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МЕТОД ВИРУСНОЙ МИМИКРИИ В ОНКОЛОГИИ И ПЕРСПЕКТИВЫ ЕГО РАЗВИТИЯ

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The Method of Viral Mimicry in Oncology and Prospects for its Improvement

Резюме

Клетки злокачественных новообразований характеризуются эволюцией клонов, устойчивых к применяемым противоопухолевым препаратам и уклонением от воздействия иммунной системы. В связи с этим перспективным и многообещающим направлением в современной онкологии является стимуляция иммунного ответа против новообразований. Данный способ может быть использован в комбинации с другими противоопухолевыми препаратами и самостоятельно. Клетки опухолей вырабатывают контрольные точки CTLA4 (CTLA4 — cytotoxic T-lymphocyte protein 4) и PD-1 (programmed cell death), подавляющие активность Т-лимфоцитов и выработку ими противоопухолевых цитокинов. В клинике применяются антитела против CTLA4, PD-1 и PD-L1, монотерапия которыми повышает эффективность применяемой химиотерапии, но значительно усугубляет развитие нежелательных реакций, что ограничивает их назначение. Монотерапия анти-PD/PD-L1 показала низкую эффективность и также высокий риск осложнений со стороны легких, печени и щитовидной железы. В связи с этим необходима разработка новых способов иммунотерапии опухолей. Наиболее перспективен в данном отношении метод вирусной мимикрии, когда в качестве триггера для выработки интерферона и активации Т-киллеров служат двуцепочечные РНК, образованные из транскриптов ретроэлементов. Для искусственной активации ретроэлементов используют ингибиторы ДНК-метилтрансфераз, деацетилаз и метилтрансфераз гистонов. Поскольку ретроэлементы располагаются в интронах генов, вирусная мимикрия может быть использована в сплайсосомной таргетной терапии. Необходимо отметить, что транспозоны служат драйверами канцерогенеза, поэтому, помимо их искусственной активации, в онкологии используются методы сайленсинга ретроэлементов с помощью ингибиторов обратной транскриптазы. Применение для этого неспецифических метилтрансфераз и ингибиторов деметилаз гистонов может привести к подавлению экспрессии других генов, с возможным провоцированием побочных эффектов. Поэтому данная методика наиболее перспективна с использованием гидов, направляющих ферменты модификации гистонов в локусы расположения генов ретроэлементов в геноме. Гиды могут быть использованы также для активации наиболее значимых ретроэлементов в развитии иммунного противоопухолевого ответа и исключения экспрессии элементов, участвующих в инициации и поддержании канцерогенеза. В качестве гидов могут быть использованы микроРНК, длинные некодирующие РНК и антисмысловые олигонуклеотиды.

Ключевые слова: *антисмысловые олигонуклеотиды, вирусная мимикрия, злокачественные новообразования, канцерогенез, микроРНК, ретроэлементы, таргетная терапия, транспозоны*

Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Malignant neoplasms cells are characterized by clonal evolution that is resistant to the applied antitumor drug and evasion from the effects of the immune system. Therefore, a promising direction in modern oncology is the stimulation of the immune response against neoplasms. This method can be used in combination with other anticancer drugs and alone. Tumor cells produce CTLA4 (CTLA4 — cytotoxic T-lymphocyte protein 4) and PD-1 (programmed cell death) checkpoints that inhibit the activity of T-lymphocytes and their production of antitumor cytokines. The clinic uses antibodies against CTLA4, PD-1 and PD-L1, monotherapy with which increases the effectiveness of the chemotherapy used, but significantly aggravates the development of adverse reactions, which limits their use. Monotherapy with anti-PD/PD-L1 showed low efficacy and also a high risk of pulmonary, hepatic, and thyroid complications. In this regard, it is necessary to develop new methods of tumor immunotherapy. The most promising in this regard is the method of viral mimicry, when double-stranded RNA formed from transcripts of retroelements serve as a trigger for the production of interferon and activation of T-killers. For artificial activation of retroelements, inhibitors of DNA methyltransferases, deacetylases, and histone methyltransferases are used. Since retroelements are located in gene introns, viral mimicry can be used in spliceosomal targeted therapy. Transposons serve as drivers of carcinogenesis, therefore, in addition to their artificial activation, oncology uses methods for silencing retroelements using reverse transcriptase inhibitors. The use of non-specific methyltransferases and inhibitors of histone demethylases for this can lead to suppression of the expression of other genes, with possible side effects. Therefore, this technique is the most promising with the use of guides that direct histone modification enzymes to the loci of the location of retroelement genes in the genome. Guides can also be used to activate the most significant retroelements in the development of the immune antitumor response and exclude the expression of elements involved in the initiation and maintenance of carcinogenesis. MicroRNAs, long non-coding RNAs, and antisense oligonucleotides can be used as guides.

