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# Molecular and Genetic Parameters of Prognosis and New Strategies for the Treatment of Peritoneal Carcinomatosis in Gastric Cancer

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## ABSTRACT

Despite advances in modern oncology, in Russia, 36% of gastric cancers are detected at an advanced stage, with a one-year mortality rate of 39.6%. One of the most common causes of death from gastric cancer is peritoneal carcinomatosis. Synchronous peritoneal carcinomatosis is diagnosed in 18–26% of cases. Metachronous carcinomatosis occurs in 7–39% of patients 8.5–26 months after the primary tumor is removed. To date, there are no effective treatments for peritoneal carcinomatosis. Tumors accompanied by peritoneal carcinomatosis are often resistant to systemic chemotherapy. Cytoreductive surgeries and intraperitoneal chemotherapy are not always possible or successful for all patients.

This review focuses on analyzing the molecular and genetic mechanisms of peritoneal carcinomatosis in gastric cancer and presents an original hypothesis suggesting that peritoneal carcinomatosis occurs when tumor cells acquire the ability to autonomously exist in a matrix-independent state in the ascitic fluid without undergoing apoptosis (anoeucsis). Using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, 10,025 scientific papers were identified, of which 228 English-language and 323 Russian-language publications met the analysis criteria. Twenty-nine articles (including four Russian-language ones) relevant to the topic of this review were included in the review. It is assumed that the identification of key molecules associated with the matrix-independent existence of tumor cells could serve as the basis for the development of technologies for predicting peritoneal carcinomatosis, as well as for the development of new targeted therapy for metastatic gastric cancer.

**Keywords:** peritoneal carcinomatosis, stomach cancer, molecular and genetic mechanisms, matrix independence, metastasis

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# Молекулярно-генетические параметры прогноза и новые стратегии терапии перитонеального канцероматоза при раке желудка

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**РЕЗЮМЕ**

Несмотря на достижения современной онкологии, в России в 36% случаев рак желудка выявляется в запущенной стадии, при этом летальность в течение года с момента установления диагноза составляет 39,6%. Одной из частых причин летальных исходов при раке желудка является перитонеальный канцероматоз. Синхронный перитонеальный канцероматоз диагностируется в 18–26% случаев. Метахронный канцероматоз после удаления первичной опухоли наблюдается у 7–39% пациентов через 8,5–26 мес после операции. До настоящего времени не существует эффективных методов прогнозирования риска развития и лечения перитонеального канцероматоза. Опухоли, сопровождающиеся перитонеальным канцероматозом, нередко устойчивы к системной химиотерапии. Выполнение циторедуктивных операций и внутрибрюшинной химиотерапии возможно не для всех пациентов и не всегда является успешным.

Обзор посвящен анализу информации, касающейся молекулярно-генетических механизмов развития перитонеального канцероматоза при раке желудка, и содержит оригинальную гипотезу, согласно которой перитонеальный канцероматоз возникает в результате приобретения опухолевыми клетками матрикс-независимости и способности к автономному существованию в асцитической жидкости, не подвергаясь апоптозу (аноикису). С использованием руководства «Предпочтительные элементы отчетности для систематических обзоров и метаанализов» (PRISMA) было выявлено 10 025 научных работ, из которых 228 англоязычных и 323 русскоязычных публикаций соответствовали критериям анализа.

В обзор включено 35 статей (в том числе четыре русскоязычные), соответствующих теме настоящего обзора. Предполагается, что выявление ключевых молекул, ассоциированных с матрикс-независимым существованием опухолевых клеток, могло бы послужить основой для разработки технологий прогнозирования перитонеального канцероматоза, а также для разработки новой таргетной терапии метастатического рака желудка.

**Ключевые слова:** перитонеальный канцероматоз, рак желудка, молекулярно-генетические механизмы, матрикс-независимость, метастазирование

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## INTRODUCTION

Despite advances in modern oncology, in Russia, gastric cancer is detected at an advanced stage in 36% of cases, with one-year mortality rate from the time of diagnosis reaching 39.6% [1]. High mortality rates for gastric cancer are also recorded in global statistics, with the overall survival from the start of treatment being only 5–12 months [2–4].

