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REVIEW

MOLECULAR FEATURES OF MALIGNANT GASTRIC TUMORS

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ABSTRACT

Gastric cancer is one of the most widespread cancers and makes a significant contribution to the global mortality rate from malignant neoplasms. The late onset of clinical symptoms is the main reason why the disease is often diagnosed at an advanced stage, and this limits the available therapeutic approaches. Despite the fact, that extensive studies have been carried out to identify the mechanisms and markers of the development and progression of the disease, their results are currently not fully included in clinical practice. As a consequence, only marginal improvement in long-term survival has been achieved and patient prognosis remains poor. Understanding the molecular genetic features of gastric malignant tumors can provide insight into their pathogenesis, help identify new biomarkers for prognosis and diagnosis, and identify new therapeutic targets. In recent decades, advances in high throughput sequencing technologies have improved understanding of the molecular genetic aspects of gastric cancer. This review considers molecular level changes, including information on tumor suppressor genes, oncogenes, cell cycle and apoptosis regulators, cell adhesion molecules, loss of heterozygosity, micro-satellite instability and epigenetic aberrations (change in methylation level and modification of histones). The review is also devoted to the molecular aspects of pathogenesis – changes in the signaling pathways involved in the gastric cancer development; the classification of sporadic and hereditary gastric cancer at the molecular genetic level is considered. The characteristics and classification of GC presented in this review at the genetic and epigenetic levels confirms that this disease is heterogeneous. These data can be used both to develop and test potential markers and new targeted therapeutic approaches.

Keywords:
gastric cancer, heredity, sporadic forms, tumor suppressor genes, oncogenes, epigenetics, microsatellite instability

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МОЛЕКУЛЯРНЫЕ ОСОБЕННОСТИ ЗЛОКАЧЕСТВЕННЫХ ОПУХОЛЕЙ ЖЕЛУДКА

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РЕЗЮМЕ

Рак желудка является одним из широко распространенных онкологических заболеваний и вносит существенный вклад в показатель глобальной смертности от злокачественных новообразований. Позднее появление клинических симптомов является основной причиной того, что заболевание часто диагностируется на запущенной стадии, а это ограничивает доступные терапевтические подходы. Несмотря на то, что были проведены обширные исследования для выявления механизмов и маркеров развития и прогрессирования заболевания, их результаты в настоящее время полностью не вошли в клиническую практику. Как следствие этого, достигнуто лишь незначительное улучшение долгосрочной выживаемости, и прогноз у пациентов остается неблагоприятным. Понимание молекулярно-генетических особенностей злокачественных опухолей желудка может дать представление об их патогенезе, помочь в идентификации новых биомаркеров для прогнозирования и диагностики, а также выявить новые терапевтические мишени. В последние десятилетия достижения в области технологий высокопроизводительного секвенирования улучшили понимание молекулярно-генетических аспектов рака желудка. В этом обзоре рассмотрены изменения на молекулярном уровне, включающие информацию о генах-супрессорах опухолей, онкогенах, регуляторах клеточного цикла и апоптоза, молекулах клеточной адгезии, потери гетерозиготности, микросателлитной нестабильности и эпигенетических аберрациях (изменение уровня метилирования и модификации гистонов). Обзор также посвящен молекулярным аспектам патогенеза – изменениям в сигнальных путях, вовлеченных в развитие рака желудка; рассматривается классификация спорадического и наследственного рака желудка на молекулярно-генетическом уровне. Представленная в данном обзоре характеристика и классификация РЖ на генетическом и эпигенетическом уровне подтверждает, что это заболевание является гетерогенным. Эти данные можно использовать как для разработки, так и для тестирования потенциальных маркеров и новых таргетных терапевтических подходов.

Ключевые слова:
рак желудка, наследственность, спорадические формы, гены-супрессоры опухолей, онкогены, эпигенетика, микросателлитная нестабильность

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INTRODUCTION

Worldwide, gastric cancer (GC) remains one of the leading causes of cancer death. The late appearance of clinical symptoms is the main reason that the disease is often diagnosed at an advanced stage, and this limits the available therapeutic approaches [1]. Despite the fact that extensive studies have been conducted to identify signaling pathways and genes involved in the development and progression of the disease, their results have not fully entered clinical practice at the present time. As a consequence, only a slight improvement in long-term survival has been achieved and the prognosis in patients with GC remains unfavorable. Adenocarcinoma is the main histological type of GC, which accounts for 90–95 % of all malignant neoplasms of the gastric. Morbidity is closely related to environmental factors reflecting the peculiarities of the geographical distribution of this disease [2].

GC is the result of a complex interaction of environmental factors and multiple genes. Obvious risk factors for GC are Helicobacter pylori infection and Epstein-Barr virus (EBV), smoking, consumption of foods with a high salt content or N-nitroso compounds, family history and molecular factors [2; 3]. The latter include multiple genetic and epigenetic changes in oncogenes, tumor suppressor genes (TSG), cell cycle regulators and DNA repair genes [4].

Thus, a systematic look at the molecular basis of GC is necessary for the development of new strategies for the prevention and treatment of this disease. Therefore, the purpose of this review was to analyze and systematize information about currently known epigenetic and genetic changes in GC of various subtypes.

1. Classification of gastric cancer based on molecular profile studies.

According to the Lawrence classification, gastric adenocarcinoma is divided into intestinal, diffuse, mixed and non-deterministic [5]. They differ not only in morphology, but also in epidemiology, the nature of progression, genetics and clinical picture. Histopathologically, the intestinal type is characterized by malignant epithelial cells that exhibit cohesiveness and glandular differentiation infiltrating surrounding tissues [6]. On the contrary, the diffuse subtype is characterized by tumor cells that exhibit poor differentiation and lack of cohesion. It is believed that the intestinal type of GC is associated mainly with the influence of environmental (exogenous) factors, whereas the diffuse type is due to genetic hereditary and non-hereditary (endogenous) factors. These histological classifications are not sufficient to reflect the molecular characteristics of GC or to develop personalized treatment strategies. Several molecular classification systems have been proposed, and individual molecular subtypes have been identified [7–9].

To date, the Cancer Genome Atlas (TCGA) has characterized 295 cases of gastric adenocarcinoma using high-throughput sequencing technologies, including gene copy number analyses, DNA methylation, matrix RNA and microRNA sequencing, proteome and microsatellite instability (MSI) analysis, as well as genome-wide sequencing data [7]. Based on this, four subtypes of GC were described in 2014 (Table 1):

(1) EBV-positive (8.8 %),
(2) microsatellite unstable (MSI, 21.7 %),
(3) genomically stable (19.7 %),
(4) chromosomally unstable (CIN, 49.8 %) [7].

