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REVIEW

MOLECULAR GENETIC CLASSIFICATION OF COLORECTAL CANCER SUBTYPES: CURRENT STATE OF THE PROBLEM

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ABSTRACT

Today, colorectal cancer (CRC) is the third most common cancer and therefore an urgent problem of oncology. Despite all modern diagnostic capabilities, the rates of advanced cases are growing steadily. CRC was proven to be a result of a phased dysplastic change in the colon mucosa, molecular genetic changes that determine the molecular biology of the tumor, its properties, morphology, disease prognosis and response to therapy. The following mechanisms of CRC tumor progression are distinguished: chromosomal instability, microsatellite instability, "methylator" phenotype, and serrated pathway of adenocarcinoma development. Application of molecular and diagnostic methods has become a promising direction in recent years. This led to the development of a molecular genetic classification with 4 CRC subtypes differing not only in their molecular genetic characteristics, but also in clinical course and response to therapy.

Keywords:
colorectal cancer, molecular biology, molecular and genetic subtypes, pattern-recognition receptors, Toll-like receptors, lymphogenous metastasis, surgical treatment.

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ОБЗОР

МОЛЕКУЛЯРНО-ГЕНЕТИЧЕСКАЯ КЛАССИФИКАЦИЯ ПОДТИПОВ КОЛОРЕКТАЛЬНОГО РАКА: СОВРЕМЕННОЕ СОСТОЯНИЕ ПРОБЛЕМЫ

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РЕЗЮМЕ

На сегодняшний день колоректальный рак (КРР) является актуальной проблемой онкологии, занимая третье место в структуре общей онкологической заболеваемости. Несмотря на все современные диагностические возможности, показатели запущенности неуклонно растут. Доказано, что КРР развивается вследствие поэтапного диспластического изменения слизистой толстой кишки, молекулярно-генетических изменений, которые определяют молекулярную биологию опухоли, её свойства, морфологию, прогноз заболевания и ответ на проводимую терапию. Выделяют следующие механизмы опухолевой прогрессии при КРР: хромосомная нестабильность, микросателлитная нестабильность, «метиляторный» фенотип, зубчатый (serrated) путь развития аденокарцином. В последние годы перспективным направлением стало использование молекулярных методов диагностики. Это привело к разработке молекулярно-генетической классификации, включающей в себя 4 подтипа КРР, которые отличаются между собой не только по молекулярно-генетическим характеристикам, но и по клиническому течению и ответу на проводимую терапию.

Ключевые слова:
колоректальный рак, молекулярная биология, молекулярно-генетические подтипы, паттерн-распознающие рецепторы, толл-подобные рецепторы, лимфогенное метастазирование, хирургическое лечение.

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Over the past decades, colorectal cancer (CRC) remains an urgent problem of oncology both in Russia and abroad, taking the third place in the structure of morbidity, disability and mortality from malignant neoplasms (MN). Every year, more than 1 million new cases of CRC are registered in the world, with approximately the same prevalence in men and women [1]. Among the male population, the incidence rate reaches 11.4 %, ranking third after malignant neoplasms of the trachea, bronchi, lungs (17.8 %), and prostate (14.4 %). Among the female population, this indicator is 11.7 %, ranking third after breast tumors (20.9 %) and skin tumors (14.6 %). In 2015, more than 68 thousand cases of colon cancer were registered in Russia.

Today, it is proven that CRC develops due to a gradual dysplastic change in the colon mucosa, molecular and genetic changes that determine the molecular biology of the tumor, its properties, morphology, disease prognosis and response to therapy [2, 3].

The following mechanisms of tumor progression in CRC are distinguished:

1. Chromosomal instability (90 %), which leads to aneuploidy and aberration of chromosomes. This mechanism is associated with mutations of the tumor suppressor gene APC (the gene for adenomatous polyposis of the colon) and with mutations of other genes-SMAD2 and SMAD4, involved in the intracellular transmission of the TGF-b signal, as well as the KRAS gene. Clinically associated with an unfavorable prognosis [4, 5].
2. Microsatellite instability (20 %) is associated with a violation of DNA repair during replication as a result of mutations in the genes of one of the proteins of the Mismatch repair system (MRS). To date, there are 7 known genes whose mutations lead to microsatellite instability in CRC-MLH1, MLH3, MSH2, MSH3, MSH6, PMS1 and PMS2 [6].
3. The "methylator" phenotype (CpG island methylator phenotype, CIMP) (15 %) is caused by the presence of hypermethylated promoter sites (CpG island), in which inactivation of tumor suppressor genes is observed and, as a rule, mutations in the KRAS, BRAF and TP53 genes are often detected in patients [7, 8].
4. Serrated pathway of adenocarcinoma development: there are 2 molecular pathways for the development of CRC from a serrated polyp. The first pathway is a sequence of toothed polyp cancers resulting from a BRAF mutation, which leads to inactivation of the MMR genes (mismatch repair system – a system of repair of unpaired DNA bases), to low and high levels of microsatellite instability (MSI-H, MSI-L).