Peritoneal carcinomatosis is considered as one of the most unfavorable forms of tumor progression with high lethality rates. Synchronous peritoneal carcinomatosis in gastric cancer is diagnosed in 18–26% of cases. The overall survival from the

time of diagnosis in these cases is only 2–9 months. Metachronous carcinomatosis, following the removal of the primary tumor, is observed in 7–39% of patients within 8.5–26 months after surgery, with the median overall survival from the detection of peritoneal recurrence being only 5 months. The success rate of therapy for peritoneal carcinomatosis in cases of its clinical manifestation is extremely low [5–7]. Therefore, the search for factors that can predict the occurrence of peritoneal carcinomatosis prior to its clinical manifestation is highly relevant.

## MATERIALS AND METHODS

A search for original studies on the incidence, diagnosis, lethality, and therapy of peritoneal carcinomatosis in gastric cancer was conducted using the PubMed database and the eLIBRARY.ru scientific electronic library. This review includes original articles published between May 5, 2020 and August 3, 2025 in English and Russian. The selection of potential studies adhered to all requirements outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The analysis was performed according to a four-stage algorithm (Figure).

*Stage 1.* Primary search for publications encompassed studies on gastric cancer and peritoneal carcinomatosis. The search utilized Boolean operators to combine the following keywords. In the PubMed database: peritoneal carcinomatosis, stomach cancer, molecular and genetic mechanisms, matrix independence, metastasis. In the eLIBRARY.ru scientific electronic library: peritoneal carcinomatosis, stomach cancer, molecular and genetic mechanisms, matrix independence, metastasis. The initial search yielded 10,025 publications: 9,624 articles in English and 401 articles in Russian.

*Stage 2.* From the total number of publications, 228 articles in English and 323 articles in Russian were selected, which contained the results of original research and were available in full text.

*Stage 3.* During the analysis of the abstracts of the selected articles, 201 publications from the PubMed database and 308 publications from the eLIBRARY.ru electronic library were excluded as they did not align with the topic of the present literature review.

*Stage 4.* A thorough analysis of the full texts of all publications was conducted. The selected articles were screened for compliance with the established inclusion criteria. Specifically, two studies investigated peritoneal carcinomatosis in cases of multiple primary malignant neoplasms, and two other published studies did not perform molecular analysis of the primary tumor tissue. One study with a small sample size (fewer than 30 patients) was also excluded, three publications did not present complete research results, and in one article, access to the results was restricted. For the preparation of this review, 35 articles (including four in Russian) that corresponded to the stated topic were included in the final analysis (Figure).

