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Regulatory Proteins of Epithelial-Mesenchymal Transition in Colorectal Cancer: From Biology to Clinical Application

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ABSTRACT

This lecture presents current data on the role of regulatory proteins of epithelial-mesenchymal transition (EMT) in colorectal cancer (CRC) in the context of tumor molecular stratification and personalized treatment selection. EMT is a key biological process associated with tumor invasion, metastasis, chemoresistance, and immune evasion. Special attention is given to the characterization of CRC molecular subtypes according to the Consensus Molecular Subtypes (CMS) classification, particularly the CMS4 subtype with mesenchymal features, which is marked by high EMT activity and poor prognosis.

The lecture discusses molecular and immunohistochemical markers indicative of EMT activation, including CDX2, ZEB1, HTR2B, FRMD6, BMI-1, and ROR1. The expression patterns and associated signaling pathways of these proteins are examined along with their influence on tumor aggressiveness, therapy resistance, and prospects for clinical application. Based on the literature analysis, the potential of these proteins as prognostic and possibly predictive biomarkers, as well as therapeutic targets, is discussed.

Keywords: colorectal cancer, molecular subtypes, CDX2, ZEB1, HTR2B, ROR1, BMI-1, FRMD6, epithelial-mesenchymal transition, prognosis

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Регуляторные белки эпителиально-мезенхимального перехода в колоректальном раке: от биологии к клиническому применению

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РЕЗЮМЕ

Представлены современные данные о роли регуляторных белков эпителиально-мезенхимального перехода (ЭМП) при колоректальном раке (КРР) в контексте молекулярной стратификации опухолей и персонализированного подбора терапии. Эпителиально-мезенхимальный переход представляет собой ключевой биологический процесс, связанный с инвазией, метастазированием, химиорезистентностью и иммунным уклонением опухоли. Особое внимание уделено характеристике молекулярных подтипов КРР согласно консенсусной классификации (CMS), в частности, CMS4-подтипу с мезенхимальными признаками, для которого характерен высокий уровень ЭМП и неблагоприятный прогноз.

В лекции обсуждаются молекулярные и иммуногистохимические маркеры, отражающие активацию ЭМП, включая CDX2, ZEB1, HTR2B, FRMD6, BMI-1 и ROR1. Рассматриваются особенности экспрессии и сигнальные каскады, с которыми ассоциированы указанные белки, их влияние на опухолевую агрессивность, устойчивость к терапии и перспективы клинического применения. На основании анализа литературных данных рассматриваются возможности использования этих белков в качестве прогностических и потенциальных предиктивных маркеров, а также терапевтических мишеней.

Ключевые слова: колоректальный рак, молекулярные подтипы, CDX2, ZEB1, HTR2B, ROR1, BMI-1, FRMD6, эпителиально-мезенхимальный переход, прогноз

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignant neoplasms globally and within Russia, being a major contributor to both morbidity and mortality rates. According to the World Health Organization, CRC is one of the three most common cancers, second only to lung and breast cancer [1]. In 2020, more than 1.9 million new cases of CRC and about 935,000 related deaths were reported worldwide [2]. In the Russian Federation in 2023, over 74,000 new cases of malignant tumors of the colon and rectum were detected, and the number of patients registered with this pathology exceeded 437,000. At the same time, during the first year after diagnosis verification, death is observed in 20.6% and 18.2% of patients with colon and rectal cancer, respectively [3]. Despite the advances in modern oncology (the development of high-tech imaging methods, screening, and targeted therapy), the 5-year survival rate in CRC remains at about 60–65%, and the prognosis significantly depends on the stage of the disease at the time of diagnosis [4].

The problem of assessing the risk of recurrence and stratification of patients with stage II–III tumors is particularly relevant, when the need for adjuvant chemotherapy often becomes the subject of discussion [4].

In recent years, considerable attention has been paid to the epithelial–mesenchymal transition (EMT) as a key mechanism of tumor invasion, metastasis, chemoresistance, and immune evasion. The study of EMT regulatory proteins is a promising area of molecular oncology that can enrich personalized medicine.