These subtypes of GC showed various epigenetic changes and mutations in different genes. Thus, EBV+ tumors had mutations in *PIK3CA* and *ARIDIA*, DNA hypermethylation and significant amplification of *JAK2*, *PD-L1* and *PD-L2*. Most EBV-positive tumors occurred in male patients in the bottom or body of the gastric. All EBV-positive RS demonstrated hypermethylation of the *CDKN2A* promoter and the absence of hypermethylation of the *MLH* promoter characteristic of the RS phenotype associated with MSI (CIMP) [7; 10].

Tumors of the MSI-H subtype, as a rule, occur in female patients, are diagnosed at late stages and are characterized by an increased frequency of mutations, including mutations of genes encoding target oncogenic signaling proteins [11].

The genomically stable subtype (GS) lacked numerous molecular changes and correlated well with the diffuse histological variant of Loren, but contained mutations in *CDH1* and *RHOA* or CLDN18-ARCHGAP fusion. It is known that the active form of RHOA associated with GTP activates STAT-3 to stimulate oncogenesis. According to the Lauren classification, GC is divided into intestinal and diffuse types, which have different clinical, pathological and prognostic

features. They differ not only in morphology, but also in epidemiology, the nature of progression, genetics and clinical picture. It has recently been observed that the location of the tumor is also important, since there is a difference between proximal and distal non-diffuse GC in terms of the expression level of different sets of genes [12; 13]. Despite significant progress in the diagnosis and treatment of GC, the survival rate is still low, only about 20 % of patients with GC can achieve 5-year survival. At the same time, surgical treatment is the only therapeutic method that provides the greatest probability of cure.

Finally, tumors of the CIN subtype were often found in the gastrointestinal junction/cardia, correlated well with the intestinal histological variant of Loren, showed pronounced aneuploidy and contained focal amplifications of receptor tyrosine kinases, in addition to TP53 mutations and RTK-RAS activation [7].

Table 1. Molecular classification of gastric adenocarcinoma based on cancer genome atlas with characteristic features of each subtype

Classification of the Cancer genome Atlas	Defining characteristics
EBV+	Mutations in *PIK3CA, ARID1A, TP53* genes
	CDKN2A inhibition
	PD-L1/L2 gene over-expression
	Hypermethylation of CpG residues
	Prevalence in males
	Over-expression of the signals by neural cells
MSI	*TP53*, *KRAS*, *PIK3A*, *ARID1A* mutations
	Hypermethylation of CpG residues
	MLH1 inhibition
	Prevalence in elderly people
	Prevalence in female
GS	*CDH1*, *RHOA* gene mutations
	Cell adhesion genes excess expression
	CLDN18-ARHGAP fusion
	Diagnosed prevalently in younger patients
	Diffuse histology
CIN	RTK-*RAS* gene activation
	Aneuploidy
	Mutations in *TP53*
	More often in the gastro-esophageal junction and cardia
	intestinal histology

In 2015, the Asian Cancer Research Group (ACRG) proposed a new classification system related to various genomic changes, disease progression and prognosis [10]. Four molecular subtypes were identified based on genome-wide sequencing, profiling of gene expression and the number of their copies, as well as targeted gene sequencing:

(1) Microsatellite unstable (MSI),

(2) with signs of epithelial-mesenchymal transition (MSS/EMT),

(3) Microsatellite stable with TP53 mutation (MSS/TP53+),

(4) microsatellite stable with wild-type TP53 (MSS/TP53) [10].

MSI tumors are hypermuted, intestinal type, usually antral, and are diagnosed at clinical stage I/II. MSI tumors had the best prognosis; their recurrence rate after surgical removal of primary GC was the lowest among all four subtypes (22 %). MSS/TP53+ tumors were associated with EBV infection and also had a good prognosis. MSS/EMT tumors appeared at a younger age, were mainly diagnosed at clinical stage III/IV and had a diffuse histological type according to Loren. The MSS/EMT subtype had the worst prognosis and the highest recurrence rate (63 %), with relapses localized mainly in the abdominal cavity [10]. In one of the studies, the RS samples were divided into two clusters according to the frequency of mutations in the genes – with a normal frequency (cluster 1) and with a high frequency of mutations (cluster 2). Cluster 1 was further divided into two subgroups, C1 and C2. The first subgroup (C1) had mutations in the TP53, XIRP2 and APC genes and was associated with a significantly better outcome than C2. And C2 was associated with mutations in the genes ARID1A, CDH1, PIK3CA, ERBB2 and RHOA (Table 2) [10].

Table 2. Molecular classification of gastric adenocarcinoma based on the Asian Cancer Research Group with characteristic features of each subtype

Classification of the Asian Cancer Research Group	Defining characteristics
MSI	Primary histology of intestinal type
	Predominantly in the antrum
	A large number of mutations in genes
	High rate of relapses and metastases confined to the liver
	Worse overall survival, higher stage at diagnosis
MSS /EMT	Worse overall survival, higher stage at diagnosis
	Young age
	Primarily diffuse histology
	Highest relapse rate, peritoneal spread
	Lowest mutation load
MSS / *TP53 +*	Second best overall survival
	The highest percentage among EBV1 related tumors
MSS / *TP53 -*	Higher rate of recurrence and metastases confined to the liver

2. Molecular profile of sporadic malignant tumors of the stomach.

The molecular characterization of GC continues to evolve. Many molecular classifications have been proposed and various molecular subtypes have been identified [9]. An important role in this was played by the study of the gene copy index.

It is known that the genes of various receptor tyrosine kinases (RTK), such as the human epidermal growth factor receptor (*EGF*), *EGFR1*, mesenchymal epithelial transition factor (MET) and GF2 fibroblast receptor (FGFR2) are amplified in GC [10; 11; 14; 15]. According to GI-screen (a nationwide cancer genome screening project), changes in gene copy are often detected: *ERBB2* (11.3 %), *CCNEI* (11.1 %), *KRAS* (3.7 %), *FGFR2* (3.3 %), *ZNF217* (3.3 %), MYC (2.7 %), *CCND1* (2.3 %) and *CDK6* (2.1 %) [16].

A change in the copy Number Variation (CNV) is a type of genetic polymorphism, the result of which may be a decrease or increase in the number of copies of a certain gene (which is often observed in various oncopathologies), and, consequently, a reduced or increased expression of the gene product – protein or non-coding RNA [17].