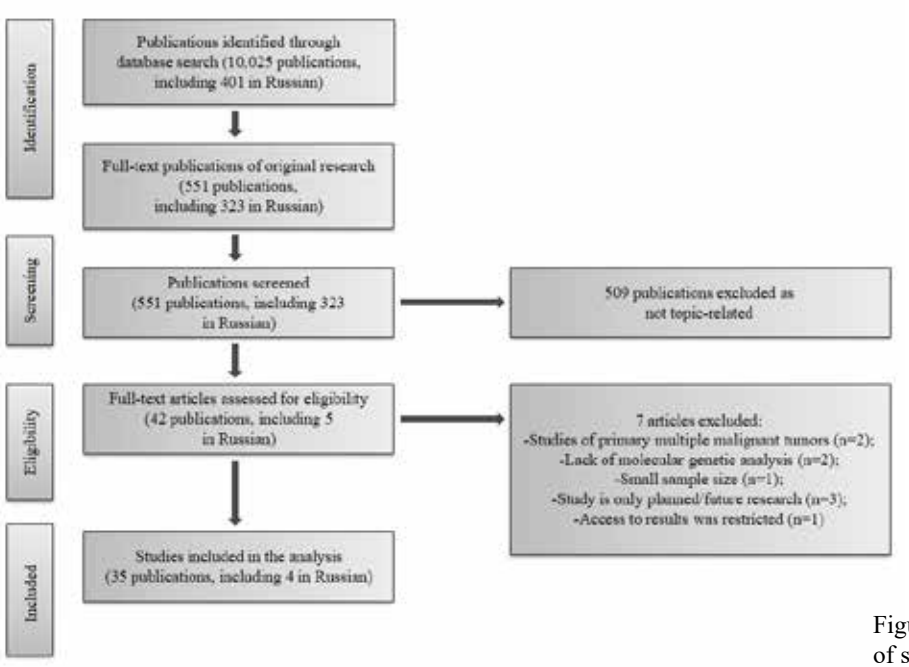


Figure. Algorithm for the identification of studies included in the review

## CLINICAL AND MORPHOLOGICAL PARAMETERS ASSOCIATED WITH PERITONEAL CARCINOMATOSIS

The widely accepted prognostic parameters in gastric cancer associated with the risk of peritoneal carcinomatosis are T and N criteria, histological type, and the differentiation grade of a primary tumor. Based on the analysis of 17 studies, A.Rijken et al. identified the following parameters associated with the risk of synchronous peritoneal carcinomatosis: age, sex, tumor location, histological type, stage, and number of metastases. The prognosis was worse in younger patients, females, with non-cardia tumor location, locally advanced tumor process corresponding to the T4 stage, signet-ring cell or diffuse histological variant, and the presence of two or more metastatic foci. Furthermore, the authors noted increased incidence of synchronous peritoneal carcinomatosis in patients of Hispanic origin. However, the occurrence of peritoneal carcinomatosis does not always align with predictions, which is why current efforts are focused on developing mathematical models to assess the prognostic significance of a combination of factors, as well as incorporating additional parameters, including results from laboratory and instrumental diagnostic methods [8].

Based on a study involving 622 gastric cancer patients, D.J. Szor et al. developed a prognostic model to predict the risk of peritoneal carcinomatosis. The model included parameters such as patient sex, T stage, metastases detected on computed tomography, and diffuse or mixed histological type of gastric cancer according to the Lauren classification. However, the sensitivity of the model was not high, reaching only 82.8% [7, 9].

G. Guan et al. performed a meta-analysis of 21 case-control studies and one cohort study to identify the prognostic value of various clinical, morphological, and laboratory parameters in predicting peritoneal carcinomatosis in gastric cancer patients. The analysis confirmed the prognostic value of well-established criteria, such as T criterion (OR 2.96 (95% CI: 1.87–4.69)), N criterion (OR = 1.22 (95% CI: 0.86–1.73)), tumor differentiation grade (OR = 1.91 (95% CI: 1.42–2.56)), and Borrmann type IV (diffusely infiltrative form) primary tumor (OR = 7.68, 95% CI: 3.62–16.27) [10]. Furthermore, the highest risk of peritoneal carcinomatosis was associated with an elevated serum CA-125 level (OR = 19.45, 95% CI: 4.71–80.30); however, only a limited number of such studies have been conducted to date [11, 12].

These circumstances underscore the necessity of developing new approaches for the early diagnosis and effective therapy of peritoneal carcinomatosis, taking into account all possible factors and mechanisms of its occurrence.

## ANATOMICAL AND PHYSIOLOGICAL FACTORS CONTRIBUTING TO PERITONEAL CARCINOMATOSIS

For a long time, it was believed that the anatomical and physiological features of the peritoneum contribute to the emergence and relentless spread of peritoneal carcinomatosis. Parietal and visceral layers of the peritoneum are a serous membrane comprising a single layer of mesothelial cells located on a basement membrane, and an underlying layer of connective tissue that includes collagen fibers, hyaluronic acid, proteoglycans, fibroblasts, immune cells, as well as blood vessels [13]. Significant importance was attributed to the stomata, which are spaces lacking a basement membrane, located between mesothelial cells. These spaces are necessary for the physiological circulation of fluid within the abdominal cavity. This specific structural feature of the peritoneum was linked to the potential for rapid progression of peritoneal carcinomatosis, as tumor cells spreading across the peritoneum can easily pass through the stomata, which expand during the respiratory movements of the diaphragm, directly into the connective tissue base of the peritoneum, bypassing the basement membrane. This significantly facilitates the progression of peritoneal carcinomatosis [14]. The potential for rapid and extensive dissemination of tumor cells, affecting the peritoneal layers in different parts of the abdominal cavity, was explained by the circulation of physiological fluid flows [15, 16].