The aim of this lecture is to examine current understanding of the role of EMT regulatory proteins in CRC with an emphasis on their relationship with molecular subtypes of the tumor, the biological characteristics of the aggressive course of the disease, and their potential significance in translational oncology.

MOLECULAR HETEROGENEITY OF COLORECTAL CANCER AND THE SIGNIFICANCE OF THE EPITHELIAL–MESENCHYMAL TRANSITION

CRC is a molecularly and clinically heterogeneous disease caused by differences in the embryonic development of the intestinal tract, multiple pathways of carcinogenesis, and features of the tumor microenvironment. This heterogeneity leads to marked

differences in a response to therapy and a clinical outcome in different patients. Based on studies of biological features of CRC, several molecular genetic classifications have been proposed [5].

Currently, the Consensus Molecular Subtypes (CMS) classification is the most widely used system. This classification is considered as the most informative and convenient, since four molecular subtypes of colorectal carcinoma are distinguished based on the similarities and differences in the molecular genetic characteristics of tumors, as well as the features of their clinical course:

– CMS1 (immune, ~14%) is characterized by high microsatellite instability (MSI-H), accompanied by intensive infiltration of tumor tissue by T-lymphocytes ($CD4^+/CD8^+$) and natural killer cells (NK cells), activation of the antitumor immune microenvironment and global hypermethylation of promoters of a number of genes;

– CMS2 (canonical, ~37%) is associated with chromosomal instability (CIN), frequent mutations in APC, TP53, and KRAS, as well as activation of the Wnt/β-catenin and MYC cascades, which provide the proliferative potential of tumor cells; it is located mainly on the left;

– CMS3 (metabolic) demonstrates pronounced metabolic shifts, including activation of glutaminolysis and lipogenesis, which is often combined with mutations in the *KRAS* and *PIK3CA* genes, as well as with dysregulation of Wnt signaling, occurs in about 13% of cases, has no clear connection with a specific localization;

–CMS4 (mesenchymal, ~23%) is characterized by the predominance of tumor-associated fibroblasts in the stroma, activation of the TGFβ signaling cascade, formation of a developed vascular network and manifestation of signs of EMT, reflecting its high invasive potential and resistance to many standard therapies [6].

CMS4 subtype is associated with the most aggressive course of the disease, poorer overall and relapse-free survival rates, reduced sensitivity to chemotherapy, and marked activation of the immunosuppressive microenvironment [7, 8]. It is in this subtype that EMT plays the most significant role forming the invasive phenotype of the tumor and contributing to the progression of the disease [9].

EMT is a fundamental phenotypic transformation during which tumor cells lose epithelial polarity, intercellular adhesion bonds, and expression of typical epithelial proteins such as E-cadherin. These changes are accompanied by the acquisition of a mesenchymal phenotype, including increased mobility, invasiveness, as well as resistance to apoptosis and antitumor therapy. The EMT is controlled by various signaling pathways (TGFβ, Wnt/β-catenin, Notch, Hippo, PI3K/Akt, etc.), transcriptomic factors (Snail, Slug, Twist, and ZEB1/2), as well as microRNA and epigenetic mechanisms [10–15].

In the context of modern CMS classification, EMT is considered as a critical process underlying aggressive CRC subtypes, as well as a potential target for therapy and risk stratification. EMT regulatory proteins are actively studied in order to assess their role as prognostic markers and possible therapeutic targets [16, 17]. The key characteristics of CMS subtypes and their relationship to EMT and immune mechanisms are shown in Fig. 1.

CDX2: A MARKER OF INTESTINAL DIFFERENTIATION AND EMT NEGATIVE REGULATOR WITH A ROLE IN SUPPRESSING TUMOR GROWTH, PROGNOSTIC VALUE, AND EFFECT ON CHEMOSENSITIVITY

CDX2 (Caudal-related homeobox 2) is a transcription factor containing a homeobox domain that plays a key role in differentiation and morphogenesis of the intestinal epithelium [18]. Due to the presence of a homeodomain, CDX2 is able to bind to specific DNA regions, regulating the activity of the target set of genes. It belongs to the ParaHox family evolutionarily related to the Hox cluster and along with CDX2 includes the *CDX1* and *CDX4* genes.