A lot of works by Russian authors have been devoted to the study of changes in the copyicity of genes in gastric cancer. In 2014–2015, the National Medical Research Centre for Oncology received data indicating the important role of changes in the copyicity of the genes *BAX*, *CASP3*, *CASP8*, *OCT4*, *C–MYC*, *SOX2*, *BCL2*, *NANOG*, *CASP9*, *NFKB1*, *HV2*, *ACTB*, *MKI67*, *IL-10*, *GSTP1* and *P53* in the malignancy of gastric tissues. It was found that the change in the copyicity of these genes is specific for cancer of a certain histological type, and also depends on the stage of differentiation of tumor cells and metastasis [18–23]. The obtained data formed the basis of the "Method of differential diagnosis of gastric cancer of various histological types" (Patent for invention No. 2613139. Date of state registration 03/15/2017), "Method for predicting the development of metastases in patients with gastric cancer" (Patent No. 2016122160 dated 06/03/2016), "Method for predicting the development of metastases to regional lymph nodes in patients with gastric adenocarcinoma" (Patent No. (19) RU(11)2661600(13) C1 dated 07/17/2018) and "Test systems for predicting the development of metastases in patients with gastric cancer" based on the determination of the number of copies of HV2 mtDNA (Patent No. 2683571 dated 03/29/2019).

Currently, the understanding of the molecular aspects of GC is improving thanks to studies using next-generation sequencing (NGS), which provide a high-performance method for the systematic detection of genetic changes in GC. By doing NGS Li-Chang et al. mutations of several driver genes were shown, including; *TP53*, *PIK3CA*, *CTNNB1*, *CDH1*, *SMAD4* and *KRAS* [24]. It was found that some of the tumor suppressor genes (TSG), such as APC, CDH1, CDH4, THBS1 and UCHL1, are inactivated by hypermethylation [25]. It has been shown that 59 % of RS have a mutation in chromatin remodeling genes such as *ARID1A*, *PBRM1* and *SETD2*. New mutated driver genes *MUC6*, *CTNN2A* and *GLI3* were found as a result of genome-wide sequencing [26; 27]. It was also found that genes involved in cell adhesion and chromosome organization demonstrate frequent mutations in patients with gastric adenocarcinoma, which confirms the presence of 30 driver mutations in primary tissues and lymph node tissues. Primary tumors show more mutations than metastatic tumors, but surprisingly, the researchers did not find any metastatic specific mutations. Several loci on chromosome 17q12 have been identified that are often amplified in GC: PPPIRIB-STARD3-T-CAP-PNMT, PERLD1-ERBB2-MAC14832-GRB7 [28]. In addition, two genes, CDKN2A and *CDKN2B*, located on chromosome 9p21, showed a decrease in the number of copies (CN = 0.8 ~ 1.32). These two genes encode proteins that perform a very important function – they inhibit cyclin-dependent kinases CDK4 and CDK6, and control cell proliferation, preventing entry into the S phase of the cell cycle, so their inactivation can lead to uncontrolled cell growth [28].

2.1 Genetic changes in gastric cancer.

Gene mutations in GC are divided into three categories:

1) Over-frequent drivers, demonstrate a high recurrence rate (> 5–10 %) in several tumors.

2) Rare drivers, mutate in the range of 1–10 %, but still contribute to the pathogenesis of the disease.

3) Mutations of the passenger/witness type arise as a consequence of the main mutational processes, but do not functionally contribute to oncogenesis [29].

Currently, the importance of mutations in the *RTK*/*RAS*/*MAPK* signaling pathway, frequent mutations in the *ERBB3* gene and *NRG1*/*ERBB4* ligand genes in GC has been established. With the help of NGS, the importance of changes in the *ARID1A* and *RHOA* genes in GC was revealed. *ARID1A*, as is known, encodes components of the chromatin remodeling complex and participates in the regulation of cell proliferation and the cell cycle, is mutated in 10–15 % of rye. *ARID1A* mutations are usually inactivating. The consequences of mutation in both *ARID1A* and RHOA are different. *ARID1A* mutations are distributed across the gene, whereas RHOA mutations are localized in the hot spot of the N-terminal region (Ty42, Arg5 and Gly17). It is assumed that *ARID1A* modulates the downstream transmission of Rho signals.

Mutations in *RHOA* can confer resistance to anoikis (a form of programmed cell death that occurs after the separation of cells from a solid substrate). From a clinical point of view, the detection of *RHOA* mutations provides a concrete pathway for the development of new targeted therapeutic approaches for diffuse type of GC, traditionally associated with an extremely poor prognosis [29].

Next, we will consider in detail changes in tumor suppressor genes, oncogenes, genes regulating the cell cycle, apoptosis and cell adhesion in GC.

1) Tumor suppressor genes (TSG). TSG (tumor suppressor genes) usually perform a protective role in preventing malignant cell transformation by repairing DNA, inhibiting cell proliferation, and initiating programmed cell death (apoptosis). TSGs are involved in the regulation of a number of cellular functions, including cell adhesion, intercellular interaction, cytoplasmic signal transmission and nuclear transcription [30]. Over the past decades, there has been a rapid increase in the number of TSG members who have been identified in connection with a wide range of hereditary and non-hereditary human oncological diseases. A better understanding of the TSG expression pattern in GC may allow the identification of specific biomarkers that can be used for early diagnosis and the development of targeted treatment. Overexpression of the P53 gene and decreased expression of the *PTEN*, *CDH1* (E-cadherin), *SMAD4*, *MGMT*, and *CD82* genes are largely associated with poor prognosis in malignant gastric tumors [30].

2) Oncogenes. Oncogenes are genes whose normal activity promotes cell proliferation. Oncogenes can be divided into five classes: secreted GF; cell surface receptors; components of intracellular signal transmission systems; DNA-binding nuclear proteins; components of a network of cyclins, CDK and kinase inhibitors that regulate the course of the cell cycle [31].

Oncogenes have the ability to turn normal cells into malignant ones. These genes make patients more predisposed or susceptible to cancer by altering or disrupting several mechanisms [31]:

(1) the production of nuclear transcription factors (TF) that control cell growth (e.g., *MYC*),

(2) signaling within cells (e.g., *RAS*),

(3) interactions of GFs and their receptors (e.g. *HER*/*NEU*).

Mutations transform proto-oncogenes into oncogenes through several processes such as amplification, translocation, and point mutation. Oncogenes are activated in many ways: by amplification, by point mutation and the formation of chimeric gene products. Consider the changes in some oncogenes.

The RAS gene is the first identified human oncogene, which is associated with the development of 20 % of all human malignancies. This gene encodes a protein that binds guanine nucleotides and performs various functions in the transmission of a mitogenic signal. And the activity of the protein itself is controlled by the GTP or GDP binding states (active – GTP-bound and inactive – GDP-bound).