The second pathway involves the emergence of a tumor from a traditional serrated adenoma (TSA), leading to a low level of microsatellite instability (MSI-L) or microsatellite-stable (MSS) dentate formations. These tumors contain KRAS mutations [9, 10].

The first attempts to create a CRR classification were made by several groups. But they did not come to a common opinion and this did not lead to the formation of a single classification [11, 12].

Subsequently, international experts, after analyzing 18 different gene expressions in CRC in more than 4,000 samples, came to an agreement and described four molecular subtypes of CRC (copsepsis molecular subtypes, CMS). Approximately 87 % of the 4,151 samples that were analyzed by the six expert groups were subdivided into 4 molecular subtypes (CMS), and the remaining 13 % of the cases remained "unclassified".

Additional data, including mutations, somatic copyicity, methylation status, and biological characteristics, correlate with CRC subtypes [13, 14] (Table 1).

1. CMS1 (MSI, immune, 14 %) develops due to defective repair by microsatellite instability (MSI) and suppression of MLH1 expression, high methylation (CpG-island methylator phenotype, CIMP-high). They are characterized by mutations in the BRAF gene and a low level of somatic copyability. Patients with early-stage CMS1 tumors (with MSI) have a better prognosis compared to patients with microsatellite stability (MSS) of the tumor. CMS1 has a good prognosis when detected before the disease progresses, in particular due to the presence of specific populations of T-lymphocytes and natural killer cells. However, patients with CMS1 tumors, which are most often right-sided, have very poor survival after relapse detection [15].
2. CMS2 (canonical, 37 %) occurs due to the sequential transition of the colon epithelium to adenoma and later to carcinoma, with the activation of the WNT-β catenin and MYC signaling

pathway. CMS2 is more often left-sided (59 %) and is characterized by the highest five-year overall survival at all stages compared to the other subtypes of CRC [14].

3. CMS3 (metabolic, 13 %) has less somatic copyability (SCNAs)and contains more heterogeneous tumors (MSI) than in CMS2 and CMS4. Although mutations in the KRAS gene are present in all molecular subtypes, they are most common in CMS3 (in 68 %) [11, 13, 14]. The metabolic subtype is characterized by a higher frequency of KRAS mutations, which affects the therapy with anti – epidermal growth factor (EGFR) monoclonal antibodies [15-17].
4. CMS4 tumors (mesenchymal, 23 %) show increased expression of genes involved in the epithelial-mesenchymal transition and indicate activation of transforming growth factor-β, with expression of genes involved in complement-related inflammation, matrix remodeling, stromal invasion, and angiogenesis. CMS4 tumors exhibit very low levels of hypermutation, MSS status, and very high levels of somatic copyability. CRC CMS4 is manifested by a mesenchymal phenotype and an inflammatory microenvironment with innate immune cells [13]. Patients with the CMS4 subtype, often diagnosed at late stages, have worse overall survival and worse relapse-free survival than patients in other CRC groups [11, 14, 15].

As can be seen from the above, the molecular subtypes of CRC differ not only in their molecular features, but also in their clinical course and sensitivity to chemo-radiation therapy.

Along with the development of molecular classification, an attempt was made to introduce it into clinical practice. In Sadanandam et al. the relationship between the molecular subtypes of cancer and the possible response to the prescribed treatment was revealed. In patients with a generalized form of the disease, the response rate to FOLFIRI first-line chemotherapy was 71 %. The response to cetuximab therapy was evaluated in a group of 80 patients by the molecular subtype, which was observed in 54 % of patients. Two groups were identified: sensitive and resistant to cetuximab [18].

Research results from Okita et al. they indicate a relationship between the molecular subtype of CRC and the effectiveness of the therapy. More than 193 patients with generalized CRC were divided into subtypes: CMS1 (N = 21), CMS2 (N = 53), CMS3 (N = 69), and CMS4 (N = 50). Then, the effectiveness of irinotecan and oxaliplatin-based chemotherapy, as well as anti-EGFR therapy in specific molecular subtypes, was analyzed. In the analyzed group, longer progression-free survival and overall survival (S) were observed in patients receiving irinotecan as first-line chemotherapy compared to oxaliplatin therapy (p<0.01). The percentage of objective responses was higher in the irinotecan group (for the CMS4 subtype, it was 80 %). The lowest response rate to the therapy was observed in the CMS1 subtype [19].