It is known that CDX2 is one of the first to be activated in embryogenesis and retains expression in the pericecal region of the intestine, including the ileocecal valve [19]. CDX2 is actively used in clinical practice as an immunohistochemical marker of intestinal differentiation, but its specificity is limited – high CDX2 expression can be observed in both ovarian mucinous carcinoma and bladder adenocarcinoma [20].

Loss of CDX2 expression in patients with CRC is associated with an unfavorable clinical course, including a decrease in both relapse-free and overall survival, especially in stage II–III tumors [21]. In addition, decreased CDX2 expression is often accompanied by vascular invasion, low differentiation, right-sided tumor location, CIMP phenotype (global hypermethylation of CpG islands; CpG island methylator phenotype), and BRAF mutation [22]. It is important to note that

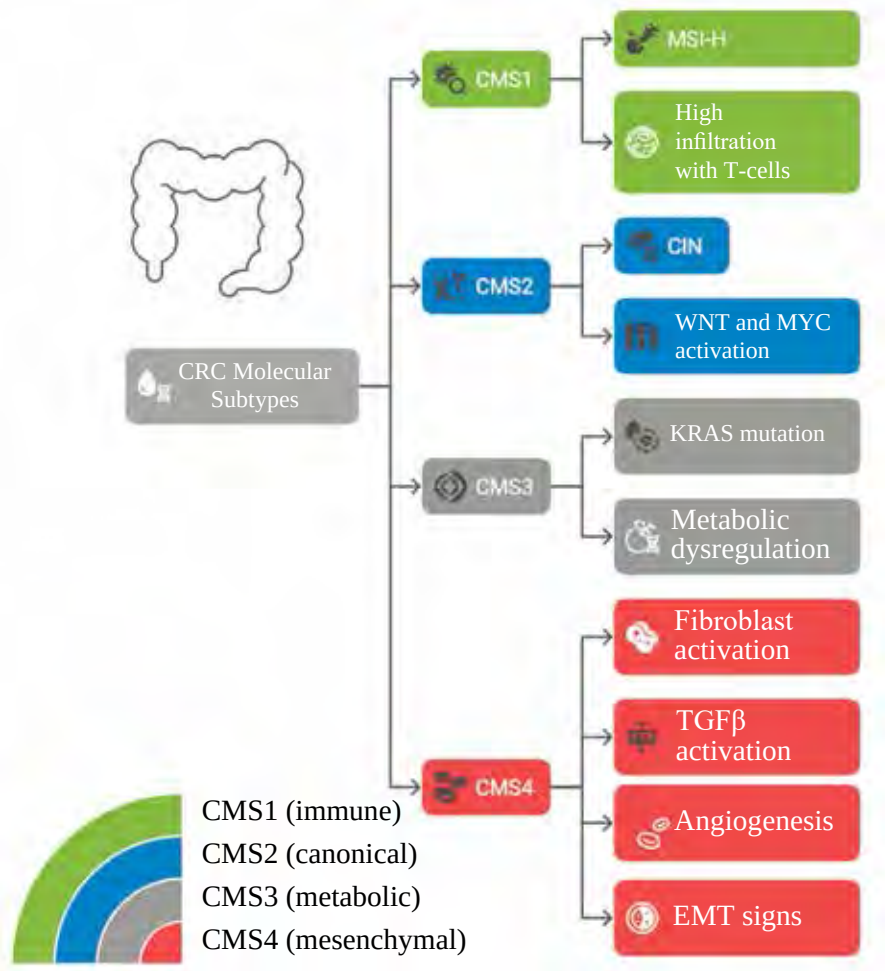

Fig. 1. Key characteristics of CRC (CMS) molecular subtypes: CMS1 (immune) – MSI-H, pronounced tumor infiltration by T-lymphocytes ($CD4^+/CD8^+$) and NK cells; more often found in the right half of the colon. CMS2 (canonical) – chromosomal instability (CIN), mutations in APC, TP53, and KRAS, activation of Wnt/β-catenin and MYC signaling; more often left-sided tumors (~37%). CMS3 (metabolic) – KRAS and PIK3CA mutations, metabolic disorders and dysregulation of Wnt signaling; ~13% of cases without clear localization. CMS4 (mesenchymal) – ~23% of cases; activation of TGFβ, EMT, angiogenesis, left-sided localization, and pronounced drug resistance

in some cases, heterogeneity of staining is revealed by immunohistochemical profile: high CDX2 expression is observed in the central areas of the tumor, while expression weakens in the periphery, especially in the area of invasive growth [23].