One mechanism underlying peritoneal carcinomatosis with rapid and extensive involvement may be the spread of tumor cells through small lymphatic vessels of the peritoneum, known as carcinomatous lymphangitis. Carcinomatous lymphangitis, manifesting as massive embolism of small lymphatic vessels in the lung parenchyma and the visceral and parietal pleura, is also observed in

gastric cancer [17–20]. In a study by T. Shigenobu et al., carcinomatous lymphangitis with embolism of the lymphatic vessels and pleura was found in 31% of patients after radical gastrectomy. The peritoneum, like the pleura, is rich in lymphatic vessels; therefore, a similar mechanism may underlie peritoneal carcinomatosis that is prone to rapid and massive spread, which requires a separate in-depth study [2].

However, anatomical and physiological factors alone cannot explain high propensity of tumor cells to develop peritoneal carcinomatosis. This necessitates the study of the molecular genetic features of tumor cells and the conditions of their survival in ascitic fluid.

## MOLECULAR GENETIC CHARACTERISTICS OF TUMOR CELLS ASSOCIATED WITH PERITONEAL CARCINOMATOSIS

The study of the molecular and genetic features of primary tumor cells that form lesions in the peritoneum and are detected in ascitic fluid could form the basis for understanding the mechanisms of peritoneal carcinomatosis and for identifying targets for targeted therapy.

J.J. Zhao et al. performed whole-exome sequencing, whole-transcriptome sequencing, and digital spatial profiling of samples from primary tumor tissue, peritoneal metastases, as well as healthy tissue from primary tumors and the peritoneum of 326 patients. It was found that the primary tumor tissue harbored mutations in ELF3, CDH1, and PIGR, along with an increased number of M2 macrophages. Furthermore, carcinomatosis lesions showed reduced expression of CLDN18.2 and FGFR2b, which are therapeutic targets for targeted therapy. The authors suggest that these conditions facilitate the formation of pre-metastatic niches prior to the clinical manifestation of peritoneal carcinomatosis [21]. The obtained results were confirmed in a mouse model of transcoelomic metastasis [12].

As a result of whole-exome sequencing and whole-transcriptome sequencing, R. Wang et al. demonstrated that tumor cells from carcinomatosis lesions differed from primary tumor cells by more frequent mutations in CDH1 and TAF1, loss of 6q, and gain of chr19. Tumor cells from metastatic foci of rapidly progressing peritoneal carcinomatosis showed an increased number of mutations in TP53, CDH1, TAF1, and KMT2C, microenvironment reprogramming, MYC activation, and impaired immune response [22].

Gastric cancer is characterized by intratumoral heterogeneity [23, 24]. X. Han et al. investigated the significance of intratumoral heterogeneity in the development of peritoneal carcinomatosis in patients with diffuse gastric cancer without microsatellite instability. The results of single-cell transcriptomic profiling of cells from peritoneal carcinomatosis lesions were compared with the Human Cell Landscape (HCL) database. This study identified 14 unique cellular clusters with differentially expressed genes and compiled a list of 12 genes associated with carcinomatosis and survival in gastric cancer patients. A common alteration in tumor cells was a gain of 17q copy number, associated with worse survival in gastric cancer patients with peritoneal carcinomatosis. The list of genes activated on 17q included genes involved in key signaling pathways (PI3K/AKT/mTOR, mTORC1, MYC, Wnt, NF-κB) or being potential therapeutic targets (HN1, GRB2, PSMB3) [25].

Improved survival rates were associated with immune mechanisms involving defensins, IL-7 signaling, the complement cascade, IL6/JAK/STAT3 signaling, and interferon alpha/gamma signaling [26].

