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REVIEW

Immunologic aspects of colorectal cancer progression

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ABSTRACT

Colorectal cancer remains in the leading positions in the structures of morbidity and mortality among both sexes. A large number of studies are aimed to reveal new biomarkers targeted at both early diagnosis and improving the effectiveness of drug therapy. Colorectal carcinoma (CC) is heterogeneous in its morphological, molecular and immunological aspects and is a heterogeneous disease. The existing molecular genetic classifications and biomarkers capable of predicting the effectiveness of therapy aren't optimal enough. New prognostic markers would make it possible to identify a subgroup of patients with a high risk of tumor recurrence, for whom enhanced monitoring and diagnostic monitoring should be established, as well as the selection of highly effective methods in the treatment of colorectal cancer. It has been established that some immune cells in the tumor microenvironment are able to stimulate the development of disease progression. Cytokines and chemokines in the tumor microenvironment stimulate the development of metastases, and their serum levels reflect the current inflammatory response in the tumor tissue. The identification and analysis of immune markers involved in the processes of metastasis and the mechanisms of progression remains an important task of modern medicine. The purpose of the study was to analyze modern ideas about the importance of the immunological microenvironment in the progression of colorectal cancer. The effect of molecular heterogeneity of the tumor on the development of metastases, as well as on resistance to ongoing antitumor therapy. The review reflects the immunological characteristics of CC, including in the context of molecular biological subtypes. It describes the involvement of cells of the immune system (lymphocytes, macrophages) and their products (cytokines, chemokines) in the progression of colorectal cancer, including in the processes of neoangiogenesis, as well as the relationship of the T- and B-cell composition of the tumor microenvironment on the course of the disease. The review also shows the immunogenomic stratification of CC, which can be used to predict the response to immunotherapy for colorectal cancer.

Keywords: colorectal cancer, molecular genetic subtypes, tumor-associated macrophages, cytokines, chemokines

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ОБЗОР

Иммунологические аспекты прогрессирования колоректального рака

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РЕЗЮМЕ

Колоректальный рак в структурах заболеваемости и смертности среди обоих полов по-прежнему остается на лидирующих позициях. Большое количество исследований нацелено на получение новых биомаркеров, направленных как на раннюю диагностику, так и на улучшение эффективности лекарственной терапии. Колоректальная карцинома неоднородна по своим морфологическим, молекулярным и иммунологическим аспектам и представляет собой гетерогенное заболевание. Существующие молекулярно-генетические классификации и биомаркеры, способные прогнозировать эффективность терапии, неоптимальны. Новые прогностические маркеры позволили бы идентифицировать подгруппу пациентов с высоким риском рецидива опухоли, за которыми должен быть установлен усиленный контроль и диагностическое наблюдение, а также подбор высокоэффективных методов терапии колоректального рака. Установлено, что некоторые иммунные клетки в микроокружении опухоли способны стимулировать развитие прогрессирования заболевания. Цитокины и хемокины в микроокружении опухоли стимулируют развитие метастазов, а их уровни в сыворотке крови отражают текущую воспалительную реакцию в опухолевой ткани. Выявление и анализ иммунных маркеров, участвующих в процессах метастазирования и механизмах прогрессирования, остается важной задачей современной медицины. Целью работы явился анализ современных представлений о значении иммунологического микроокружения, в прогрессировании колоректального рака. Влияние молекулярной гетерогенности опухоли на развитие метастазов, а также на резистентность к проводимой противоопухолевой терапии. В обзоре отражены иммунологические характеристики колоректальной карциномы, в том числе в контексте молекулярно-биологических подтипов. Описывается участие клеток иммунной системы (лимфоцитов, макрофагов) и их продуктов (цитокинов, хемокинов) в прогрессировании колоректального рака, в том числе в процессах неоангиогенеза, а также взаимосвязи Т- и В-клеточного состава микроокружения опухоли на течение заболевания. Также в обзоре отображена иммуногеномная стратификация колоректальной карциномы, которая может быть применена для прогнозирования ответа на иммунотерапию колоректального рака.

Ключевые слова: колоректальный рак, молекулярно-генетические подтипы, опухоль-ассоциированные макрофаги, цитокины, хемокины

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Colorectal cancer (CC) occupies a leading position in the structures of morbidity and mortality [1–6]. Despite the successes achieved in recent years in the diagnosis and therapy of cancer (targeted therapy, immunotherapy), the life expectancy of patients with this disease does not increase significantly. The reason for this may be the progression of the disease, as well as the development of resistance to therapy [7–9]. Molecular mechanisms of progression play a key role in metastasis [10].