Table 1. Molecular subtypes of CRC

Characteristics	CMS1 Immune (microsatellite unstable)	CMS2 (canonical)	CMS3 (metabolic rate)	CMS4 (mesenchimal)
Frequency of occurrence	14 %	37 %	13 %	23 %
Molecular characteristics:	Increased MSI gene expression	epithelial differentiation; activation of the WNT and MYC signaling pathway; high somatic copyability	heterogeneous by MSI; metabolic dysregulation; low somatic copyability	TGF-b activation; epithelial-mesenchymal transition; high somatic copyability
BRAF/KRAS mutations' presence	BRAF mutations		KRAS mutations	
Tumor's localisation	Right-sided localisation	Left-sided localisation	Mixed localisation	Left-sided localisatio
Clinical flow, prognosis:	Positive flow	better survival rates after relapse		worst survival after relapse

Conclusions of Marta Frąckowiak et al. they correspond to the results presented by Fontan and Sandals at the ASCO GI conference (2018). In the group of patients with "wild type" RAS, the objective response to anti-EGFR therapy was differentiated depending on the subtype: CMS1-20 %, CMS2-76 %, CMS3-23 %, and CMS4-88 % [20].

It is believed that there is a relationship between the molecular subtypes, the localization of the primary tumor, and the prognosis. In the course of the FIRE-3, CRYSTAL study, it was proved that the localization of the primary tumor in the proximal colon is an unfavorable prognostic factor [21].

A retrospective analysis of data from 728 patients participating in the CALGB/SWOG 80405 study (comparing bevacizumab and cetuximab in combination with first-line chemotherapy for metastatic CRC) showed that patients with left-sided localization have a significantly higher survival rate than patients with right-sided localization. The median OS for left-sided localization was 32.9 months compared to 19.6 months for right-sided localization (p<0.0001). In patients with the "wild" type of KRAS/BRAF treated with cetuximab, OS was greater in left-sided localization than in right-sided localization (40.3 months and 18.4 months, respectively, p=0.003). In the group with the BRAF mutation treated with bevacizumab, the results were more favorable for right-sided localization (23.7 months and 12.0 months, respectively, p=0.035). Of the cases of left-sided tumor location, the majority were subtypes CMS2 and CMS4, and of the cases of right-sided location-CMS1 and CMS3 [22].

Results of the study by Sagawa et al. it was shown that in the group of patients treated with cetuximab, OS was better in patients with left-sided tumors (50.6 months and 10.5 months, p=0.0004) [23].

An additional analysis conducted in the framework of the FIRE-3 project (AIO KRK-0306), which compared the effectiveness of cetuximab and bevacizumab in combination with FOLFIRI first-line chemotherapy, depending on the subtype, noted an association between OS and the CRC subtype and the type of treatment. In the CMS4 group, this relationship was statistically significant, and the median OS for cetuximab and bevacizumab was 41.3 months and 22.3 months, respectively (p=0.016) [24].

The availability of molecular genetic studies currently used in other types of cancer may be a prerequisite for targeted therapy of specific subtypes of CRC. Approximately 3 % of CMS3 and 5 % of CMS4 have high expression of the HER2 receptor protein. In these cases, antibodies against HER2 or tyrosine kinase inhibitors, such as lapatinib and neratinib, may be active. Attempts to use immunotherapy with checkpoint inhibitors (in particular, pembrolizumab and nivolumab) may be most effective in CMS1 [25].

CONCLUSIONS

The molecular genetic classification of CRC subtypes is of prognostic importance and may influence the selection of optimal treatment. According to the literature analysis, the advantage of bevacizumab in CMS3 and cetuximab in CS4 and CS2 was noted. The benefits of irinotecan therapy were mainly noted in patients with CS3 and CS4, and in CMS2 it is less effective.

The optimal treatment for CMS 1 is a combination of oxaliplatin with bevacizumab, CMS 2-cetuximab in combination with oxaliplatin or irinotecan, CMS3-oxaliplatin with cetuximab, and CMS4-irinotecan with cetuximab.

The molecular genetic classification of CRC subtypes is important for predicting the clinical course of the disease and the adequate selection of drug therapy regimens, and today requires further study.

Authors contribution:

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