The C-myc gene is another oncogene located on chromosome 8 encoding a nuclear phosphoprotein that acts as a transcription factor whose main function is to regulate the transcription of target genes by induction and suppression of expression [32]. It is also involved in the modulation of proliferation, differentiation and angiogenesis, as well as DNA repair and apoptosis [32]. Overexpression of *C-myc* is found in more than 40 % of gastric tumors and is associated with poor patient survival. It was found that in benign gastric lesions, including chronic atrophic gastritis, gastric ulcer and *H. pylori* infection, high expression of the *C-myc* gene is also observed [32].

The PRR11 gene was identified in 2013 as a new important regulator of the progression and oncogenesis of GC. Switching off *PRR11* in several gastric cell lines inhibited the rate of proliferation, migration of cancer cells, formation of cell colonies and

tumor growth *in vivo* experiments [33]. The results showed that mRNA and *PRR11* protein are activated in the tissues of the GC compared to the normal gastric mucosa. The expression of the PPR11 gene is associated with aggressive cancer phenotypes, including tumors with an increased degree of invasion, increased tumor differentiation and late-stage disease [33].

3) Regulators of the cell cycle. Cyclins are proteins that control the passage of key control points in the cell cycle by binding and activating specific cyclin–dependent kinases (CDKs). The transition from the G1-S phase is regulated by the activity of cyclin D, cyclin E, cyclin A and their catalytic partners, such as CDK 2, 4 and 6. The G2/M transition is regulated by cyclin-associated B-type kinase. Cyclin-CDK complexes stimulate cell cycle progression, and CDKI (CDK inhibitors) cause cell cycle arrest by suppressing CDK activity [34]. Moreover, unregulated expression of these molecules associated with the cell cycle leads to uncontrolled proliferation and malignant transformation of the cell [34]. Cell cycle control is regulated by D-type cyclins, which are most often mutated in tumor cells. There is increasing evidence that gastric carcinogenesis is associated with abnormalities in the expression of cyclins and other genes associated with the cell cycle [34].

4) Apoptosis regulatory genes. Initially, apoptosis was described by its morphological characteristics, including cell shrinking, membrane swelling, chromatin condensation and nuclear fragmentation [35]. The realization that apoptosis is a gene-driven program has had profound implications for understanding the biology of development and tissue homeostasis, it implies that the number of cells can be regulated by factors affecting cell survival, as well as those that control proliferation and differentiation. Moreover, the genetic basis of apoptosis implies that cell death, like any other program of metabolism or development, can be disrupted by mutation. In fact, it is now believed that defects in the pathways of apoptosis contribute to a number of human diseases, from neurodegenerative disorders to malignant neoplasms [35]. What triggers apoptosis during tumor development? Various factors are important. Extracellular factors include depletion of growth factors, hypoxia, radiation, and loss of cell-matrix interaction. Internal imbalance can also cause apoptosis, including DNA damage, telomere disruption, and inadequate proliferative signals caused by oncogenic mutations.

Cloning and characterization of the *Bcl-2* oncogene have established the importance of apoptosis in tumor development. *Bcl-2* was first identified at the chromosomal break point t (14; 18) in the human leukemia cell line [36]. To date, at least 15 *Bcl-2* family member proteins have been identified in mammalian cells, including proteins that promote apoptosis and those that prevent it [36]. In the gastric mucosa of patients with GC, compared with subjects with superficial gastritis, there is a decrease in the expression of the GKN1 protein and its mRNA [37]. GKN1 maintains the integrity of the gastric mucosa, protects it from the action of gastric juice and enzymes, as well as from mechanical damage, bacteria or foreign antigens [38]. It has been shown that GKN1 inhibits the growth of tumor cells and reduces the number of cell colonies, stopping the G2/M cell cycle instead of inducing apoptosis [39].

5) Genes are regulators of cell adhesion. Classical cadherins are transmembrane adhesion molecules containing five calcium-dependent domains that provide homotypic interactions, and cytoplasmic contact that binds to a number of effectors for transmitting physical and biochemical signals to the cell.

The names of cadherins were originally based on the type of cells in which their expression was first described, but now the generally accepted nomenclature defines classical cadherins as *CDH1* (E-cadherin), *CDH2* (N-cadherin), *CDH3* (P-cadherin), *CDH4* (R-cadherin) and *CDH15* (M-cadherin) [40]. The key role of E-cadherin during normal epithelial function is the function of a tumor suppressor. Mutations inactivating E-cadherin during RJ deletion inside the reading frame caused by the omission of exons 7 or 9, or random mutations of the reading frame shift.

The expression of E-cadherin is mainly limited to epithelial cells, whereas cells of neural or mesenchymal origin usually express N-cadherin. Epithelial cells differ phenotypically from mesenchymal cells; from an oncological point of view, the latter are more mobile and migrate. "Cadherin switching" (epithelial-mesenchymal transition, EMT) in cancer is defined as the absence of E-cadherin expression and N-cadherin expression [41], which induces or increases the metastatic ability of the tumor cell.

During EMT, type I cadherin (epithelial cadherin, E-cadherin encoded by the *CDH1* gene on human

chromosome 16q22.1), which supports key intracellular binding structures such as desmosomes and claudins, switches to neural cadherin (N-cadherin encoded by the *CDH2* gene), which is predominantly expressed among mesenchymal cells [42]. Reduction of E-cadherin with an immunoglobulin-like domain on the cell surface (capable of uniting neighboring cells) and an intracellular region (binds α- and β-catenin to the actin cytoskeleton) plays a crucial role in EMT, changing the components of intercellular adhesion and regulating various signaling pathways [43].

In GC, the expression of E-cadherin is suppressed by increased expression of aquaporin 3 (AQP3), thereby activating EMT. The *PI3K*/*AKT*/*SNAIL* signaling pathway is also involved in the induction of EMT in GC [44]. Caveolin-1 is modulated by HSP90 and functions as an important EMT regulator in GC. Insulin-like IGF-I induces EMT by increasing levels of Zeb2, which depends on the PI3K/Akt signaling pathway in GC cells [45].

GC is one of the typical malignant neoplasms associated with oxidative stress [46]. Hypoxia is also a significant inducer of EMT in gastric cancer. Under hypoxic conditions, the expression of E-cadherin decreases, and the expression of N-cadherin, vimentin, Snail, Sox2, Oct4, and Bmi1 increases, indicating that the hypoxic microenvironment induces EMT, accompanied by cytoskeletal remodeling [47]. Recent data indicate that EMT is a key factor in the progression of GC and plays a fundamental role in the early stages of invasion, metastasis and recurrence of GC [47].

