontaneous and enzymatic deamination due to the action of a number of enzymes, in particular APOBEC proteins), oxidation, alkylation, replication errors [113, 114]. To restore DNA integrity, there are the mechanisms that can be inhibited and malfunction in carcinogenesis, namely: replicative repair, recombinant repair, excision repair, and mismatch repair [113].

The APOBEC (apolipoprotein B mRNA editing catalytic polypeptide-like) family of proteins has diverse and important functions in normal and pathological human conditions. These proteins have the ability to bind to both RNA and single-stranded DNA and have the enzymatic function of cytidine deamination. This function, as well as tissue-specific expression, varies widely for each of the APOBEC proteins. The loss of cellular control over the activity of APOBEC family proteins leads to DNA hypermutability and impaired RNA editing, which are closely associated with DNA repair defects and cancer development [115]. This effect is associated with the formation of promutagenic uracil in genomic DNA [116]. APOBEC enzymes have dinucleotide specificities that affect mutational characteristics. Although numerous crystal structures of the interaction of enzymes with single-stranded DNA have been obtained, the mechanisms of global recognition and local selection of target sequences remain unclear [117]. However, this does not prevent the development of small enzyme inhibitors for the treatment of various cancer types [111, 117].

Somatic mutations in malignant tumors that are clinically significant require a separate

thorough analysis. These data are presented in numerous databases due to the development and implementation of modern next-generation sequencing methods [8, 10, 118].

Epigenetic alterations in carcinogenesis

In contrast to genetic aberrations, epigenetic changes are reversible and include key processes of genomic DNA methylation, histone modification, chromatin modification, changes in nucleosome positioning, and expression of non-coding RNA profiles. Disruptions in epigenetic processes can lead to altered gene functions and cause cellular neoplastic transformation. The epigenetic modifications precede genetic changes and usually occur at the early stage of tumor development [119, 120]. Among the epigenetic disorders in carcinogenesis, the most studied processes are the abovementioned ones, namely, gene promoter methylation, histone acetylation and methylation, changes in chromatin state, and expression of non-coding RNAs. These aberrations are being studied to establish the mechanisms of tumor initiation, development, and metastasis, to identify biomarkers associated with early diagnosis, prognosis, and to develop effective cancer therapeutic agents [121].

The altered epigenetic state in cancer cells is characterized by global genomic hypomethylation as opposed to hypermethylation of CpG islands of tumor suppressor gene promoters [122, 123]. Global genomic hypomethylation provokes an increase in oncogene expression [121]. In eukaryotes, the state of DNA methylation is a common epigenetic change, and these epigenetic features are characteristic of heterochromatin. DNA methylation plays an important role in maintaining genome stability, genomic imprinting, inactivation of the X chromosome in women, transcriptional regulation, and in the development of the organism [124]. The conversion of cytosine to 5-methylcytosine (5mC) is carried out by DNA methyltransferases (DNMTs). These enzymes use S-adenosyl methionine (SAM) as a key methyl group donor. There are two main categories of DNMTs in mammalian cells, maintenance methyltransferase (DNMT1) and *de novo* methyltransferases (DNMT3A, DNMT3B) [125].

Although it is generally accepted that DNA methyltransferases are specific in their functions and do not overlap, the recent data suggest that *de novo* methyltransferases overlap with the maintenance methyltransferases [126]. Additionally, the methylation state depends not only on the activity of DNMTs, but also on the activity of DNA demethylase and the rate of DNA replication [127]. Methylation of promoter CpG islands prevents the binding of various transcription factors to their sites and directly activates Methyl-CpG-binding domain proteins (MBD family) that bind to 5-methylcytosine. MBD proteins utilize histone modifying enzymes and chromatin remodeling complexes in methylated regions and facilitate transcriptional repression [128]. The NuRD-like chromatin remodeling complex binds to the MBD2 protein and methylates DNA. Mutations within the MBD domains occur in many diseases, including neurological disorders and cancer, leading to a loss of specificity of MBD binding to methylated sites and gene deregulation [129]. These mechanisms play a central role in establishing the critical role of DNA methylation in the epigenetic regulation of gene expression.

Among the genes with frequent genetic disorders in carcinogenesis (Table 1), there are some, which also have the changes in promoter methylation status, i. e. hypo- or hypermethylation. In particular, *RASSF1, SEMA3B* have hypermethylated promoter regions in lung cancer [48, 56], *PTEN, CDH1* in breast cancer [61], *GSTP1, NKX3.1* in prostate cancer [68, 98], *VHL* in renal cancer [79], *RASSF1, CDH1, RB1* in cervical cancer [87], *CDKN2A, GATA4* in ovarian cancer [95, 96].