To date, two classifications of colorectal cancer have been proposed reflecting the molecular genetic characteristics of the tumor [11–13]. In 2012, Cancer Genome presented a molecular analysis of colorectal carcinoma using genome-wide sequencing technology [11]. During the study, CC was divided into 2 groups, the first included tumors with a high mutational load or having microsatellite instability (MSI), the second group consisted of tumors with a low mutational load or having microsatellite stability (MSS).

However, the criteria used in this classification turned out to be insufficient. During the data analysis, new biomarkers of colorectal carcinoma were identified, which formed the basis of the new classification. In 2016, Guinney et al., considering new data from the Consensus Molecular Subtype (CMS) consortium, the CC was divided into 4 subtypes (CMS1-CMS4) (Table. 1) [12]. The first subtype of CMS1 was characterized by the presence of MSI, the phenotype of methylation of CpG islands (CIMP), the presence of a mutation in the BRAF gene and was called MSI – immune. The second subtype of CMS2 is canonical, characterized by the presence of a high level of somatic copies (SCNA), activation of MYC and the WNT signaling pathway. CMS3 or the third subtype is metabolic, it can include tumors with a mixed MSI status, low levels of SCNA and CIMP, and the presence of a mutation in the KRAS gene. The fourth CMS4 is mesenchymal, with the presence of high levels of SCNA, stromal infiltration, activation of TGFß and angiogenesis. At the same time, the authors not only classify colorectal carcinoma into certain subtypes, considering their molecular and genetic characteristics, but also give a prognosis regarding patient survival [12].

For example, patients with CMS1 are less likely to survive a relapse of the disease than patients with other subtypes, and patients with CMS4 have the worst prognosis for overall relapse-free survival compared to other subtypes.

However, this classification is not enough, since the cause of the progression CC is also associated with the molecular heterogeneity of the tumor, which is part of the evolutionary and temporal process [14, 15]. Heterogeneity is also regarded as the cause of resistance to ongoing antitumor therapy (Fig. 1).

Tumor heterogeneity is often caused by a change in the RAS signaling pathway, which, in turn, is a component of the RAS-MEK-ERK cascade. Combinations of drugs, primarily anti-EGFR, are used to overcome resistance to EGFR inhibitors [16]. But even this approach provides only a slight improvement in the

Table 1. Molecular subtypes of colorectal cancer [12]

CMS1 Immune	CMS2 (canonic)	CMS3 (metabolic)	CMS4 (mesenchymal)
14 %	37 %	13 %	23 %
Increased expression of MSI genes; High level of epithelial differentiation; High mutational activity	Epithelial differentiation; High somatic copyability	Mixed status by MSI; Low level of epithelial differentiation; Low somatic copyability	Epithelial-mesenchymal transition; High somatic copyability
BRAF mutations		KRAS mutations	
Immune infiltration	Activation of the WNT and MYC signaling pathway	Metabolic dysregulation	Activation of TGF-b; Stromal infiltration; Angiogenesis

Note: MSI – microsatellite instability; TGF – a transformative growth factor

survival rate of patients with metastatic CC. In order to find alternative ways to overcome resistance to ongoing therapy, as well as markers of drug efficacy, tumor genotyping based on blood samples is carried out, the effect of the immune system on tumor tissue is studied, including the search for new biomarkers.

In the classification proposed by Guinney et al. [12] the immunological characteristics of CC are partially affected, in particular, the CMS1 subtype is characterized by the presence of infiltration of tumor stroma by immune cells. In addition, this subtype carries the ability to have a high level of mutational activity with the formation of neoantigens (resulting from somatic mutation of a tumor cell) that stimulate an antitumor immune response. This explains the high immunogenicity of the tumor and its infiltration by immune cells, especially activated lymphocytes – CD8+ T cells, CD4+ memory T cells, Th1, activated dendritic cells, NK cells and M1 macrophages. It is also known that CMS1 subtype tumors are able to express genes with subsequent release into the intercellular space of CXCL9 and CXCL10 involved in T cell chemotaxis, as well as IL-15, IFNy, CXCL13, etc. [17]. In addition, it has been shown that the expression of molecules of immune control points (PD-1, PD-L1, CTLA-4) of tumors of this subtype allows them to evade immune surveillance [18], although it suggests the effectiveness of immunotherapy with inhibitors of these control points in the treatment of such tumors.

The CMS2 subtype is characterized by low levels of lymphocytes, monocytes and myeloid cells, and, consequently, a weak antitumor response. In addition, tumors of the "canonical" subtype practically do not express PD-1, PD-L1 [12].