2.1.1. Loss of heterozygosity (LOH).

This is a genetic phenomenon often observed with tumor suppressor genes in cancer. Since the human karyotype is diploid, mutation of one allele of the tumor suppressor gene is not enough to cause cancer. In heterozygous individuals, the wild-type allele provides a functional phenotype. However, when a "second strike" occurs, for example, due to improper chromosome segregation, this individual (or cell) may lose its "heterozygosity", which leads to a complete tumor phenotype. Karaman et al. [48] found a significant correlation between the prevalence of 17p (*TP53*) LOH and precancerous gastric lesion, indicating that the loss of TP53 may be an early event of gastric carcinogenesis [48].

Recent studies have shown that, although *PTEN* mutations in GC are rare, LOH of this gene is more common. Byun et al. (2003) found a decrease in the expression of PTEN and LOH to 47 % in 5 GC cell lines and 36 % of GC tissue samples [49]. The LOH level was significantly higher in the late stages than in the early stages of GC; it was also significantly higher in low-differentiated than in high- and medium-differentiated GC. This suggests that complete functional inactivation of *PTEN* does not necessarily cause gastric carcinogenesis, the loss of one allele is sufficient [49].

Malignant gastric tumors are characterized by high LOH frequencies in chromosomal regions 1p, 2q, 3p, 4p, 5q, 6p, 7p, 7q, 8p, 9p, 11q, 12q, 13q, 14q, 17p, 18q, 21q and 22q [50]. LOH at these sites leads to the loss of fragments/whole genes (tumor suppressor genes, cell cycle regulators and DNA repair).

2.1.2. Microsatellite instability.

In hereditary (most cases) and sporadic GC, another type of genomic instability, MSI (microsatellite instability), was also detected [51]. In patients with gastric cancer with the MSI phenotype, there is a high frequency of DNA replication errors leading to insertions/deletions of nucleotides in microsatellite repeats in tumor tissues [51]. These errors are detected and corrected by the MMR (repair of unpaired bases) protein complex. The development of the MSI phenotype in gastric cancer is usually associated with the inactivation or loss of MMR genes (for example, *MLH1* or *MSH2*), which leads to additional genetic anomalies (for example, inactivation of tumor suppressor genes and LOH) [51; 52].

MMR disruption can occur:

(1) as a result of mutational inactivation of one or two MMR genes

(2) as a result of epigenetic inactivation of MMR (CIMP) genes [51].

The MSI-type of GC is mainly associated with epigenetic disorders in MMR genes [52; 53], which leads to multiple mutations in other loci regulating cell growth (*TGF-β.RII*, *IGFIIR*, *RIZ*, *TCF4* and *DP2*), apoptosis (*BAX*, *BCL10*, *FAS*, *CASPASE5* and *APAF1*) and DNA repair (*hMSH6*, *hMSH3*, *MED1*, *RAD50*, *BLM*, *ATR* and *MRE11*) [54]. These changes further contribute to genetic instability and enhance the development of a malignant phenotype [54]. The genomes of gastric tumor cells with MSI are characterized by the presence of multiple mutations at many loci [55]. A high incidence of MSI in GC (MSI-H GC) is more

likely to occur with antral localization, with intestinal type, with expansive type and with seropositivity to *H. pylori* and correlates with a lower prevalence of lymph node metastasis [55]. MSI is a promising tool for identifying patients with genetic instability and patients with precancerous lesions [54; 52].

2.2. Epigenetic disorders.

Epigenetic disorders include changes in the transcriptional activity of genes, the regulation of which is not associated with a violation of the native DNA sequence [52; 56]. DNA methylation and histone modifications are usually studied as epigenetic events. Currently, the term epigenetics has been expanded to include inherited and transient/reversible changes in gene expression that are not accompanied by a change in the DNA sequence. A comprehensive understanding of various biological activities, such as DNA methylation, chromatin structure, transcriptional activity and histone modification, contributed to the development of epigenetics. The two main epigenetic modifications are DNA methylation and chromatin remodeling. DNA methylation is a chemical change in nucleosides that most often occurs in the cytosine portion of CpG dinucleotides. Chromatin remodeling occurs through histone modifications (mainly at the N-terminal tails), which ultimately affect the interaction of DNA with the chromatin-modifying protein. Both DNA methylation and histone modifications are associated with suppression of critical TSG and activation of oncogenes involved in cancer development [56].

2.2.1. Hypermethylation.

DNA methylation is a reversible chemical modification of cytosine in the CpG islands of the promoter sequence, catalyzed by a family of DNA methyltransferases. DNA methylation does not change the genetic information, but changes the "reading" from DNA and can lead to gene inactivation [56]. In general, methylation of CpG islands results in gene silencing. Methylated CpG islands also recruit histone deacetylases (HDACs) and other factors involved in transcriptional repression [56]. TSG inactivation via hypermethylation of CpG islands in promoter regions is an important event in carcinogenesis [56]. Hypermethylation of the p16 INK4a promoter was found in gastric carcinoma. Hypermethylation of *CDKN2A* may contribute to the malignant transformation of premalignant gastric lesions. *DAPK* hypermethylation is observed in intestinal, diffuse, and mixed types of gastric cancer and correlates with the presence of lymph node metastases, late stage, and poor survival [57]. Epigenetic silencing of the *XAF1* gene by aberrant promoter methylation has been reported in gastric cancer [57]. Caspase-1, a member of the cysteine protease family, exhibits a loss of expression in 19.3 % of gastric carcinomas [57], with the expression level being reversed when the cell line is treated with 5-aza-2'-deoxycytidine and/or trichostatin.

Hypomethylation of certain genes also contributes to gastric carcinogenesis. Initially, global genome hypomethylation was thought to be an exceptional event in the development of cancer [57]. Loss of methylation in cancer is mainly due to hypomethylation of repetitive DNA sequences. During the development of a neoplasm, the degree of hypomethylation of genomic DNA increases as the lesion passes from a benign disease to a metastatic one [57]. DNA demethylation can promote mitotic recombination, leading to deletions, translocations, and chromosomal instability [56]. Demethylation of MAGE, synuclein-γ (SNCG), and cyclin D2 has been described in gastric carcinoma [57].

In parallel with global hypomethylation, hypermethylation of CpG islands also has a silencing effect on miRNAs. MicroRNAs are short, 18–22 nucleotides, non-coding RNAs that regulate many cellular functions, including cell proliferation, apoptosis, and differentiation, by suppressing specific target genes through translational repression or mRNA degradation [58].