Genetic and epigenetic alterations in the same genes are not casual. For example, the associations between 737 clinically significant mutations in the genes involved in cancer development (driver genes) and site-specific methylation changes in these genes have recently been identified [130]. Furthermore, other researchers have studied the correlations between genomic DNA methylation and gene expression in 33 cancer types and approximately 11,000 patients according to the TCGA project [131, 132]. The analysis of three regions of gene promoters revealed different patterns of methylation of their CpG islands, which has a multidirectional effect on the expression of the studied genes. Some of these data contradict the classical concept of correlations between methylation and expression, which requires more detailed research [132].

The phenomenon of methylation of many suppressor genes in carcinogenesis is called the CpG island methylation phenotype (CIMP), which was first identified and most widely studied in colorectal cancer [133, 134]. The term "CIMP" has been used repeatedly in recent decades to describe simultaneous methylation of gene promoters in other tumor types, including bladder, cervical, stomach, liver, brain (glioma), lung, kidney, ovarian, and other cancers [134–139]. There is still controversy whether CIMP is a universal phenomenon for all cancers or it represents a specific phenotype for a particular type of cancer [135, 140, 141].

The next level of epigenetic alterations in carcinogenesis is a change in histone modifications: acetylation, methylation, phosphorylation, ubiquitination [142, 143], comprising the so-called "histone code" [144]. An octamer of four globular histone proteins (H2A-H2B dimer and H3-H4 tetramer) forms the core of the nucleosome, which is connected by the fifth linker histone H1. The free N-terminal tails of these proteins are very flexible and rich in lysine and arginine residues, they can be widely modified, which may lead to changes in the charge of proteins in general, loss of their binding to DNA [145] and changes in their interaction with other proteins [146]. The most studied modifications are acetylation and methylation of lysine residues on the N-terminal tails of histones and arginine methylation [147]. Acetylation of the lysine residue of histone tails is very common and their levels are associated with transcriptionally active chromatin. Acetylation inactivates the positive charge on histone proteins by acetylating the ε-amino group of lysine residues with acetyltransferases (HATs), which use acetyl-CoA as an acetyl group donor [143, 148]. The enzymes involved in histone modifications, such as histone acetylases (HATs), histone deacetylases (HDACs), histone methylases (HMTs), histone demethylases (HDMTs), and other epigenetically associated proteins [149, 150], can be deregulated in the carcinogenesis of various types of cancer and have genetic disorders (mutations, translocations, deletions,

amplifications) and, as a result, the changes in expression in tumors [151]. The identification of these disorders is the basis for the development of targeted inhibitor drugs for cancer treatment (epi-drugs) [150, 152–154]. Noteworthy, a number of promising molecular targets have already been identified among small molecules or biological inhibitors that counteract the epigenomic-metabolic interactions in cancer [155].

The next level of epigenetic regulation of carcinogenesis is represented by a large group of non-coding RNAs (ncRNAs), which consists of a number of classes that have their own structure and functions in both normal and tumor development, and are involved in almost all cellular processes in the body and intercellular interactions [156]. According to their main functions, ncRNAs can be divided into infrastructural and regulatory. Constitutively expressed infrastructure ncRNAs are represented by ribosomal, transfer, small nuclear, and small nucleolar RNAs (snoeRNAs). Regulatory lncRNAs, in turn, are divided into classes: microRNAs, Piwi-interacting RNAs, circular RNAs, small interfering RNAs, siRNAs, and long non-coding RNAs. In addition, a new class of promoter-associated RNAs (PARs) and enhancer RNAs (eRNAs) has recently been described [157, 158]. The size of ncRNAs varies from 20 nt for miRNAs to 9000 nt for enhancer RNAs. Initially, regulatory lncRNAs were thought to simply control gene expression at the post-transcriptional level, but recent studies have shown that these RNAs, especially lncRNAs, are widely associated with various chromatin remodeling complexes and target specific genomic loci to alter DNA methylation or histone modifications [159]. It has been shown that ncRNAs modulate intracellular signaling to control various cellular processes, including receptor levels and activity, proliferation, invasion, migration, apoptosis, and stemness in the development of epithelial tumors [160–162].

