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Clinical, epidemiological and genetic features of colorectal cancer

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Introduction. The incidence of colorectal cancer for 2020 was 1 931 590 cases, which is 10 % of all new cases of incidence, and mortality from colorectal cancer ranks 2nd among cancer deaths, it is 935 173 cases (9.4 %) according to Globocan 2020. According to statistics of the Kazakh Research Institute of Oncology and Radiology for 2019–2020 colorectal cancer ranks 3rd in the structure of oncopathology, both in terms of morbidity and mortality. The occurrence of colorectal cancer is associated with an interaction that occurs at several levels between hereditary, environmental and individual factors. Understanding the molecular basis is important because it can identify factors that initiate development, maintain progression, and determine response or resistance to anticancer agents.
Aim. To describe the main genetic mutations and their impact on treatment prognosis, diagnosis and course of colorectal cancer.
Materials and methods. A systematic literature review of scientific databases Cochrane, PubMEd, MedLine, Elsevier was carried out. For the main search, the main search terms are formulated: colorectal cancer, mutations in colorectal cancer, molecular genetic studies in colorectal cancer, mutation of the *KRAS* gene. Also, a time range was set no later than 5 years, i. e. all articles published from 2017 to the current year.
Results. The main molecular changes in colorectal cancer are Chromosome instability, microsatellite instability, and abnormal DNA methylation. Suppressor genes, such as *Ras*, *EGFR* (*Erb-B1*), *Erb-B2*, *TGF-alpha,* and *TGF-beta 1*, are also of great importance.
Conclusion. Research that contributes to the understanding of the molecular basis of colorectal cancer helps in the early diagnosis of familial cancer, treatment prognosis and a personalized approach to patient treatment.

Keywords: colorectal cancer, *KRAS* gene, targeted therapy

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Клинико-эпидемиологические и генетические особенности колоректального рака

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Введение. Заболеваемость колоректальным раком за 2020 г. составила 1 931 590 случаев, что составляет 10 % всех новых случаев заболеваемости раком, а смертность от КРР, по данным Globocan 2020, занимает 2-е место среди всех случаев смерти от рака – 935 173 случая (9,4 %). По данным статистики КазИОР на 2019–2020 гг., колоректальный рак занимает 3-е место в структуре онкопатологии как по заболеваемости, так и по смертности. Возникновение колоректального рака связано с взаимодействиями между наследственными, экологическими и индивидуальными факторами на разных уровнях. Важным является понимание его молекулярной основы, поскольку оно может выявить факторы, которые инициируют развитие, поддерживают прогрессирование и определяют реакцию на противораковые агенты или устойчивость к ним.
Цель. Описать основные генетические мутации и их влияние на прогноз лечения, диагностику и течение колоректального рака.
Материалы и методы. Проведен систематический обзор литературы научных баз данных Cochrane, PubMed, MedLine, Elsevier. Сформулированы основные поисковые термины: колоректальный рак, мутации при колоректальном раке,

молекулярно-генетические исследования при колоректальном раке, мутация гена *KRAS*. Временной диапазон поиска составлял не более 5 лет, т. е. в анализ вошли все статьи, опубликованные с 2017 г. по настоящее время.
Результаты. Основными молекулярными изменениями при колоректальном раке являются хромосомная нестабильность, микросателлитная нестабильность и аномальное метилирование ДНК. Гены-супрессоры, такие как *Ras, EGFR (Erb-B1), Erb-B2, TGF-альфа* и *TGF-бета1*, тоже имеют большое значение.
Заключение. Исследования, которые способствуют пониманию молекулярной основы колоректального рака, помогают в ранней диагностике семейного рака, прогнозе лечения и индивидуальном подходе к лечению пациентов.

Ключевые слова: колоректальный рак, ген *KRAS*, таргетная терапия

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Introduction

The human genome has been sequenced, making it feasible to pinpoint genetic alterations in cancer with previously unheard-of precision. The order of human protein-encoding genes, each of which plays a specific job in the body, was essential for the methodical examination of such modifications [1]. Due to the genetic heterogeneity of colorectal cancer, it is challenging to assess the clinical significance of certain mutations. It has been demonstrated that some people mistakenly think that uncommon mutations in colorectal cancer are actually extremely prevalent and may be linked to the development of other malignancies [2, 3]. These findings have paved the way for new directions in tumor biology research and established new targets for diagnostic and therapeutic approaches [4]. Genome stability is required to keep cells healthy. Due to the acquisition of additional mutations linked to the tumor phenotype and the loss of genomic stability, colorectal cancer progresses. Multiple genetic alterations that affect genes that regulate cell maturation and proliferation have been discovered over the past 15 years, pointing to a genetic component to cancer.