Y. Fang et al. identified autocrine expression of laminin gamma-1 (LAMC1) in primary tumor cells and carcinomatosis lesions in gastric cancer. To investigate the role of autocrine LAMC1 expression in the initiation and progression of peritoneal carcinomatosis, the authors conducted a comprehensive study utilizing single-cell sequencing, co-culture modeling, RNA immunoprecipitation (RIP), and chromatin immunoprecipitation (ChIP). This approach revealed the palmitic acid/p-STAT3/miR-193a-3p/LAMC1 signaling pathway, which paracrinally regulated preadipocyte differentiation, pre-metastatic niche formation, and tumor cell invasion and proliferation within the peritoneum, leading to the development of carcinomatosis lesions. Furthermore, the authors established a correlation between high serum levels of LAMC1 in gastric cancer patients and a high risk of peritoneal carcinomatosis. According to ROC analysis data, the area under the curve (AUC) was 0.785 [27].

X.Z. Huang et al. discovered clusters of tumor cells with high plasticity in the ascitic fluid of patients with peritoneal carcinomatosis, exhibiting

propensity to transition into a highly proliferative phenotype. The authors attribute this transformation to a plasticity program driven by autophagy and paligenosis. Paligenosis is understood as the process where mature, quiescent cells revert to a stem cell-like progenitor state in response to injury. This high tumor cell plasticity was associated with autophagy-related genes — MARCKS and TXNIP [28].

Through spatial analysis, H. Peng et al. demonstrated that MUC1+ tumor cells with a high potential for epithelial – mesenchymal transition were located in proximity to macrophages and fibroblasts. Furthermore, the authors revealed that in cases of immunoresistance, MUC1+ tumor cells located near C1Q+ macrophages exhibited hyperexpression of TGFβ [29].

The necessity for a comprehensive approach to identifying the molecular and genetic features of tumor cells from the primary tumor, metastases, and ascitic fluid is emphasized in the meta-analysis by D. Ng et al. The authors express hope for the possibility of developing new strategies based on the accumulated knowledge about the combined involvement of various molecules and signaling pathways in the initiation and progression of peritoneal carcinomatosis [30].

Despite the discovery of molecular and genetic differences between primary tumor cells and the tumor cells forming carcinomatosis lesions, key molecules with prognostic significance or potential as therapeutic targets have not yet been identified.

## THE ROLE OF THE INFLAMMATORY MICROENVIRONMENT IN THE DEVELOPMENT OF PERITONEAL CARCINOMATOSIS

In studying the mechanisms of peritoneal carcinomatosis, a significant emphasis is placed on the investigation of parenchymal – stromal interactions. Research into the tumor microenvironment of carcinomatosis lesions has revealed a number of patterns, leading Y. Li et al. to describe peritoneal carcinomatosis as a unique “ecosystem” with an immunosuppressive effect. This effect is attributed to the formation of a stromal – myeloid niche, composed of tumor-associated SPP1+ macrophages (TAMs), thrombospondin-2 (THBS2), and matrix cancer-associated fibroblasts (MCAFs). These very conditions are thought to explain the resistance of tumor tissue to therapy in patients with peritoneal carcinomatosis. According to the authors, niche formation is initiated by the accumulation of thrombospondin-2 and cancer-associated fibroblasts, which leads to the recruitment of peritoneum-specific tissue macrophages and their transformation into SPP1+ TAMs via complement C3 and its C3a receptor 1 (C3AR1). Ultimately, this results in the formation of a pro-tumor stromal – myeloid niche. Blocking the C3-C3AR1 axis significantly enhances the efficacy of immunotherapy for peritoneal carcinomatosis in *in vivo* models [14].

Recently, considerable attention has been paid to investigating the role of claudin 18 in determining indications for immunotherapy in metastatic gastric cancer [31–34]. There is evidence of an association between PD-L1 expression in the primary tumor and the risk of peritoneal carcinomatosis [35].

A more comprehensive understanding of the patterns governing microenvironment formation and its role in the development of peritoneal carcinomatosis could facilitate the development of methods to regulate cellular composition and the extent of inflammatory infiltration within the tumor microenvironment, aimed at treating peritoneal carcinomatosis.