The long non-coding and micro RNAs are the most studied in the process of carcinogenesis [163]. It is known that long non-coding RNAs (lncRNAs) act as competing endogenous RNAs (ceRNAs), with microRNAs (miRNAs) and lncRNAs regulating each other through their binding sites [164]. But these are not the only relationships between different types of ncRNAs. For example, some lncRNAs encode miRNAs and small nuclear RNAs (snoRNAs) and can regulate the expression of these small RNAs as precursors. Small nuclear RNAs, as precursors for piRNAs, can also regulate their expression. The miRNAs and piRNAs target mRNAs and regulate gene expression [165, 166]. This complex system of interactions, which covers all levels of function regulation in the cell, can manifest itself as both oncogenic factors and tumor suppressive effects [167] and serves as markers for diagnosis and prognosis of the disease. However, the functions performed by lncRNAs, as well as other types of ncRNAs in normal cells and in the development of pathologies, do not end there. For example, lncRNAs are involved in various epigenetic regulatory processes in carcinogenesis, including coordination of chromatin dynamics, regulation of DNA methylation, modulation of other ncRNAs, influence mRNA stability and splicing, miRNA-mediated regulation of gene expression, acting as a microRNA sponge, and control the availability of epigenetic substrates through impaired metabolism in tumors [168–170].

It is known that altered cellular metabolism in tumors affects all parts of epigenetic regulation, including histone modifications due to the availability of donor substrates (acetyl-CoA and SAM) for acetylation and methylation reactions [171]. Mutations in metabolic enzymes such as isocitrate dehydrogenase 1 and 2 cause the accumulation of metabolites that disrupt the balance of histones and DNA methylation, leading to widespread deregulation of epigenetically controlled expression genes. Moreover , modifications of the catalytic activity and subcellular localization of metabolic enzymes in cancer can affect epigenetic modifications and gene expression programs, which contributes to tumor progression [172]. However, on the other hand, the reversibility of epigenetic processes and the possibility of influencing them through diet [173], physical exercises [174], correction of chronic stress [175], and other factors related to the human lifestyle give hope for the development of auxiliary and preventive anti-cancer methods and effects. These approaches should be used to develop effective treatment for patients and to identify and implement therapeutic and preventive measures in the presence of risk factors for cancer.

Thus, the cancer cells contain multiple genetic and epigenetic abnormalities. Despite the complexity, the cell survival and tumor progression can often be prevented by inactivating a single oncogene. This phenomenon is called “oncogenic dependence”. It provides a rationale for molecularly targeted/targeted therapy [176, 177]. However, combination therapy may also be necessary to prevent the cancer from becoming oncogenic [178]. It is important to note the important role of oncogenic inactivation in tumor regression by the immune system and changes in tumor-stromal interactions [179].

Reactivation of suppressor genes is another promising approach to stop tumor growth. To date, the ways of epigenetic restoration of suppressor gene expression have been shown, if they do not have genetic disorders in the tumor, such as *MGMT, MLH1*, and *RASSF1A* in head and neck squamous cell carcinomas [180], and the *MLH1* gene in cell tumor lines [181]. The activation of suppressor genes was observed with the introduction of energy restriction agents due to the effect on the methylation of the *GADD45a, GADD45b, IGFBP3, LAMB3, BASP1, GPX3, GSTP1* genes in prostate cancer, increasing their expression [182]. Another approach is possible at the protein level, which is the inactivation of negative regulators of the function of suppressor genes, such as the inhibition of *MDM2* to reactivate p53 in tumors [183]. Currently, there is a whole range of anti-cancer epigenetic drugs in various stages of clinical trials, including histone deacetylase inhibitors, histone demethylases, DNA methyltransferase inhibitors and bromodomain inhibitors [184].

Modern approaches to the large-scale search for genetic and epigenetic alterations and gene expression aberrations in human cancers.

In recent decades, a number of technologies have been developed worldwide for large-scale screening of heterogeneous disorders of a number of human pathologies, including human cancers [185, 186]. These include microarray technologies (DNA, RNA, proteins) [187–189], next-generation sequencing, such as

whole-genome, whole-transcriptome (exome, mRNA, ncRNA), and epigenomics [190, 191], microbiome studies in cancer [192, 193], and next-generation mass spectrometry technologies [194].

These studies make it possible to identify multilevel alterations in the development of various types of cancer and metastasis and to evaluate the effectiveness of treatment of patients by detecting genetic changes (microsatellite instability, variations in single nucleotide polymorphisms and mutations, and gene copy variation), epigenetic changes (DNA methylation, histone modification, microRNAs), and differential gene expression at various stages of the tumor process [195, 196]. Next-generation sequencing allows us to establish the "mutational fingerprints" of various carcinogens, which allows us to detect the effects of exogenous and endogenous genotoxic agents [197], and to talk about a new generation of genotoxic tests [198].

