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Options for the development of colorectal cancer immunotherapy

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Abstract

In colorectal cancer immunotherapy, the use of antibodies against the PD-1/PD-L1 checkpoints showed low efficacy and the development of a number of side effects with damage to the liver, lung, and thyroid gland. For this reason, to stimulate the antitumor immune response, it is necessary to search for other targets, which can be used as retroelements. Epigenetic activation of their expression with inhibitors of histone methyltransferases and deoxyribonucleic acids (DNA) leads to the formation of double-stranded ribonucleic acids (RNA) that stimulate the antiviral response of interferon, which causes apoptosis of tumor cells. This method of viral mimicry shows an objective response in colorectal cancer and other malignant neoplasms. However, activation of retrotransposons is an inducer of carcinogenesis and a necessary condition for clonal evolution and the development of chemoresistance. Therefore, the most rational combination of the method of viral mimicry is with selective inhibition of retroelements involved in the pathogenesis of colorectal cancer. For this purpose, specific miRNAs, that recruit DNA methyltransferases to the loci of the location of retroelements due to the complementarity of nucleotide sequences, which is due to their evolutionary relationship, can be used. An analysis of the scientific literature revealed 28 miRNAs derived from transposons and associated with colorectal cancer, some of which exhibit oncosuppressive activity, while others exhibit oncogenic activity. These miRNAs can be used as guides for epigenetic effects on retroelements involved in colorectal cancer carcinogenesis.

Keywords: immunotherapy, colorectal cancer, microRNA, retroelements.

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Introduction

According to the International Agency for Research on Cancer (https://gco.iarc.fr), colorectal cancer (CRC) is the third most common malignant neoplasm (MNP) worldwide. In 2020, CRC affects 24.8 per 100,000 people. In the Russian Federation, colon, rectal, rectosigmoid junction, and anal cancers accounted for 12.3% of all MNPs [1]. Therefore, effective methods for treating CRC are urgently needed.

Immunotherapy is a promising direction for cancer treatment. The progression of carcinogenesis is caused by the immune response being eluded because of the activation of negative regulatory pathways, known as control points. Two known control points are programed cell death (PD-1) and cytotoxic T-lymphocyte protein 4 (CTLA4).

Upon activation, T cells express the cell surface receptor PD-1, which binds to either PD-L1 or PD-L2 on tumor cells, resulting in the suppression of T-lymphocyte activity. Antibodies that block the interaction between PD-L1 and PD-1 activate the immune antiviral response to MNP cells. However, because PD-L1 and PD-L2 ligands are also present in normal cells [2], autoimmune reactions provoked by anti-PD-1/PD-L1 drugs cannot be ruled out.

In addition, meta-analyses have shown that anti-PD-1/PD-L1 medications can cause liver damage, immune-related pneumonitis, and thyroid dysfunction (particularly hypothyroidism) [3–5]. When coadministered with BRAF and MEK inhibitors, anti-PD-L1/PD-1 significantly increases the risk of fever, asthenia, myalgia, arthralgia, hypothyroidism, and liver damage, as evidenced by changes in the levels of aspartate aminotransferase and alanine aminotransferase [6].

The effectiveness of anti-PD-L1/PD-1 monotherapy is limited. These treatments are generally ineffective for patients with CRC and only affect tumors with high microsatellite instability (which accounts for approximately 15% of all CRC cases) and total mutational load. Objective response was observed in only 31% of patients within 12 months of therapy [7].

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Resistance to anti-PD-L1/PD-1 develops because of several factors, including severe T-cell depletion, activation of alternative immune checkpoints, suppression of major histocompatibility complex class I molecules, and production of metabolites such as PEG2, ROS, and IDO that suppress T-cell antitumor response by MNP cells. In addition, various immunosuppressive factors, such as interleukin-6 and interleukin-10, transforming growth factor-β, vascular endothelial growth factor, and ROS, contribute to this resistance [8]. To improve immunotherapy for MNPs, new ways that target specific aspects involved in carcinogenesis are needed. A promising approach is the use of retroelements (RE) found in the human genome, which are dysregulated in CRC.

REs are mobile genetic elements that move within the host genome by reverse transcription of their ribonucleic acids (RNA) and integration of the resulting complementary deoxyribonucleic acid (DNA) into new loci. Autonomous REs encode reverse transcriptase and integrase. They include long terminal repeat (LTR)-containing endogenous retroviruses (ERV) and long interspersed elements (LINE) that do not contain LTRs. Nonautonomous REs, such as short interspersed elements (SINE)— including the most common Alu elements v and complex SVAs (SINE-R, VNTR, and Alu), play a role in carcinogenesis by inserting into oncosuppressor genes, inhibiting them, and activating oncogenes [9].