CDX2 exhibits antitumor activity by suppressing EMT. The mechanism is described through the activation of the tumor suppressor let-7b, which leads to a decrease in the expression of collagen XI α1 (COL11A1) associated with cell migration, infiltration of immune elements, and chemoresistance [24, 25]. The research results show that a decrease in CDX2 expression is significantly associated with the proximal location of the tumor, a low degree of differentiation, mucinous phenotype, microsatellite instability, CIMP phenotype, and the presence of mutations in the *BRAF* gene. Such tumors are also characterized by increased cytokeratin CK7 expression and decreased CK20 expression [26].

CDX2-negative tumors are more common in the metastatic stage of CRC – up to 19% of cases [27]. In the study by Y. Shigematsu et al., low CDX2 expression was associated with a deterioration in relapse-free survival (245 vs. 420 days) and overall survival (1,024 vs. 3,145 days) after resection of liver metastases; it was also shown that such patients did not significantly benefit from adjuvant or neoadjuvant therapy [28].

Interesting results were obtained in the 2023 study: in 14 patients with metastatic MSI-H CRC who

received immunotherapy, the CDX2-positive group had a 1-year relapse-free survival of 81%, while in the CDX2-negative group, there was not a single relapse-free case [29]. This indicates the potential of CDX2 as a predictive marker of the immunotherapy response. In another study, P. Dalerba et al. showed that adjuvant chemotherapy was beneficial only in patients with CDX2 loss: their 5-year relapse-free survival rate was significantly higher, whereas in CDX2-positive patients, chemotherapy did not improve survival [30].

ZEB1: TRANSCRIPTIONAL EMT INDUCER AND MEDIATOR OF DRUG RESISTANCE AFFECTING INVASIVENESS, IMMUNOSUPPRESSION, AND TUMOR STEM PHENOTYPE FORMATION

ZEB1 (Zinc finger E-box binding homeobox 1) is a transcription factor that plays a key role in EMT regulation. Under normal physiological conditions, ZEB1 is involved in the regulation of cellular differentiation, homeostasis, and the development of nervous, smooth muscle, and bone tissues [31].

In the context of malignant growth, ZEB1 acts as an EMT activator, inducing the expression of mesenchymal markers and suppressing the expression of epithelial markers, in particular E-cadherin. ZEB1 induction occurs under the influence of several signaling pathways: WNT, TGFβ, COX2, HIF, etc. [32]. One of the mechanisms involves the interaction of ZEB1 with the ELK3 transcription factor, resulting in the suppression of the E-cadherin gene and activation of the migration phenotype of tumor cells [33].

According to data obtained by Y. Guo et al., activation of TGFβ leads to an increase in ZEB1 expression on the invasive tumor front, which initializes the EMT cascade [34]. Moreover, hypermethylation of the *ZEB1* gene promoter is associated with its reduced expression and a more favorable prognosis in CRC. This epigenetic phenomenon is more often observed in patients with CMS1 subtype and correlates with higher relapse-free and overall survival, regardless of the stage and other clinical factors [35].

ZEB1 is also associated with immune evasion mechanisms. According to data obtained by M.Z. Noman et al., ZEB1 induces PD-L1 expression, which contributes to the suppression of the T-cell immune response in the tumor [36]. This makes ZEB1 a potential predictor of sensitivity to immune checkpoint inhibitors.

ZEB1 is involved in the development of chemoresistance, in particular, it is associated with increased expression of Bcl-xL and cyclin D1, key factors of resistance to antitumor drugs [37]. In studies on breast cancer models, high ZEB1 expression correlated with a decrease in relapse-free survival and the frequency of pathologic complete response (pCR) in patients receiving neoadjuvant therapy [38].