2.2.2. Histone modification.

In a normal cell, a precise balance maintains the nucleosomal DNA in either active/acetylated or inactive/deacetylated form. This adequate balance is controlled by acetylating enzymes (histone acetyltransferases) and deacetylating enzymes (HDACs). The modification involves methylation of the arginine and lysine residues of the histones. This methylation is catalyzed by histone methyltransferase and this process is involved in the regulation of a wide range of gene activity and chromatin structures. In general, lysine methylation at H3K9, H3K27, and H4K20 is associated with the suppression of gene transcription, while methylation at H3K4, H3K36, and H3K79 is associated with gene activation [59].

3. Features of the molecular profile of hereditary gastric cancer.

While the vast majority of gastric cancer cases are sporadic, familial aggregation occurs in about 10 % of cases, and of these, only 1–3 % are clearly hereditary. Hereditary gastric cancer includes syndromes such as hereditary diffuse gastric cancer, gastric adenocarcinoma and proximal gastric polyposis (GAPPS) and familial intestinal gastric cancer (FIGC). Gastric cancer has also been identified as part of other hereditary cancer syndromes such as hereditary nonpolyposis colorectal cancer, Li-Fraumeni syndrome, familial adenomatous polyposis, and Peutz-Jeghers syndrome [60].

Hereditary diffuse gastric cancer (HDGC) is one of the most genetically characterized forms of hereditary gastric cancer. HDGC is mainly associated with heterozygous *CDH1* (E-cadherin) mutations, including frameshift, nonsense and missense mutations, and large rearrangements [60]. A pathogenic mutation in *CDH1* increases the risk of developing diffuse gastric cancer at the age of 80 years to 70 % [60]. The histopathology of HDGC is comparable to sporadic diffuse gastric cancer, although the presence of typical precancerous lesions, *in situ* or *pagetoid* signet cells, is specific for CDH1-associated HDGC.

CONCLUSION

GC is a collection of various genetic and epigenetic changes, and its molecular landscape is extremely complex. Improvement in our understanding of the genetics of gastric cancer has accelerated significantly over the past decades, allowing us to redefine the definition of disease at the molecular level. These results may lead to the identification of high-risk groups and ultimately to improved treatment outcomes. The TGCA and ACRG classifications have opened the door to a complete understanding of the complex molecular landscape of gastric cancer. Studies of the genomic and epigenomic profile provide a better understanding of the molecular basis of gastric cancer. In this review, the characterization and classification of gastric cancer at the genetic and epigenetic levels confirms that this disease is highly heterogeneous. Clinicians should use the information gained from these studies to both develop and test potential markers and new targeted therapeutic approaches.

References

1. Kit OI, Gevorkyan YUA, Frantsiyants EM, Dashkov AV, Soldatkina NV, Ilchenko SA, et al. Results of chemotherapy with ozonized media in complex treatment sick of resectable gastric cancer. Modern Problems of Science and Education. 2012;(6):172. (In Russ.). EDN: TODMQF

2. Fujino Y, Tamakoshi A, Ohno Y, Mizoue T, Tokui N, Yoshimura T, et al. Prospective study of educational background and stomach cancer in Japan. Prev Med. 2002 Aug;35(2):121–127. https://doi.org/10.1006/pmed.2002.1066

3. Kit OI, Samoylenko NS, Frantsiyants EM, Soldatkina NV, Sagakyants AB, Kharagezov DA, et al. Gastric cancer: modern directions in basic research. Modern problems of science and education. 2019;(4):136. (In Russ.). EDN: QRPQPE

4. Nagini S. Carcinoma of the stomach: A review of epidemiology, pathogenesis, molecular genetics and chemoprevention. World J Gastrointest Oncol. 2012 Jul 15;4(7):156–169. https://doi.org/10.4251/wjgo.v4.i7.156

5. Marqués-Lespier JM, González-Pons M, Cruz-Correa M. Current Perspectives on Gastric Cancer. Gastroenterol Clin North Am. 2016 Sep;45(3):413–428. https://doi.org/10.1016/j.gtc.2016.04.002

6. The Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014 Sep 11;513(7517):202–209. https://doi.org/10.1038/nature13480

7. Cristescu R, Lee J, Nebozhyn M, Kim KM, Ting JC, Wong SS, et al. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. Nat Med. 2015 May;21(5):449–456. https://doi.org/10.1038/nm.3850

8. Li X, Wu WKK, Xing R, Wong SH, Liu Y, Fang X, et al. Distinct Subtypes of Gastric Cancer Defined by Molecular Characterization Include Novel Mutational Signatures with Prognostic Capability. Cancer Res. 2016 Apr 1;76(7):1724–1732. https://doi.org/10.1158/0008-5472.CAN-15-2443

9. Geddert H, zur Hausen A, Gabbert HE, Sarbia M. EBV-infection in cardiac and non-cardiac gastric adenocarcinomas is associated with promoter methylation of p16, p14 and APC, but not hMLH1. Cell Oncol (Dordr). 2011 Jun;34(3):209–214. https://doi.org/10.1007/s13402-011-0028-6