Materials and methods

A systematic literature review of scientific databases Cochrane, PubMEd, MedLine, Elsevier was carried out. For the main search, the main search terms are formulated: colorectal cancer, mutations in colorectal cancer, molecular genetic studies in colorectal cancer, mutation of the *KRAS* gene. Also, a time range was set no later than 5 years, i. e. all articles published from 2017 to the current year. Further, the range of keywords entered was expanded. 7620 articles were found. After removing duplicate articles, clinical studies, conference abstracts and descriptions of isolated clinical cases, 151 articles remained. After reading all the articles, clinical recommendations for physicians were also excluded from the review, as well as articles by the same authors with duplicate information. In total, 35 articles were used for this review.

Results

Chromosome instability, microsatellite instability, and abnormal DNA methylation are the three kinds of genomic instability that have been identified in colorectal cancer.

Chromosomal precariousness

This can be the foremost predominant sort of genomic instability, which causes various changes to chromosome shape and number [5]. Adenomatous colon polyposis (APC), a gene implicated within the WNT/-catenin signaling pathway, is the target of loss-of-function changes in around 85 % of CRCs, which comes about within the creation of histologically anomalous tomb foci [6]. Chromosomal insecurity causes silencer qualities like APC, P53, and SMAD4 to lose their wild alleles, which frequently halt the advancement of a dangerous phenotype [7]. In spite of the reality that the majority of colorectal tumors appear chromosomal instability (CIN), exceptionally few qualities have been found to actuate this phenotype and don't result in any shared component supporting how these malignancies function. Barber et al. In arrange to distinguish somatic mutations in qualities with CIN potential in colorectal cancer methodically, 102 human homologues from 96 known qualities were sequenced. In 132 cases of colorectal cancer, there were 11 somatic mutations in five diverse qualities. It was afterward built up that these changes result in chromosomal flimsiness and anomalies in chromatin coupling in human cells [8]. Chromosomal instability-induced atomic forms are dependable for tumor initiation, advancement, and dissemination. Natural factors, hereditary, and obtained substantial changes of the colonic epithelium all play a part in this process.

Microsatellite instability

A study of DNA base mismatches in colorectal cancer patients uncovered that the repair-related genes were dormant. DNA mismatch repair qualities are the title given to these qualities (mismatch repairs, MMRs). Inactivation can be procured or acquired (hereditary non-polyposis cancer). The event of so-called microsatellite instability is associated to the loss of DNA mismatch repair work. Changes within the amount of mono-, bi-, tri-, and tetraploid nucleotides that are regularly repeated in genomic DNA (microsatellites) or in protein translation are alluded to as microsatellite precariousness, or MSI [9]. The MLH 1, MSH 2, MSH 6, and PMS 2 qualities are transformed, which comes about in Lynch disorder and raised hazard of developing cancer [10]. The larger part of these

malignancies commonly influence elderly individuals and are found within the proximal colon. Tumor suppressor genes are as often as possible concurrently inactivated in these patients [11]. More than a million patients are analyzed with colorectal cancer each year, and 3 % of these patients have a Lynch syndrome, which puts them at an increased chance of developing a hereditary nonpolyposis colorectal cancer (HNPCC). When colorectal cancer develops 36 months after a negative colonoscopy, genetic instability enormously impacts the chance of cancer improvement in these individuals [12]. The usual age of cancer onset is 45, and localization is near to the splenic flexure in 70–80 % of cases. In this manner, a colonoscopy is prompted for these individuals annually between the ages of 25 and 40, or every two years a long time after that. Subtotal colectomy could be essential due to the critical probability of synchronous and/or metachronous RCC in these patients. Prophylactic hysterectomy is additionally exhorted since 40–60 % of female patients are at chance of developing endometrial cancer [9, 10, 12]. In Figure 1 you'll see a graph of danger of typical epithelium with chromosomal and microsatellite insecurity in colorectal cancer. Freely of the pathway, a defect within the APC/beta-catenin axis marks the onset of the transformation process from typical epithelia to early adenoma. A defect along the *KRAS/BRAF* pathway is required to advance to middle adenoma. Loss or quieting of diverse tumor silencer qualities at last decides the movement to late adenoma and after that to carcinoma. Within the CIn pathway, the move to the carcinoma arrange is stamped by the inactivation of the tumor-suppressor quality *TP53*, whose item is urgent in controlling DNA repair, cell cycle capture, senescence, apoptosis and digestion system in reaction to a assortment of stretch signals. In this manner, its misfortune contributes to drug resistance and to the engendering of harmed DNA to girl cells, expanding the mutational stack. *TP53* transformation or misfortune of it has been detailed in 50–75 % of CRC cases and it is related with the movement and result of scattered CRC [13–15].