The results of two meta-analyses published in 2017 and 2019 confirmed the negative prognostic role of high ZEB1 expression, as the most pronounced decrease in overall survival with high ZEB1 levels was found in patients with CRC, gastric, and pancreatic cancers [39].

FRMD6: CONTEXT-DEPENDENT EMT SUPPRESSOR THROUGH ACTIVATION OF THE HIPPO PATHWAY

FRMD6 (FERM domain-containing protein 6) is a protein from the family of FERM domain–containing proteins (4.1/ezrin/radixin/moesin) involved in a number of processes: regulation of cell proliferation, differentiation, apoptosis, and cell-extracellular matrix interaction [40–43]. It plays a role in neurophysiological processes, and is also involved in Hippo, ERK/MAPK, c-MYC, and mTOR signaling pathways. In CRC, the FRMD6 protein exhibits the properties of a tumor suppressor, primarily due to its involvement in the Hippo signaling pathway, which regulates cell proliferation, apoptosis, and growth restriction. The main components of the Hippo cascade are kinases MST1/2 and LATS1/2, which inhibit nuclear translocation and the activity of transcriptional coactivators YAP/TAZ. Phosphorylation of YAP by serine-127 prevents its transfer to the nucleus and thereby suppresses transcription of genes responsible for growth and EMT [44–47]. FRMD6 promotes the activation of LATS kinases and YAP phosphorylation, which leads to a restriction of the transcriptional activity of the latter, resulting in a decrease in the expression of EMT-inducing factors, including Snail, Slug, and ZEB1 [48].

In prostate cancer research, decreased FRMD6 expression was associated with overactivation of the YAP and MYC pathways, as well as with an increased risk of biochemical relapse after prostatectomy [49].

Similar protective properties of FRMD6 were also revealed in CRC. According to the results of a major study led by A.Von Koskull et al. (2024), which included 538 patients with CRC, a high level of FRMD6 expression was associated with improved survival rates, and therefore the protein was considered as an independent prognostic marker

in a multifactorial analysis model [50]. However, in some other malignant tumors, this molecule, on the contrary, demonstrates pro-tumor activity.

Thus, in adenocarcinoma and squamous cell lung cancer, high FRMD6 expression is associated with an unfavorable prognosis. In these cases, FRMD6 activates the mTOR pathway, which leads to increased proliferation and drug resistance of tumor cells [51]. Thus, FRMD6 is a molecule with a context-dependent function. In CRC, it acts as a suppressor of tumor growth and EMT, but its role in tumors of other locations requires further study.

HTR2B: SEROTONIN-DEPENDENT EMT ACTIVATOR AND MEDIATOR OF INTERCELLULAR COMMUNICATION – INVOLVED IN GROWTH AND MIGRATION CASCADES, ASSOCIATED WITH CRC PROGRESSION AND IMMUNE EVASION

The HTR2B serotonin receptor (5-HT_2B), which is actively involved in the regulation of neurohumoral and metabolic processes, is expressed in the tissues of the nervous system, heart, and gastrointestinal tract [52]. It is known that the serum serotonin (5-HT) level in patients with CRC is significantly higher than in healthy individuals, which contributes to tumor progression through activation of the 5-HT-Wnt and 5-HT-YAP signaling axes [53].

High expression of HTR2B has been detected in various malignant neoplasms: melanoma, gastrointestinal stromal tumors, breast, ovarian, kidney, and pancreatic carcinomas, as well as in CRC [54]. Activation of HTR2B triggers the Akt/mTOR cascade, which leads to phosphorylation and activation of the transcription factor CREB1, which stimulates ZEB1 expression, which is known to play a key role in triggering EMT [55]. Suppression of HTR2B activity is accompanied by a decrease in the migration potential of tumor cells and partial blockade of EMT processes, which confirms the role of this receptor in maintaining an aggressive phenotype. Additionally, it was found that stimulation of HTR1B and HTR2B activates the MAPK/ERK signaling cascade, which plays a key role in cell proliferation and differentiation [55–57].