Transposons and their sequence residues comprise over two-thirds of the human genome [10]. They help in controlling gene expression through cis- and trans-regulation and influence epigenetic factors, such as DNA methylation, histone modifications, and RNA interference by noncoding RNAs [9]. LINE-1 (L1) accounts for 17% of all DNA sequences and contributes to somatic movements of nonautonomous Alu elements, SVA, and processed pseudogenes in addition to retrotranspositions of their copies. ERVs account for 8% of the human genome.

Role of REs in the pathogenesis of CRC

CRC is characterized by high expression levels of REs [13] because of epigenetic dysregulation. In a 2012 study of CRC tissues, RE insertions were found in 69 of 107 samples [14]. Whole-genome sequencing of CRC samples showed the presence of multiple L1 retrotranspositions in a single tumor (14–15) with new insertions (25 events) in subclones, suggesting a role of REs in the clonal evolution of CRC [15]. Under the influence of antitumor drugs, such as etoposide, RE expression contributes to the development of chemoresistance in CRC. This was demonstrated in relation to the activation of human endogenous retrovirus (HERV)-WE1, HERV-FRD1, HERV-31, and HERV-V1 [16].

In 2019, a study analyzed 7769 samples of various MNPs and found that 70% of CRC samples had RE insertions with the activation of proto-oncogenes under the influence of integrated HERV and LINE-1 promoters [17]. The severity of RE expression affects the survival of patients with MNPs, indicating the significance of REs in the mechanisms of tumor progression [18].

Insertional mutagenesis in CRC can lead to the inactivation of oncosuppressor genes *BRAF, TP53*, and *APC*, contributing to the progression of carcinogenesis [19]. In addition, *APC* mutation causes hereditary adenomatous polyposis of the colon (Gardner syndrome) and contains mutagenesis hotspots for L1 insertions, which can initiate CRC development [20].

Mutagenesis hotspots for AluYa5 insertions have been identified in hereditary CRC (Lynch syndrome), which accounts for 3% of all cases [21]. A 2020 study of somatic retrotranspositions in the Pan-Cancer Analysis of Whole Genomes project showed observed events in 70% of CRC samples [11].

Studies of patients with metastatic CRC have shown high levels of ERVs because of increased expression of the *TET2* DNA demethylase gene. This was accompanied by an immune and antiviral response [12]. REs are upregulated with long noncoding RNAs, which can be used for epigenetic therapy of CRC. For instance, in 22, 53% of CRC samples exhibited high expression levels of the long noncoding RNA endogenous retroviral-associated adenocarcinoma RNA (EDAVR) associated with ERV MER48. The promoter of ERV MER48 acts as a driver of EDAVR transcription.

Prospects for RE inhibition during tumor treatment

Given that hyperactivated REs play a crucial role in CRC pathogenesis, the use of nucleoside reverse-transcriptase inhibitors (NRTIs), typically employed in viral infection therapy, could represent a promising direction for treating this malignancy. Clinical trials have demonstrated the significant efficacy of NRTIs in the treatment of CRC. In addition to eliminating RE-induced genomic instability, NRTIs induce DNA damage and an interferon response to the tumor [13].

In 2015, experimental studies have demonstrated the efficacy of antiviral medications such as amantadine, ribavirin, and pleconaril in overcoming chemoresistance in CRC caused by HERV activation because of antitumor drug influence [16].

In addition, reverse-transcriptase inhibitors can enhance the effect of immune checkpoint inhibitors by suppressing the expression of telomerase reverse transcriptase [23].

The antitumor efficacy of NRTIs was determined in hormone-resistant prostate cancer [24]. A significant increase in the number and rate of cell death, as well as the inhibition of cell migration ability, was observed in breast cancer cell lines treated with the NRTIs abacavir and stavudine, particularly when used in combination with paclitaxel [25]. A meta-analysis study showed that patients with chronic viral hepatitis B taking NRTI tenofovir have a reduced risk of developing hepatocellular carcinoma [26].

Non-NRTIs, such as efavirenz, have demonstrated antitumor efficacy on pancreatic cancer cells [27]. In vitro, etravirine causes the degradation of AGR2, an endoplasmic reticulum protein secreted by the tumor microenvironment, and suppresses the proliferation, migration, and invasion of tumor cells. In mouse models, the combination of paclitaxel and etravirine more effectively inhibited the progression of ovarian cancer [28].

Histone demethylase inhibitors, such as KDM1A, show promise in suppressing RE activity in CRC by promoting RE silencing. KDM1A demethylates H3K9 and enhances the acetylation of H3K27 and methylation of H3K4, which suppresses the expression of HERV and genes containing LTR in their promoters [29].