## CHARACTERISTICS OF ASCITIC FLUID IN PERITONEAL CARCINOMATOSIS

Ascitic fluid in peritoneal carcinomatosis contains not only tumor cells but also immune cells and cytokines. There is a view that ascitic fluid provides optimal conditions for the survival of tumor cells, contributing to the rapid and relentless progression of peritoneal carcinomatosis.

Studying the molecular composition of ascitic fluid could be useful for understanding the ligand – receptor mechanisms that activate the proliferative and invasive capabilities of tumor cells, and could also help identify target receptors for targeted therapy. However, most such studies focus on detecting markers indicating the presence of tumor cells, such as carcinoembryonic antigen (CEA), CA 19-9, CA 72-4, CA 125, and cytokeratin 20 (CK20), rather than investigating the conditions of their survival [36, 37].

The detection of tumor cells in ascitic fluid is often observed in advanced cases of peritoneal carcinomatosis from gastric cancer, when all possible

treatment options are no longer effective. Therefore, the search for markers that can predict the development of peritoneal carcinomatosis is highly relevant.

Z. Allan et al. proposed an effective marker detectable in ascitic fluid, associated with reduced 3-year progression-free survival and overall survival in gastric cancer patients: the detection of tumor-derived DNA, termed peritoneal tumor DNA (ptDNA) [38]. While this kind of approach holds high value for diagnosing early stages of peritoneal carcinomatosis development, it does not open prospects for understanding the molecular and genetic mechanisms of this process, nor does it allow for predicting the risk of developing peritoneal carcinomatosis or suggesting potential targets for targeted intervention.

X.Z. Huang et al., in a study of the single-cell transcriptome of ascitic fluid from 35 patients with peritoneal carcinomatosis from gastric cancer, discovered an increased number of monocyte-like dendritic cells (DCs) with pro-angiogenic activity and reduced antigen-presenting capacity [28]. H. Peng et al. found that macrophages present in the ascitic fluid of gastric cancer patients had significantly greater pro-angiogenic activity compared to macrophages from the primary tumor stroma and carcinomatosis lesions [29].

Significant importance is also placed on cytokines detected in the ascitic fluid of gastric cancer patients. O. Kersy et al. found that cytokines TNFα, IL-6, and IL-1β were present in the ascitic fluid of gastric cancer patients with peritoneal carcinomatosis. TNFα induce increased expression of adhesion molecules ICAM-1 and VCAM-1 on mesothelial cells, while interleukins 6 and 8 potentiate tumor cell motility and their chemoresistance [39].

Furthermore, cytokines CXCL12/CXCR4 and CCL22/CCR4 are detected in ascitic fluid; these are involved in migration, chemotaxis, adhesion, and metastasis. The interaction between the chemokine receptor CXCR4 on tumor cells and its ligand CXCL12, contained in the ascitic fluid, promotes tumor cell migration and carcinomatosis [30, 40, 41].

Experimental evidence confirms that soluble growth factors, such as VEGF and TGFβ, secreted by tumor cells, participate in preparing the peritoneum for metastasis by activating the vascular endothelium, leading to its remodeling, a process termed pre-metastatic angiogenesis [42, 43].

Analysis of the protein spectrum of ascitic fluid aimed at identifying ligand molecules associated with the acquisition of invasive and proliferative capabilities by tumor cells, as well as with creating conditions for the growth of metastatic foci, opens up possibilities for identifying prognostic factors and potential targets for targeted therapy.

## NEW THERAPEUTIC STRATEGIES FOR PERITONEAL CARCINOMATOSIS

To date, there are no effective treatments for peritoneal carcinomatosis. Tumors accompanied by peritoneal carcinomatosis are often resistant to systemic chemotherapy. A significant reason for this resistance to systemic chemotherapy is considered to be the plasma – peritoneal barrier [44]. Cytoreductive surgery and intraperitoneal chemotherapy are not feasible for all patients and are not always successful [5, 45, 46].