In a 2023 study, it was shown that HTR2B expression is associated with lipid metabolism in gastric adenocarcinoma. Thus, an increased level of HTR2B was associated with decreased survival, which indicates the role of the molecule in maintaining the viability of tumor cells and the possibility of its use as a prognostic marker [58]. In hepatocellular cancer, the role of serotonin HTR2B with its involvement in the process of tumor growth was similarly noted [59]. In contrast, the results of another study showed a correlation between high HTR2B expression and lower tumor spread in ovarian cancer, which demonstrates the ambiguity of its prognostic value [60].

Thus, despite convincing experimental data on the role of HTR2B in the induction of EMT and the metastatic potential of tumors, its clinical significance in CRC has not been definitively determined and requires further study. Nevertheless, HTR2B blockade is considered as a promising area of antitumor therapy in translational oncology.

BMI-1: EPIGENETIC REGULATOR OF TUMOR STEMMING AND THERAPY RESISTANCE, PARTICIPATING IN THE MAINTENANCE OF PROGENITOR CELLS AND THE INDUCTION OF EMT THROUGH THE AKT/SNAIL CASCADE

BMI-1 (B-cell-specific Moloney murine leukemia virus integration site 1), also known as RNF51 or PCGF4, is a transcription factor that plays a key role in maintaining stem cell functions, especially in the nervous and hematopoietic systems. In experiments on animal models, switching off this gene led to impaired embryonic development, and its overexpression led to the development of lymphomas [61].

BMI-1 belongs to the Polycomb (PcG) family of epigenetic transcription regulators, it is part of Polycomb repressive complex 1 (PRC1) and, together with the Ring1B/Rnf2 component, ubiquitinates histone H2A by lysine–119 (H2AK119ub), which suppresses the transcription of genes regulating apoptosis, differentiation, and aging [62]. BMI-1 promotes EMT induction through activation of the Akt/GSK-3b/Snail pathway, as well as through stimulation of the TGF-β/SMAD cascade [63, 64].

The study by Z.Y.Jiang et al. showed on experimental CRC models that BMI-1 activates peritumoral stellate liver cells, contributing to the formation of a pre-metastatic niche and increased migration of tumor cells, while inhibition of BMI-1 restored the expression of E-cadherin and disrupted the processes of migration, invasion, and drug resistance [65]. High expression of BMI-1 has been observed in many malignant neoplasms, including tumors of the stomach, breast, ovaries, prostate, lung, and pancreas.

The correlation of the marker expression with more intensive proliferation, high metastatic potential, and drug resistance of tumors was noted [66, 67].

The meta-analysis by M. Pourjafar et al. (2022), which included nine studies (seven Asian and two European), revealed population differences in the prognostic value of BMI-1 expression in CRC. It was found that high expression was associated with an unfavorable prognosis (decreased overall and relapse–free survival) in the Asian population, whereas in the European population, on the contrary, more favourable outcomes were noted. In addition, increased BMI-1 levels were more often associated with a large tumor size, the presence of distant metastases, an older age of patients ,and a male sex. No reliable relationship was found with the parameters of TNM, the degree of differentiation, and localization of the tumor [68].

Thus, BMI-1 is a potential marker of aggressive tumor development and a prognostic biomarker, but its significance in different populations requires additional validation in multicenter studies.

ROR1 IN COLORECTAL CANCER: ONCOEMBRYONIC RECEPTOR, ITS SIGNALING PATHWAYS AND THERAPEUTIC POTENTIAL

ROR1 (Receptor tyrosine kinase-like orphan receptor 1) is a receptor tyrosine kinase from the ROR family, expressed mainly at the stage of embryogenesis and practically absent in healthy tissues in adults. Under normal conditions, the highest expression of ROR1 is observed in the pancreas and adipose tissue, whereas it is minimal in most other tissues (colon, lungs, uterus, and parathyroid glands) [69, 70].

ROR1 contains several evolutionarily conserved domains: an extracellular immunoglobulin-like domain, a Frizzled domain, a kringle domain, and an intracellular tyrosine kinase-like domain [69]. The biological role of ROR1 is related to the regulation of cell migration, polarity, and organogenesis during embryonic development [69, 70]. In oncology, ROR1 is involved in the non-canonical Wnt signaling pathway through binding to the Wnt5a ligand. This pathway regulates cell migration, apoptosis, EMT, and chemoresistance [71]. Increased expression of ROR1 has been found in various solid tumors (breast cancer, ovarian cancer, lung cancer, hepatocellular carcinoma, CRC, etc.) [71, 72].