10. Deng N, Goh LK, Wang H, Das K, Tao J, Tan IB, et al. A comprehensive survey of genomic alterations in gastric cancer reveals systematic patterns of molecular exclusivity and co-occurrence among distinct therapeutic targets. Gut. 2012 May;61(5):673–684. https://doi.org/10.1136/gutjnl-2011-301839
11. Kwak EL, Ahronian LG, Siravegna G, Mussolin B, Borger DR, Godfrey JT, et al. Molecular Heterogeneity and Receptor Coamplification Drive Resistance to Targeted Therapy in MET-Amplified Esophagogastric Cancer. Cancer Discov. 2015 Dec;5(12):1271–1281. https://doi.org/10.1158/2159-8290.CD-15-0748
12. Shah MA, Khanin R, Tang L, Janjigian YY, Klimstra DS, Gerdes H, et al. Molecular classification of gastric cancer: a new paradigm. Clin Cancer Res. 2011 May 1;17(9):2693–2701. https://doi.org/10.1158/1078-0432.CCR-10-2203
13. Shah MA, Kelsen DP. Gastric cancer: a primer on the epidemiology and biology of the disease and an overview of the medical management of advanced disease. J Natl Compr Canc Netw. 2010 Apr;8(4):437–447. https://doi.org/10.6004/jnccn.2010.0033
14. Kuboki Y, Yamashita S, Niwa T, Ushijima T, Nagatsuma A, Kuwata T, et al. Comprehensive analyses using next-generation sequencing and immunohistochemistry enable precise treatment in advanced gastric cancer. Ann Oncol. 2016 Jan;27(1):127–133. https://doi.org/10.1093/annonc/mdv508
15. Nagatsuma AK, Aizawa M, Kuwata T, Doi T, Ohtsu A, Fujii H, et al. Expression profiles of HER2, EGFR, MET and FGFR2 in a large cohort of patients with gastric adenocarcinoma. Gastric Cancer. 2015 Apr;18(2):227–238. https://doi.org/10.1007/s10120-014-0360-4
16. Yuki S, Shitara K, Kadowaki S, Minashi K, Takeno A, Hara H, et al. The nationwide cancer genome screening project in Japan SCRUM-Japan GI-SCREEN: Efficient identification of cancer genome alterations in advanced gastric cancer (GC). JCO. 2018 May 20;36(15_suppl):4050–4050. https://doi.org/10.1200/JCO.2018.36.15_suppl.4050
17. Kutilin DS, Airapetova TG, Anistratov PA, Pyltsin SP, Leiman IA, Karnaukhov NS, et al. Copy Number Variation in Tumor Cells and Extracellular DNA in Patients with Lung Adenocarcinoma. Bull Exp Biol Med. 2019 Oct;167(6):771–778. https://doi.org/10.1007/s10517-019-04620-y
18. Kit OI, Vodolazhsky DI, Kutilin DS, Gudueva EN. Changes in the number of copies of genetic loci in gastric cancer. Mol Biol (Mosk). 2015;49(4):658–666. https://doi.org/10.7868/S0026898415040096
19. Kit OI, Vodolazhsky DI, Gevorkyan YuA, Kutilin DS, Maleyko ML, Dvadnenko KV, et al. Changes in the relative copy number of oct4 and sox2 genes in malignancy of gastric tissue. Fundamental Studies. 2014;(10-4):671–674. (In Russ.). EDN: SVQVMB
20. Kit OI, Vodolazhsky DI, Kutilin DS, Maleyko ML, Dvadnenko KV, Enin YaS, et al. The copyicity of the GSTP1, NFKB1 and HV2 genes of mitochondrial DNA in some histological types of gastric cancer. The successes of modern natural science. 2015;(1-6):918–921. (In Russ.). EDN: TSNHUH
21. Kit OI, Vodolazhsky DI, Kutilin DS, Maleyko ML, Dvadnenko KV, Enin YaS, et al. Relative copyicity of apoptosis – regulating genes as an indicator of malignancy of stomach tissues. The successes of modern natural science. 2015;(3):40–45. (In Russ.). EDN: UDZVXH
22. Kutilin DS, Vodolazhsky DI, Trifanov VS, Przhedetsky YuV. Relative copy number variation of genes in malignant gastric tissues. Journal of Clinical Oncology. 2015 May 20;33:e15033–e15033. https://doi.org/10.1200/jco.2015.33.15_suppl.e15033
23. Kit OI, Kutilin DS, Vodolazhsky DI, Maleyko ML, Dvadnenko KV, Antonets AV, et al. Changes in the copyicity of genes during malignancy of stomach tissues. Eurasian Journal of Oncology. 2014;3(3):436–437. (In Russ.). EDN: TJNRQM
24. Li-Chang HH, Kasaian K, Ng Y, Lum A, Kong E, Lim H, et al. Retrospective review using targeted deep sequencing reveals mutational differences between gastroesophageal junction and gastric carcinomas. BMC Cancer. 2015 Feb 6;15:32. https://doi.org/10.1186/s12885-015-1021-7
25. Hu XT, He C. Recent progress in the study of methylated tumor suppressor genes in gastric cancer. Chin J Cancer. 2013 Jan;32(1):31–41. https://doi.org/10.5732/cjc.011.10175
26. Wang K, Kan J, Yuen ST, Shi ST, Chu KM, Law S, et al. Exome sequencing identifies frequent mutation of ARID1A in molecular subtypes of gastric cancer. Nat Genet. 2011 Oct 30;43(12):1219–1223. https://doi.org/10.1038/ng.982
27. Wang K, Yuen ST, Xu J, Lee SP, Yan HHN, Shi ST, et al. Whole-genome sequencing and comprehensive molecular profiling identify new driver mutations in gastric cancer. Nat Genet. 2014 Jun;46(6):573–582. https://doi.org/10.1038/ng.2983
28. Katoh M, Katoh M. Evolutionary recombination hotspot around GSDML-GSDM locus is closely linked to the oncogenomic recombination hotspot around the PPP1R1B-ERBB2-GRB7 amplicon. Int J Oncol. 2004 Apr;24(4):757–763.
29. Gonzalgo ML, Jones PA. Mutagenic and epigenetic effects of DNA methylation. Mutat Res. 1997 Apr;386(2):107–118. https://doi.org/10.1016/s1383-5742(96)00047-6