Aberrant DNA methylation

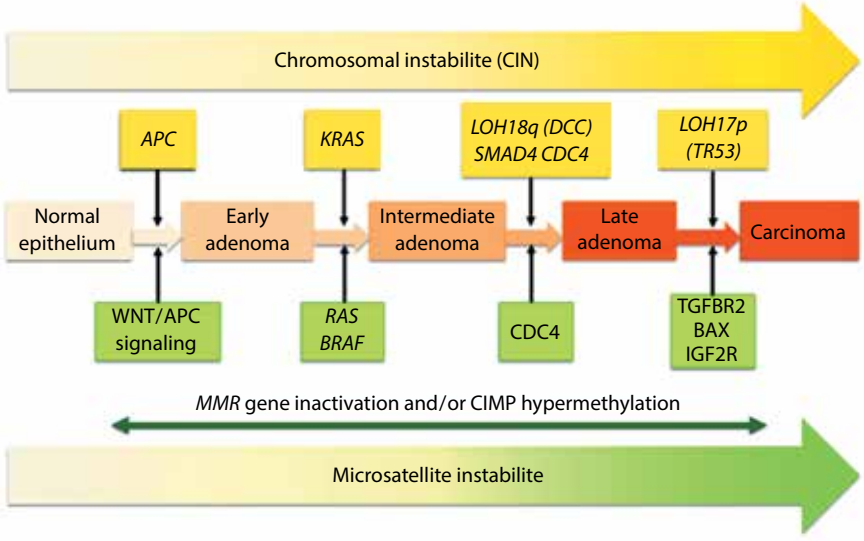
In mammalian CpG sequences, cytosine methylation at the fifth position of the pyrimidine ring could be a visit alter. CpG islands are unconstrained in typical cells, be that as it may sporadic CpG dinucleotides are methylation all through the leftover portion of the genome. With maturing, the methylation profile continuously changes, coming about in methylation of CpG islands and a misfortune of by and large methylation; this alter is especially highly noticeable amid oncogenesis. In colorectal cancer, there's diminished cytosine methylation as well as unusual significant methylation of CpG islands connected to particular promoters. In scattered colorectal cancer with satellite instability, somatic epigenetic inactivation hinders the expression of MLH 1 [16].

Tumor progression

One of the most accurate indicators of the stage of cancer is still the appearance and progression of colorectal cancer. The acquisition of mutations that promote the tumor phenotype by choosing variants with better cancer cell survival, growth, and colony invasion is the basis for the sequence by which an adenoma transforms into a carcinoma [17].

Tumor suppressor genes and oncogenes associated with colorectal cancer

Oncogenes are genes whose expression is intimately linked to the development of cancer cells from normal cells. Tumor suppressor genes: These are genes that produce proteins necessary for preserving regular cell activity. *Ras*, *EGFR* (*Erb-B1*), *Erb-B2*, *TGF-alpha*, and *TGF-beta1* are oncogenes having a known association with colorectal



Schematic representation of CRC progression along the three different pathways according to the Fearon and Vogelstein model (adapted from [13])

cancer. *APC, p53, p27, MSI, LOH 18q*, loss of the 5q allele, and DNA hypermethylation are examples of suppressor genes [1].

***Ras* gene mutation**

40–50 % of all instances of colorectal cancer have been reported to contain Ras gene mutations [16, 17]. Ras family oncogenes produce proteins that bind guanine nucleotides and exhibit GTPase activity on the inner surface of the plasma membrane. Ras oncogenes actively participate in the cell cycle, which is regarded as an early step in the genesis of colorectal cancers [18], to create trigger signals for cell proliferation. *KRAS* mutations have been investigated to discover how they affect how chemotherapy treatment outcomes can be predicted. In contrast to patient groups without this mutation, patients with colorectal tumors and *KRAS* mutations showed worse responses to adjuvant 5-FU therapy [19, 20].

APC acts as a brake for beta-catenin; APC gene signaling is improperly activated [21, 22]. The most frequent mutation in colorectal cancer is a loss of function in the APC gene. Familial adenomatous polyposis (FAP), an autosomal dominant disorder in which hundreds to thousands of adenomatous colonic polyps form, expresses the Wnt gene in the absence of APC, leading to an almost 100 % lifetime chance of developing colorectal cancer in the absence of partial colectomy [1].

Gene *TP 53*

It is a tumor suppressor gene, and because solid malignancies frequently cause damage to it, it is regarded as the "guardian of the genome". It promotes oncogenesis and is found on chromosome 17 and 50 % of sporadic colorectal tumors [20]. A study of homozygous cell lines for the *p53* mutation revealed a high level of resistance to radiation therapy and some types of chemotherapy, including 5-FU, in regards to the role of *p53* status in response to therapy [23].

There are also other changes in the biology of tumor cells.