CRC studies have revealed significantly higher ROR1 expression in tumor cells compared to healthy tissues. ROR1 expression correlates with the stage of the disease, lymph node damage, and decreased overall survival [73]. Similar data were obtained in ovarian cancer, where high ROR1 expression was also associated with low rates of relapse-free and overall survival [74]. A meta-analysis in 2022, including the results of 14 studies, showed that high ROR1 expression was significantly associated with poorer overall survival. A particularly strong association was found in endometrial cancer, ovarian cancer, and B-cell lymphoma [75].

Earlier in the 2019 meta-analysis, similar results were obtained for solid tumors, including lung cancer; there were no differences in prognostic significance between solid and hematological tumors [75]. Due to its high tumor-specific expression and lack of expression in healthy tissues, ROR1 is a promising therapeutic target. Currently, the effectiveness of a number of targeted ROR1 kinase inhibitors that cause apoptosis of tumor cells has been shown [75, 76].

Of particular interest is the use of ROR1 as an antigen for chimeric antigen receptors of T-lymphocytes (CAR-T; Chimeric antigen receptor to T-cells). CAR-T therapy, which involves the modification of patient's T cells to attack tumor cells, is already actively used in hematological malignant neoplasms [75]. Preliminary results of phase I clinical trials demonstrate encouraging efficacy of therapy using CAR-T cells directed against ROR1 in patients with triple negative breast cancer in cases of expression of this receptor [75–79]. These data open up the prospect for adapting a similar approach in the treatment of CRC with positive ROR1 expression.

Thus, ROR1 simultaneously acts as a prognostic marker and a promising target for targeted therapy, especially in the context of immuno-oncological approaches, including CAR-T.

EMT AND THE PROBLEM OF CRC STRATIFICATION OF STAGES II–III

Despite the advances in molecular diagnostics and the improvement of drug therapy, the rationale for the need and scope of adjuvant chemotherapy in stage II-III CRC remains the subject of active discussion. Current guidelines (for example, ESMO) suggest dividing stage II patients into low-, intermediate-, and high-risk groups based on a combination of clinical and morphological factors. The "significant" risk factors include the pT4 stage (regardless of the presence of intestinal wall perforation) and the examination of less than 12 lymph nodes; the "less significant" ones include a low degree of tumor differentiation, vascular and perineural

invasion, intestinal lumen obstruction, and a high level of cancerous embryonic antigen (CEA) [4].

Microsatellite instability (MSI) is recognized as an important prognostic and, in some cases, predictive factor. Patients with early-stage MSI-H tumors have a more favorable prognosis, and in the presence of a single "less significant" risk factor, it is possible to safely refrain from prescribing fluoropyrimidine chemotherapy without worsening relapse-free and overall survival [80]. Nevertheless, the existing stratification based on a combination of morphological and molecular parameters (TNM stage, MSI status, RAS/BRAF mutations, Immunoscore index, and circulating tumor DNA – ctDNA level) does not allow for predicting the risk of recurrence or a response to therapy in a particular patient with high accuracy [81–85], relapse within 5 years develops in 12–38% of stage II patients and in almost half of stage III patients.

EMT regulatory proteins represent a promising group of biomarkers potentially capable of improving the accuracy of prognosis. Loss of CDX2 expression is associated with a lower survival rate. In addition, data obtained by P. Dalerba et al. showed that adjuvant chemotherapy was effective mainly in patients with CDX2-negative tumors, whereas its administration did not improve the results in CDX2-positive patients [30].

ZEB1, in turn, can be identified as a marker of an immunosuppressive phenotype (mediating an increase in PD-L1) and a predictor of drug resistance. ROR1, FRMD6, BMI-1, and other EMT proteins are also involved in the regulation of chemosensitivity and metastatic potential. The analyzed protein molecules considered as EMT regulators and their phenotypic effects in the context of CRC are shown in Fig. 2.