30. Lee HS, Lee HK, Kim HS, Yang HK, Kim WH. Tumour suppressor gene expression correlates with gastric cancer prognosis. J Pathol. 2003 May;200(1):39–46. https://doi.org/10.1002/path.1288
31. Wu XX, Li H, Zhao M. Medical Molecular Biology Beijing: Science Press; 2009, 303–304 p.
32. Calcagno DQ, Leal MF, Assumpcao PP, Smith MAC, Burbano RR. MYC and gastric adenocarcinoma carcinogenesis. World J Gastroenterol. 2008 Oct 21;14(39):5962–5968. https://doi.org/10.3748/wjg.14.5962
33. Song Z, Liu W, Xiao Y, Zhang M, Luo Y, Yuan W, et al. PRR11 Is a Prognostic Marker and Potential Oncogene in Patients with Gastric Cancer. PLoS One. 2015;10(8):e0128943. https://doi.org/10.1371/journal.pone.0128943
34. Kishimoto I, Mitomi H, Ohkura Y, Kanazawa H, Fukui N, Watanabe M. Abnormal expression of p16(INK4a), cyclin D1, cyclin-dependent kinase 4 and retinoblastoma protein in gastric carcinomas. J Surg Oncol. 2008 Jul 1;98(1):60–66. https://doi.org/10.1002/jso.21087
35. Kerr JF, Winterford CM, Harmon BV. Apoptosis. Its significance in cancer and cancer therapy. Cancer. 1994 Apr 15;73(8):2013–2026. https://doi.org/10.1002/1097-0142(19940415)73:8<2013::aid-cncr2820730802>3.0.co;2-j
36. Gross A, McDonnell JM, Korsmeyer SJ. BCL-2 family members and the mitochondria in apoptosis. Genes Dev. 1999 Aug 1;13(15):1899–1911. https://doi.org/10.1101/gad.13.15.1899
37. Guo XY, Dong L, Qin B, Jiang J, Shi AM. Decreased expression of gastrokine 1 in gastric mucosa of gastric cancer patients. World J Gastroenterol. 2014 Nov 28;20(44):16702–16706. https://doi.org/10.3748/wjg.v20.i44.16702
38. Mao W, Chen J, Peng TL, Yin XF, Chen LZ, Chen MH. Helicobacter pylori infection and administration of non-steroidal anti-inflammatory drugs down-regulate the expression of gastrokine-1 in gastric mucosa. Turk J Gastroenterol. 2012 Jun;23(3):212–219. https://doi.org/10.4318/tjg.2012.0345
39. Yan GR, Xu SH, Tan ZL, Yin XF, He QY. Proteomics characterization of gastrokine 1-induced growth inhibition of gastric cancer cells. Proteomics. 2011 Sep;11(18):3657–3664. https://doi.org/10.1002/pmic.201100215
40. Shimada S, Mimata A, Sekine M, Mogushi K, Akiyama Y, Fukamachi H, et al. Synergistic tumour suppressor activity of E-cadherin and p53 in a conditional mouse model for metastatic diffuse-type gastric cancer. Gut. 2012 Mar;61(3):344–353. https://doi.org/10.1136/gutjnl-2011-300050
41. Chun N, Ford JM. Genetic testing by cancer site: stomach. Cancer J. 2012;18(4):355–363. https://doi.org/10.1097/PPO.0b013e31826246dc
42. Chen Y, Kingham K, Ford JM, Rosing J, Van Dam J, Jeffrey RB, et al. A prospective study of total gastrectomy for CDH1-positive hereditary diffuse gastric cancer. Ann Surg Oncol. 2011 Sep;18(9):2594–2598. https://doi.org/10.1245/s10434-011-1648-9
43. Van der Post RS, Vogelaar IP, Carneiro F, Guilford P, Huntsman D, Hoogerbrugge N, et al. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. J Med Genet. 2015 Jun;52(6):361–374. https://doi.org/10.1136/jmedgenet-2015-103094
44. Chen J, Wang T, Zhou YC, Gao F, Zhang ZH, Xu H, et al. Aquaporin 3 promotes epithelial-mesenchymal transition in gastric cancer. J Exp Clin Cancer Res. 2014 May 3;33(1):38. https://doi.org/10.1186/1756-9966-33-38
45. Kannan A, Krishnan A, Ali M, Subramaniam S, Halagowder D, Sivasithamparam ND. Caveolin-1 promotes gastric cancer progression by up-regulating epithelial to mesenchymal transition by crosstalk of signalling mechanisms under hypoxic condition. Eur J Cancer. 2014 Jan;50(1):204–215. https://doi.org/10.1016/j.ejca.2013.08.016
46. Liu WF, Ji SR, Sun JJ, Zhang Y, Liu ZY, Liang AB, et al. CD146 expression correlates with epithelial-mesenchymal transition markers and a poor prognosis in gastric cancer. Int J Mol Sci. 2012;13(5):6399–6406. https://doi.org/10.3390/ijms13056399
47. Chiba T, Marusawa H, Ushijima T. Inflammation-associated cancer development in digestive organs: mechanisms and roles for genetic and epigenetic modulation. Gastroenterology. 2012 Sep;143(3):550–563. https://doi.org/10.1053/j.gastro.2012.07.009
48. Karaman A, Kabalar ME, Binici DN, Oztürk C, Pirim I. Genetic alterations in gastric precancerous lesions. Genet Couns. 2010;21(4):439–450.
49. Byun DS, Cho K, Ryu BK, Lee MG, Park JI, Chae KS, et al. Frequent monoallelic deletion of PTEN and its reciprocal associatio-in with PIK3CA amplification in gastric carcinoma. Int J Cancer. 2003 Apr 10;104(3):318–327. https://doi.org/10.1002/ijc.10962
50. Rumpel CA, Powell SM, Moskaluk CA. Mapping of genetic deletions on the long arm of chromosome 4 in human esophageal adenocarcinomas. Am J Pathol. 1999 May;154(5):1329–1334. https://doi.org/10.1016/S0002-9440(10)65386-2
51. Ottini L, Falchetti M, Lupi R, Rizzolo P, Agnese V, Colucci G, et al. Patterns of genomic instability in gastric cancer: clinical implications and perspectives. Ann Oncol. 2006 Jun;17 Suppl 7:vii97–102. https://doi.org/10.1093/annonc/mdl960

52. Skierucha M, Milne AN, Offerhaus GJA, Polkowski WP, Maciejewski R, Sitarz R. Molecular alterations in gastric cancer with special reference to the early-onset subtype. World J Gastroenterol. 2016 Feb 28;22(8):2460–2474. https://doi.org/10.3748/wjg.v22.i8.2460
53. Benusiglio PR, Malka D, Rouleau E, De Pauw A, Buecher B, Noguès C, et al. CDH1 germline mutations and the hereditary diffuse gastric and lobular breast cancer syndrome: a multicentre study. J Med Genet. 2013 Jul;50(7):486–489. https://doi.org/10.1136/jmedgenet-2012-101472
54. Nobili S, Bruno L, Landini I, Napoli C, Bechi P, Tonelli F, et al. Genomic and genetic alterations influence the progression of gastric cancer. World J Gastroenterol. 2011 Jan 21;17(3):290–299. https://doi.org/10.3748/wjg.v17.i3.290
55. Simpson AJ, Caballero OL, Pena SD. Microsatellite instability as a tool for the classification of gastric cancer. Trends Mol Med. 2001 Feb;7(2):76–80. https://doi.org/10.1016/s1471-4914(01)01916-5
56. Hirst M, Marra MA. Epigenetics and human disease. Int J Biochem Cell Biol. 2009 Jan;41(1):136–146. https://doi.org/10.1016/j.biocel.2008.09.011
57. Chan AWH, Chan MWY, Lee TL, Ng EKW, Leung WK, Lau JYW, et al. Promoter hypermethylation of Death-associated protein-kinase gene associated with advance stage gastric cancer. Oncol Rep. 2005 May;13(5):937–941.
58. Dimitriadi TA, Burtsev DV, Dzhenkova EA, Kutilin DS. Differential expression of microRNAs and their target genes in cervical intraepithelial neoplasias of varying severity. Advances in Molecular Oncology. 2020;7(2):47–61. (In Russ.). https://doi.org/10.17650/2313-805X-2020-7-2-47-61, EDN: NNFZRI
59. Mulero-Navarro S, Esteller M. Epigenetic biomarkers for human cancer: the time is now. Crit Rev Oncol Hematol. 2008 Oct;68(1):1–11. https://doi.org/10.1016/j.critrevonc.2008.03.001
60. Oliveira C, Pinheiro H, Figueiredo J, Seruca R, Carneiro F. Familial gastric cancer: genetic susceptibility, pathology, and implications for management. Lancet Oncol. 2015 Feb;16(2):e60–70. https://doi.org/10.1016/S1470-2045(14)71016-2

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