Tumors belonging to the CMS3 subtype, as well as tumors with the CMS2 subtype, are characterized by an immunologically depleted cellular composition. However, unlike the previous subgroup, tumor cells carry PD-L1 on their surface, and there are Th17, "naive" B and T cells in their microenvironment [12, 19, 20]. Such a microenvironment, apparently, cannot provide an effective antitumor response, since Th17 has pro-oncogenic properties, and "naive" lymphocytes do not have functional activity.

The fourth subgroup of colorectal carcinomas is characterized by a high level of infiltrating lymphocytes and macrophages, with the M2 phenotype, while the number of M1 is reduced. A high content of regulatory T cells (T-reg) is also found, and the concentration of CD8+, CD4+ T cells is reduced. The presence of TGF-β, CXCL12 and VEGF contributes to the maintenance of the inflammatory environment and, as a result, causes the development and progression of the tumor [12, 13, 19, 20].

A number of authors believe that, knowing the immunological, molecular and genetic component of various subtypes of colorectal cancer, it is possible to predict the response to antitumor treatment [13, 19, 20].

Currently, immunological markers are being ac-

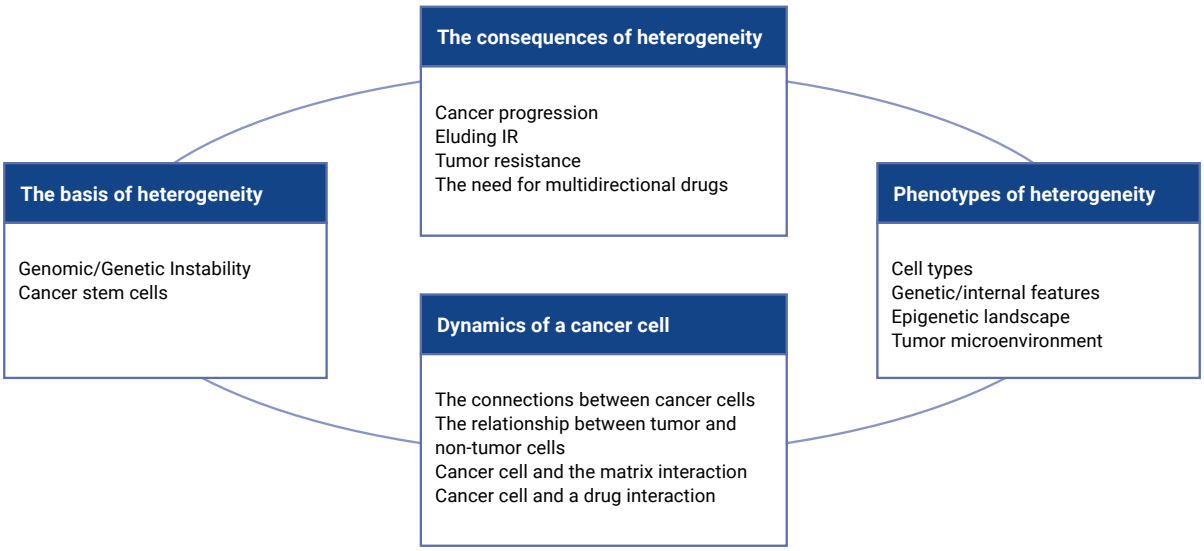

Fig. 1. Principles of evolutionary and temporal heterogeneity of cancer [14]

tively investigated as prognostic indicators of progression [19–21], in particular, not only the type of immune cells infiltrating the tumor, which are part of the tumor microenvironment, but also the density of infiltration by these cells. At the same time, the approach to the study can be complex or multiplex and single-factor – the study of specific biomarkers. The relevance of the study of immunological markers is due to the involvement of immune cells in the progression of cancer [22, 23]. Cytokines and chemokines both form an inflammatory environment and activate antitumor immunity. For example, IL-12, IL-15, IL-18, IFN-γ stimulate the response to tumor antigens, and promote tumor progression – IL-6, IL-17A, IL-22, IL-23; affect neoangiogenesis, growth and survival of tumor cells – TNF-α, EGFR ligands, TGF-β, IL-6 [24]. Tumor-associated macrophages (TAM) play a key role in the development of both an inflammatory response and in the processes of progression and are also a source of a wide range of cytokines.

Macrophages are the most common immune cells in the microenvironment of colorectal carcinoma. Macrophages are able not only to influence the processes of inflammation in the microenvironment, but also participate in carcinogenesis and tumor progression. In addition, they can modulate the response to standard treatment methods (chemotherapy, radiation therapy, therapy with drugs suppressing neoangiogenesis), leading to the development of resistance and subsequent tumor progression [25–28]. For example, the expression of IL-6 and TNF-α macrophages promotes the transmission of signals by tumor cells and the development of resistance to antitumor therapy. The invasion of neoplastic cells is facilitated by the targeted release of cytokines/chemokines, such as EGF, CCCL18, IL-4. Macrophages participate in the processes of neoangiogenesis by stimulating the expression of VEGF-A by endothelial cells, which in turn leads to the formation of an abnormal vascular network, which is characterized by excessive branching, a large number of capillaries, lack of vascular tightness, thereby changing hemodynamics in tumor tissue, making it difficult to deliver drugs. Macrophages are also able to influence cytotoxic lymphocytes by modulating the immune response. The inhibition of the cytotoxic T lymphocyte response can occur through the expression of B7 family ligands or by the release of IL-10 through CCL22 with suppression of IL-12 production by dendritic cells.