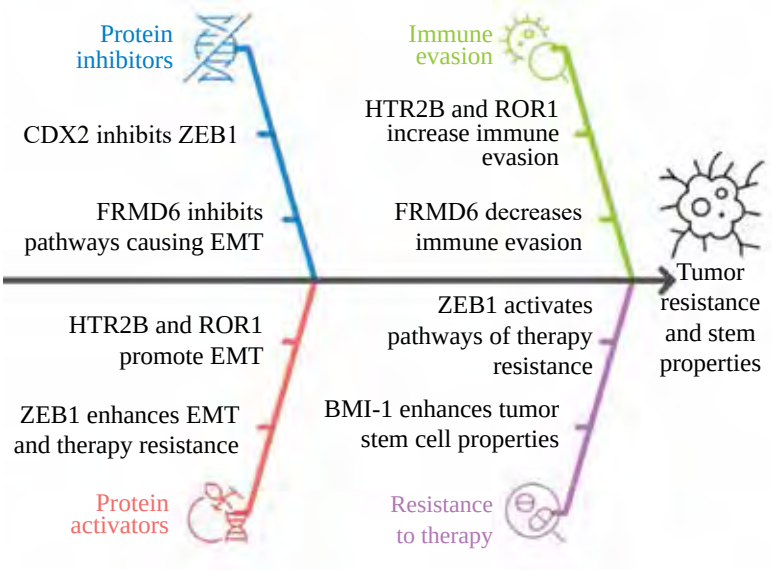

Fig. 2. Key molecular links between EMT regulators, signaling pathways, and phenotypic effects in CRC: CDX2 suppresses ZEB1 expression, reducing EMT activity and reducing tumor stemming. On the contrary, ZEB1 activates cascades that enhance EMT and the formation of drug resistance. FRMD6 blocks the signaling pathways that induce EMT, which leads to a decrease in the immune evasion. HTR2B and ROR1 contribute to the activation of EMT, accompanied by increased therapy resistance and avoidance of immune elimination. BMI-1 enhances the stem properties of the tumor, playing an important role in the development of chemoresistance

CONCLUSION

EMT is a complex biological process that plays a key role in the progression, metastasis, formation of chemoresistance, and immunosuppressive microenvironment in CRC. Modern molecular studies show that EMT is not a binary phenomenon, but rather a spectrum of transitional phenotypes with both epithelial and mesenchymal features, reflecting the plasticity of tumor cells and their adaptive capabilities. This phenotypic shift is closely related to the activation of the Wnt/β-catenin, Notch, TGFβ, and Hippo-YAP/TAZ signaling pathways, as well as the expression of transcriptional regulators, including ZEB1, SNAIL, and TWIST.

Of particular interest is the interaction of EMT with components of the tumor microenvironment, including macrophages, fibroblasts, and neurotransmitter signaling pathways (for example, serotonergic HTR2B receptors) that contribute to the maintenance of stem cells and invasiveness of tumor cells. In addition, PD-L1 expression during EMT activation may contribute to evading immune surveillance, which underscores the importance of a comprehensive analysis of the CRC immune landscape, including the use of immunoscoring and circulating tumor DNA.

The markers CDX2, ZEB1, FRMD6, BMI1, ROR1, and HTR2B presented in the review demonstrate a wide range of biological functions

from regulation of differentiation and invasiveness to involvement in the formation of therapy resistance. The potential of their use as prognostic and predictive biomarkers is confirmed by both meta-analyses and data on expression in primary tumors and metastases. Moreover, a number of these molecules are being considered as promising therapeutic targets for the development of targeted drugs and CAR-T-cell therapy.

Despite significant advances, the translation of knowledge about the mechanisms of EMT and its regulators into routine clinical practice requires standardization of assessment methods, validation on large cohort samples, and integration into existing prognostic models. Particular attention should be paid to the phenotypic heterogeneity of the tumor and the dynamics of expression of key markers during treatment. Progress in this area may provide the basis for a personalized approach to CRC therapy and enhance the effectiveness of existing strategies, including immunotherapy and signaling pathway inhibitors.

Thus, a deep understanding of the role of EMT and its regulators in the pathogenesis of CRC opens up new horizons for diagnosis, risk stratification, and the development of innovative therapeutic approaches aimed at overcoming the metastatic potential and resistance of the tumor to therapy.

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