Large-scale genomic studies and technological innovations in next-generation sequencing have revealed many details of somatic and germline mutations in solid tumors. This approach makes it possible to classify tumor subtypes based on genetic changes in solid tumors, and on the basis of this information to select new drugs and targeted therapies for patients and adjust standard treatment [199, 200]. These data are used to create specific kits for research and clinical screening of mutations, amplifications, and translocations in solid tumors [201–203].

In Japan and the United States, National Cancer Centers and university hospitals have introduced the new-generation of cancer diagnostic tests for patients using sequencing. Based on the identified molecular changes, doctors can provide an approved targeted therapy and other effective drugs for cancer patients. However, the interpretation of the clinical significance of genomic alterations remains the most difficult bottleneck in evidence-based medicine in cancer despite the availability of databases for the interpretation of tumor changes and clinical decisions [200, 204, 205]. Tumor DNA profiling is now a new standard in the cancer research and treatment [206].

Although large-scale next-generation cancer sequencing studies hold promise for providing evidence-based oncology, challenges remain in integrating these data with clinically validated biomarkers, so it is important to create an integrated platform for analyzing detected changes at the multiomic level [207]. One of the important aspects, in addition to accurate diagnosis and prognosis of the disease course, which can also be analyzed using multicellular data [208, 209], is the establishment of sensitivity to both targeted and general-acting chemotherapeutic agents. This problem can be solved in a more evidence-based and comprehensive way not only by genomic status in relation to the target drug, but also at the level of multiomic studies using machine learning methods and determining classifiers to predict drug efficacy [210, 211].

For personalized medicine and the general public, these technologies are still quite expensive, but they make it possible to identify the characteristics of certain tumors, molecular subtypes of cancer, to establish a more accurate diagnosis and prognosis of the disease, to validate the already known ones, to discover potential biomarkers, drugs, targets, and to

develop new therapeutic approaches to cancer treatment [212].

Thus, the current level of development of science and medicine allows us to talk about significant achievements in identifying genetic and epigenetic alterations in various types of cancer and understanding the molecular mechanisms of carcinogenesis, developing the latest methods of diagnosis and prognosis of various types of cancer and generating new therapeutic approaches, effective for certain types of tumors. Despite all these successes, the current task of experimental and clinical oncology and related sciences, such as molecular biology, genetics, cell biology and others, is to ascertain the mechanisms of tumor growth and methods of influencing this process, to search for genetic, epigenetic, and expression features of certain tumors and specific molecular driver events, tumor-stromal interactions, and molecular subtypes and targets for successful therapy to prevent growth and tumor spread as well as to develop the efficient methods for early diagnosis and prognosis of cancer.

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Генетичні та епігенетичні порушення у раках людини

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У процесі канцерогенезу клітини пухлин набувають певних ракових ознак, в основі яких лежать зміни на різних молекулярних рівнях. В даному огляді розглянуто порушення у ракових клітинах на генетичному та епігенетичному рівнях. Генетичні порушення розглянуто на прикладі семи видів раків, серед яких рак легені, молочної залози, передміхурової залози, колоректальний, нирки, шийки матки та ячників. Генетичні зміни порушують функціонування як онкогенів, так і генів супресорів пухлин та спостерігаються як делеції або ампліфікації, аберації хромосом та локусів хромосом, тисячі соматичних мутацій у генах, поява онкогенних гібридних транскриптів тощо. Епігенетичні порушення також є багатоплановими. Серед них гіперметилювання та гіпометилювання промоторів генів, модифікації пістонів, зміна профілів експресії некодувальних РНК та інші. Генетичні та епігенетичні порушення мають як пухлино-специфічний характер, так і загальний, притаманний багатьом видам епітелійних пухлин. Завдяки розробці сучасних широкомасштабних методів детекції генетичних та епігенетичних порушень є змога одночасного виявлення цих порушень та молекулярного профілювання різних типів раків. Багато з цих порушень можуть бути мішенями для діагностики раку та розробки ефективних методів лікування.

Ключові слова: канцерогенез, гени супресори росту пухлин, онкогени, делеція, ампліфікація, втрата гетерозиготності, соматичні та зародкові мутації, метилювання промотора, некодуючі РНК, секвенування нового покоління

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