Various tumor types exhibit high levels of histone demethylase subfamily members KDM5A/B/C/D of the JARID1 family, which demethylate H3K4me2 and H3K4me3. Selective inhibitors of these members include CPI-455 and 1,7-naphthyridines, which are effective against chemotherapy-resistant MNPs [30].

However, RE silencing does not always exert antitumor effects. For instance, the DNA methyltransferase (DMT) SETDB1 (also known as KMT1E or ESET), which forms repressive tags on H3K9, represses RE expression; however, it is an oncogene because it simultaneously inhibits the *TP53* gene. Therefore, SETDB1 expression plays a crucial role in the survival of most MNPs, including CRC [31]. When considering targets for epigenetic MNP therapy, certain properties must be considered to prevent tumor growth.

Epigenetic activation of REs for CRC treatment

Although RE activation plays an important role in tumor progression and its inhibition is effective in treating CRC and other MNPs, CRC immunotherapy takes a diametrically opposite approach by stimulating antiviral immunity directed at double-stranded RNAs formed from RE transcripts. This method, known as viral mimicry, is associated with the artificial epigenetic activation of RE by inhibiting DMT and histone methyltransferase [32].

Upon the enhanced RE expression and double-stranded RNA formation, the interferon response is activated, leading to the apoptosis of MNP cells. Double-stranded RNAs can be sensed by mitochondrial antiviral signaling proteins MAVS and the Toll-like receptor TLR3 [33]. In addition, T-killers recognize HERV transcription products, leading to the destruction of MNP cells [34]. This mechanism can be used for DNA vaccination based on viral vectors [35].

The use of the DMT inhibitors 5-aza-2-deoxycytidine and 5-azacytidine (5AS) for viral mimicry was first explored in 1979 during the treatment of myeloleukemia [36]. Preclinical studies conducted in 2015 on CRC [37] and breast cancer [38] cells have also reported viral mimicry under the influence of 5-aza-2-deoxycytidine [37, 38].

In 2017, clinical trials demonstrated the efficacy of guadecitabine (SGI-110), a non-nucleoside DMT inhibitor, in patients with acute myeloblastic leukemia [39]. Tazemostat inhibits EZH, a histone methyltransferase that establishes H3K27me tags in RE loci. The efficacy of Tazemostat in clinical trials for mesothelioma, epithelioid sarcoma, and large B-cell lymphoma [40] served as the foundation for the use of EZH2 inhibitors in treating chemotherapy-resistant breast cancer [41] and prostate cancer in combination with anti-PD-1 [42]. Histone methyltransferase G9a inhibitors were found to be effective against ovarian cancer [43].

SUV39H1 histone methyltransferase, which is recruited by FBXO44 to the RE loci in the genome, may be a target for viral mimicry in antitumor therapy [44]. However, REs not only stimulate the antiviral response but also have immunosuppressive effects, which explain their key role in carcinogenesis. For instance, injecting metastatic CRC cells with activated HERV expression into Danio fish embryos significantly decreased interleukin-1 and myeloperoxidase levels [45]. This favors a selective approach for viral mimicry aimed at stimulating specific REs that have a stimulatory antiviral response and are not involved in CRC pathogenesis.

Furthermore, the search for drugs with additional antitumor properties is promising. For instance, the DMT inhibitor procaine activates *PAX9*, which promotes the differentiation of oral carcinoma cells, leading to their subsequent apoptosis [46].

DMT inhibitors can demethylate the promoter regions of hypermethylated tumor-suppressor genes such as *MGMT, MLH1*, and *RASSF1A*, resulting in additional antitumor effects [47].

Table 1. Pattern of changes in the expression of microRNAs originating from transposons in colorectal adenocarcinoma