Consequently, there is growing interest in intraperitoneal therapy for treating peritoneal carcinomatosis, which is performed in three modalities: hyperthermic intraperitoneal chemotherapy (HIPEC), neoadjuvant hyperthermic intraperitoneal chemotherapy, and pressurized intraperitoneal aerosol chemotherapy (PIPAC) [47]. When combining surgical intervention with prophylactic HIPEC, the three-year mortality rate was 32%, compared to 55% in the control group [48]. F. Tajik et al. believe that hyperthermic intraperitoneal chemotherapy combined with systemic therapy provides survival benefits for patients [49]. Personalized systemic and intraperitoneal chemotherapy is used in patients with gastric cancer and peritoneal carcinomatosis, based on determining the expression levels of eight genes in the primary tumor, lymph nodes, and peritoneal metastases [50].

Given the significant influence of the tumor microenvironment on the development and progression of peritoneal carcinomatosis, considerable attention is paid to optimizing immunotherapy. Whole-exome sequencing and whole-transcriptome sequencing have identified two main molecular subtypes of peritoneal carcinomatosis: a chemotherapy-resistant "mesenchyme-like" subtype and a chemotherapy-sensitive "epithelium-like" subtype. R. Wang et al. found that the "mesenchyme-like" subgroup exhibited high expression of potential targets for immunotherapy, such as TIM-3, galectin-9, VISTA,

and TGFβ [22]. Recently, significant attention has been given to investigating the role of claudin 18 in determining indications for immunotherapy in metastatic gastric cancer [31–34].

Intraperitoneal immunotherapy is also aimed at improving treatment efficacy. In 2009, catumaxomab, a trifunctional bispecific (anti-EpCAM × anti-CD3) antibody, was approved for clinical use.

Chemoresistance of carcinomatosis lesions is associated with features of the tumor microenvironment in metastases. H. Peng et al. discovered that in cases of tumor insensitivity to chemotherapy, there is a combination of a higher level of infiltration by C1Q+ macrophages with a low level of infiltration by GZMA+ T lymphocytes in the microenvironment of carcinomatosis lesions [29].

To enhance the efficacy of intraperitoneal therapy, a method using engineered CAR-T cells (M28z1XXPD1DNR) is being developed in mouse models of peritoneal carcinomatosis, achieving longer survival compared to systemic administration [51].

## CONCLUSION

Peritoneal carcinomatosis in gastric cancer represents one of the most unfavorable variants of the disease course. Despite efforts to study the molecular and genetic characteristics of tumor cells underlying peritoneal carcinomatosis, the composition of ascitic fluid, features of immune and inflammatory responses, and the development of new combined regimens of local and systemic therapy, effective methods for predicting and treating peritoneal carcinomatosis are still lacking. This is largely due to an insufficient understanding of the mechanisms behind carcinomatosis generalization within the abdominal cavity.

Among the hypotheses proposing mechanisms for the development of peritoneal carcinomatosis, none fully explain how tumor cells lose connection with neighboring cells and the matrix, becoming capable of autonomous survival in ascitic fluid. Matrix-independent survival was studied by D.K. Lee et al. and termed adherent-to-suspension transition. Genes conferring these properties were identified in a model system. However, our evaluation of the expression of these genes in circulating tumor cells from breast cancer, performed using single-cell sequencing, revealed a low percentage of circulating tumor cells expressing these genes (unpublished data). This may indicate that intravasation and the emergence of matrix-independent circulating tumor cells can occur without the activation of these genes [52].

In our view, it is the matrix independence of tumor cells that is the key factor determining the very likelihood of developing peritoneal carcinomatosis. Elucidating the molecular basis of matrix independence would not only allow for predicting the risk of peritoneal carcinomatosis in gastric cancer but also identify targets for therapy. Corresponding markers could potentially be assessed in biopsy material from the primary tumor. Furthermore, the identified molecules could serve as targets for targeted intervention. The results of research aimed at identifying key molecules associated with the acquisition of matrix independence and the adherent-to-suspension transition could pave the way for developing novel targeted therapies for peritoneal carcinomatosis in gastric cancer.

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