The immunosuppressive role is played by regulatory T cells (T-reg) due to the production of anti-inflammatory cytokines IL-10 and TGF-β [29]. B-cell infiltration in CC is often observed due to the large representation of these cells in tertiary lymphoid structures that originate from peripheral lymphoid tissue under prolonged exposure to inflammatory

GROUP A		GROUP B		GROUP C		GROUP D	
14 %		26 %		16 %		43 %	
MSI-H	(82 %)	MSS	(86 %)	MSS	(94 %)	MSS	(75 %),
Right side	(82 %)	Left side	(63 %)	Left side	(94 %)	MSI	(25 %)
CIMP high	(68 %)	CIMP negative	(77 %)	CIMP negative	(66 %)	Left side	
BRAF mt	(50 %)	BRAF mt	(4 %)	BRAF mt	(3 %)	CIMP negative	(69 %)
KRAS mt	(18 %)	KRAS mt	(47 %)	KRAS mt	(22 %)	KRAS mt	(49 %),
PI3K mt	(39 %)	TP53 mt	(65 %)	TP53 mt	(62 %)	NRAS mt	(13 %)

Fig. 2. Cluster typing of the immune response (CIRC)

Table 2. Genes of clusters coordinating the immune response [33]

Group	Genes						
Group A	HLA-DQA1	HLA-DQA2	HLA-DRB5	HLA-DMA	PDCD1LG2	ICAM1	CD274
Group B	STAT1	IRF1	IFNG	CTLA4	TBX21	CCL5	LAG-3
Group C	CD247	ICOS	IL18RAP	GNLY	CXCL10	HLA-DPB1	HLA-DPA1
Group D	HLA-DMB	HLA-DRA	HLA-DMA	CD80	HLA-DOA	CD4	HAVCR2

signals mediated by chemokines and cytokines [30]. B cells in the tumor microenvironment along with the T-cell component (cytotoxic CD3+CD4+ and CD3+CD8+ T cells, other subpopulations of T cells) are associated with a favorable prognosis. However, the presence of macrophages in the CC microenvironment stimulates the development of inflammation and, as a result, affects tumor progression [31].

The phenomena occurring in immunocompetent cells of the CC microenvironment may also differ at the molecular genetic level. Thus, Laghi L., et al., in 2020 published a paper aimed at identifying the relationship between the genetic and immune components of colorectal cancer [32]. It is known that tumors with MSI have a large number of tumor infiltrating lymphocytes (TILs), however, tumors with MSS may also have high levels of TILs. A favorable prognosis in CC is associated with a high level of TILs, which in turn can be a biomarker for identifying a cohort of patients with a low probability of disease recurrence and influence the choice of therapy.

The search for biomarkers capable of predicting the effectiveness of therapy in CC continues. Lal N, et al., published a paper on the immunogenomic stratification of colorectal carcinoma used to describe the response to CC immunotherapy [33]. The basis for stratification was cluster typing of the immune response (CIRC) (Fig. 2) [33], which divides patients with CC into four groups depending on the level of expression of a set of genes that do not completely coincide with the molecular genetic subtypes (Table 2).

Stratification links the genetics and immunobiology of CC. At the same time, the expression of immune control points and cytokine/chemokine genes were found to correspond to the expression of some variants of the main histocompatibility complex HLA (Table 2).

Group A is characterized by MSI-H and POLE gene mutations, high mutational load and high immune infiltration, which can be useful when using immune checkpoint inhibitors (ICIs). Whereas in group D and B, mutations in the RAS family genes were present, and these patients were resistant to ICI therapy. Nevertheless, the question remains which of the CC classifications to focus on when predicting the response to, particularly, immunotherapy treatment [34]. The development of new approaches to the stratification of patients with CC continues, as well as the search for new directions to eliminate resistance in the population of patients resistant to existing treatment methods.

CONCLUSION

The tumor microenvironment by immune cells plays one of the key roles in the progression of colorectal cancer and the mechanisms of development of resistance to therapy, which may be significant for a personalized approach to antitumor treatment and the search for predictive markers of the effectiveness of therapy, including immunological ones.

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