MicroRNA	Transposon, a source of microRNAs [authors]	Changes in microRNA expression [48]
miR-1249	LINE/L2 [51–53]	Decrease
miR-1266	SINE/MIR [52, 53]	Decrease
miR-1271	LINE/L2 [51–52]	Decrease
miR-1296	LINE/L2 [54]	Decrease
miR-151a	LINE/L2 [50–52, 55]	Increase
miR-192	LINE/L2 [54]	Increase
miR-1976	SINE/MIR [54]	Increase
miR-2355	LINE/RTE-BovB [52, 53, 55]	Increase
miR-28	LINE/L2 [50–52, 55]	Decrease
miR-320b	DNA/hAT-Charlie, LINE/L2 [54]	Decrease
miR-320c	LINE/L1, LINE/L2 [54]	Decrease
miR-326	DNA-TE/hAT-Tip100 [52, 53]	Decrease
miR-335	SINE/MIR [52, 53, 55]	Increase
miR-340	DNA-TE/TcMar [51–53, 55]	Increase
miR-342	SINE/tRNA-RTE [51–53, 55]	Decrease
miR-374a	LINE/L2 [52, 53, 55]	Increase
miR-374b	LINE/L2 [50, 52]	Increase
miR-378a	SINE/MIR [50, 52, 55]	Decrease
miR-450b	LINE/L1 [51–53, 55]	Increase
miR-495	ERV-L/MaLR [54]	Increase
miR-502	LINE/L2 [54]	Decrease
miR-577	LINE/L2 [52, 53]	Increase
miR-582	LINE/CR1 [50–52]	Increase
miR-652	DNA/hAT-Tip100 [50–52, 55]	Decrease
miR-708	LINE/L2 [51–53]	Increase
miR-769	LINE/CR1 [54]	Decrease
miR-942	LINE/L2 [54]	Decrease
miR-95	LINE/L2 [50, 52, 55]	Increase

Note: RNA, ribonucleic acid.

Prospects for targeted immunotherapy for CRC

To achieve the best antitumor effect in treating CRC, specific REs involved in carcinogenesis must be inhibited, and the expression of the most immunogenic REs that do not contribute to the pathogenesis of CRC must be stimulated. Identifying these REs as targets can be performed by analyzing their interactions with microRNAs, which play a crucial role in MNP development [48].

The expression pattern of specific microRNAs in tumors may reflect the participation of mobile genetic elements in MNP development. In addition, the evolutionary relatedness of microRNAs with these elements implies the possibility of using microRNAs as guides for DMT recruitment to the region of mobile genetic element location for their inhibition. Antisense oligonucleotides, RNA sequences that are 12–25 nucleotides long that inhibit gene expression, show promise in targeting microRNAs derived from transposons with oncogenic properties [49].

Since 2008, several publications have presented data on the origin of microRNA genes from REs [50–55]. In addition, OncoMIR, an online resource, stores data on microRNAs involved in the pathogenesis of MNP-specific microRNAs [48]. By analyzing this resource and data from the scientific literature, 28 microRNAs originating from REs (Table 1) have altered expression in CRC. Of these, 14 miRNAs (miR-1249, miR-1266, miR-1271, miR-1296, miR-28, miR-320b, miR-320c,

miR-326, miR-342, miR-378a, miR-502, miR-652, miR-769, and miR-942) exhibited oncosuppressor activity. They could guide the silencing of REs involved in CRC carcinogenesis because of RNA-directed DNA methylation [56]. Because 14 of these microRNAs (miR-151a, miR-192, miR-197b, miR-2355, miR-335, miR-340, miR-374a, miR-374b, miR-450b, miR-495, miR-577, miR-582, miR-708, and miR-95) are oncogenic (high expression in CRC), antisense oligonucleotides can be used as tools to inhibit them for treating CRC.

In addition to microRNAs, long noncoding RNAs can be used as guides in CRC immunotherapy. These RNAs, whose genes evolved from REs [57] and are involved in carcinogenesis, include the long noncoding RNA TROJAN, which evolved from HERV and is involved in the progression of triple-negative breast cancer [58]. HERVs are sources of long noncoding RNAs involved in carcinogenesis, such as HCP5 [59], PRLH1 [60], and lncMER52A [61]. In addition, specific long noncoding RNAs serve as guides for histone modification (ANRASSF1, ANRIL, BORDERLINE, Kcnq1ot1, NeST, and PINT) and DNA methylation (Airn, ecCEBP, H19, Kcnq1ot1, PAPAS, pRNA, PTENpa1-AS, TARID, and Xist) [62]. This suggests the possibility of using them for epigenetic influence on RE activity in CRC antitumor therapy.

Conclusions

The search for new immunotherapy methods for the treatment of CRC is promising because of the low efficacy and dangerous side effects of checkpoint inhibitors. Targets such as REs, whose double-chain transcription products stimulate interferon synthesis and tumor cell apoptosis, have shown clinical efficacy in CRC and other MNPs. Because RE activation is a key factor in CRC development, the safest approach is to target highly immunogenic REs that are not involved in CRC pathogenesis. RE activation drives tumorigenesis in CRC, leading to clonal evolution and chemoresistance. Therefore, selective inhibition of REs involved in CRC carcinogenesis shows promise as a complex therapy in conjunction with viral mimicry. Reverse-transcriptase inhibitors may be included in the complex treatment of preventing RE insertions. MicroRNAs that are involved in carcinogenesis and originated from REs during evolution can guide the targeting of specific REs.

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