Aberrant regulation of signaling by prostaglandins

Colorectal cancer is characterized by the activation of growth factors. Prostaglandin signaling is a critical stage in the growth of adenomas. An enzyme called COX-2 is responsible for the prostaglandin E2 production linked to colorectal cancer. COX levels were raised in roughly two thirds of colorectal malignancies [24]. Non-steroidal anti-inflammatory drugs, or NSAIDs, have been shown in clinical studies to inhibit COX-2, which stops the growth of new adenomas [24–27].

Epidermal growth factor receptor (EGFR)

The soluble protein tyrosine kinase known as the epidermal growth factor receptor, commonly referred to as EGFR, ErbB-1, or HER 1, controls the numbness of intestinal cells. The cell surface protein EGFR is present and activated by binding to several ligands, such as epidermal growth factor. Malignancies, mostly lung and colorectal cancers, have been linked to genetic abnormalities that result in EGFR overexpression. According to clinical evidence, anti-EGFR treatment is ineffective in treating colorectal cancer with this mutation [28, 29].

Vascular growth factor (VEGF)

The vascular growth factor, or VEGF, is the cause of angiogenesis and the development of vascular tumors. This factor has a tight connection to the deadly course of colorectal cancer. Compared to patients receiving standard therapy, patients treated with VEGF antibodies (bevacizumab) lived longer [30].

Molecular diagnosis of colorectal cancer

The creation of molecular diagnostic techniques to identify cancer at an early stage represents a significant application of colorectal cancer genetics data to medical practice. With a sensitivity of 46–77 % for early-stage cancer detection (72 % in stage I/II, 43.7 % in stage III/IV), methods have been developed to identify specific mutations in colorectal cancer and aberrant DNA methylation in DNA isolated from the feces of patients with colorectal cancer or advanced adenomas. The *APC* gene, *p53*, *KRAS*, *BAT-26* (a marker of microsatellite instability), and a marker of aberrant apoptosis are among the alterations that are typically found using multitarget panels [31]. Studies of monozygotic twins and genetic epidemiology have revealed that 35–100 % of adenomas and colorectal malignancies occur in people with a hereditary susceptibility. Additionally, some families have a syndrome resembling HNPCC without a repair gene mutation or a DNA mismatch being present [32, 33].

Discussion

The development of new therapeutic approaches for the treatment of colorectal cancer brought on by genomic instability is now possible because to knowledge of the molecular foundation. The *KRAS* gene mutation is being suppressed at the moment. One of the earliest studies found that blocking the immune checkpoint axis, such as by targeting PD-L1 (programmed cell death ligand 1) or its PD-1 receptor, led to a remarkable remission of a variety of cancers [34]. However, due to their low immunogenicity, the majority of CRC patients, with the exception of those who have high levels of microsatellite instability (MSI) or deficient mismatch repair (dMMR), cannot benefit from immunotherapy [35]. Additionally, numerous immune-related pathways, including the interferon- (IFN-) pathway, are downregulated in *KRAS*-mutant CRC [36]. These findings may therefore point to a more immunosuppressive microenvironment in *KRAS*-mutant CRC, which significantly restricts the use of immune checkpoint inhibitors as monotherapy in this subset of CRC patients [34].

The next step was the development of adaptive cell therapy. Neoantigens derived from *KRAS* variants are considered "foreign" by the immune system and can be recognized by antigen-specific T cells, making them a potential target for immunotherapy. In a patient with a metastatic $KRAS^{G12D}$ mutant CRC, CD8+ T cells with human leukocyte antigen (HLA)-C*08:02-restricted T cell receptors (TCR) specifically recognize the $KRAS^{G12D}$ mutant. After expansion *ex vivo*, patients were injected with tumor infiltrating lymphocytes (TIL) containing approximately 75 % $KRAS^{G12D}$-specific CD8+ T cells. Subsequently, all seven metastatic lung lesions regressed and the patient experienced a partial response (PR) lasting 9 months [37]. This approach is currently being used in two clinical trials to treat patients with advanced $KRAS^{G12D}$ or $KRAS^{G12V}$ mutant solid tumors, including CRC (NCT03745326, NCT03190941).

At the moment, studies are also underway in Kazakhstan to suppress the mutation of the *KRAS* gene by inducing oxidative stress.

Conclusions

Research that advances understanding of colorectal cancer at the molecular level has provided data used for genetic tests of familial forms, identification of prognostic markers to select patients susceptible to certain forms of therapy, and development of molecular diagnostic tests to detect early non-invasive cancer.

New biological pathways have been identified that have led to the discovery and improvement of new therapeutic agents. Understanding the signals that dictate the metasta_tic phenotype will provide the necessary information for the development of new drugs to prevent and control the progression and spread of the disease.

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A.M. Kukanova: contribution to the concept, scientific design, execution of the claimed scientific research, interpretation of the claimed scientific research, creation of a scientific article;
A.T. Bekisheva: scientific design, interpretation of the claimed scientific research, creation of a scientific article;
A.K. Makishev: contribution to the concept, creation of a scientific article.

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