Key words: *antisense oligonucleotides, viral mimicry, malignant neoplasms, carcinogenesis, microRNA, retroelements, targeted therapy, transposons*

Conflict of interests

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AZA — 5-aza-2-deoxycytidine, CTLA4 — cytotoxic T-lymphocyte protein 4, HERV — human endogenous retrovirus, LINE — long interspersed nuclear element, MAVS — mitochondrial antiviral-signaling protein, ORR — objective response rate, PD-1 — programmed cell death (programmed cell death checkpoints), PD-L – programmed cell death ligand, SINE — short interspersed nuclear element, TLR3 — toll-like receptor 3, TNF-α — tumor necrosis factor alpha, ASO — antisense oligonucleotide, HDM — histone demethylase, lncRNA — long non-coding RNA, dsDNA — double-stranded DNA, MN – malignant neoplasm, DNMT — DNA methyltransferase, HDACi — histone deacetylase inhibitors, DNMTi — DNA methyltransferase inhibitors, NRTI — nucleoside reverse transcriptase inhibitors, NNRTI — non-nucleoside reverse transcriptase inhibitors, ncRNA — non-coding RNA, RE — retroelements, STT — spliceosome-targeted therapy, TNBC — triple negative breast cancer

Introduction

One of the factors for malignant neoplasm (MN) progression can be immune evasion by tumor cells due to affected secretory and regulatory function of T lymphocytes, antigen presentation, and a change in the production of immunosuppressive mediators. These mechanisms can be utilized for the targeted action of anticancer agents through their stimulation (for example, stimulation of T cells producing cytotoxines and interferon-γ) or inhibition (inhibition of immunosuppressive mediators such as transforming growth factor beta (TGF-β), tumor necrosis factor alpha (TNF-α), interleukins IL-1, IL-6, IL-8, IL-10, colony-stimulating factor (CSF-1), and type I interferon) [1]. MN cells effectively suppress the immune response by activating negative regulatory pathways called “checkpoints.” Tumors use these checkpoints to evade detection by the host’s immune system. There are known checkpoints of programmed cell death (PD-1) and cytotoxic T-lymphocyte protein 4 (CTLA4) [2]. The PD-1 cell surface receptor is expressed by T lymphocytes being activated during priming or expansion and binds to one of two ligands PD-L1 or PD-L2, which are produced by normal and tumor cells under the influence of cytokines (such as interferon-γ). When PD-L1 or PD-L2 binds with PD-1 receptors, a signal inhibiting the T lymphocyte activity is generated. CTLA4 also acts as a negative regulator, which controls T cell activation due to competition with co-stimulating molecule CD28 to bind common ligands CD80 and CD86. Antibodies blocking the PD-L1/PD-1 interaction have anticancer effect due to activation of immune response to MN cells [3].

Antibodies to α-PD-1 (anti-PD-1), including nivolumab, pembrolizumab, cemiplimab, sintilimab, camrelizumab, toripalimab, tislelizumab, zimberelimab, prolgolimab, and dostarlimab, as well as antibodies to α-PD-L1 (anti-PD-L1) atezolizumab, durvalumab, and avelumab have found their clinical use in the treatment of hemoblastosis and solid tumors [4]. According to the meta-analysis data, anti-PD-1/PD-L1 can enhance the efficacy of the conducted chemotherapy in cancer patients when combined with CTLA4 inhibi-

tors [5], in patients with gastric and gastroesophageal cancer [6], stage 3/4 melanoma [7], and nasopharyngeal carcinoma [8].

Meta-analyses of trials in cancer patients have demonstrated that the PD-L1 and PD-1 inhibitors alone or in combination with other anticancer agents can significantly increase the risk of hepatotoxicity [9], immune-related pneumonitis [10], thyroid dysfunction (especially, hypothyroidism) [11], and rash (especially when anti-PD-L1 and anti-PD-1 are used in combination) [12]. Concomitant use of anti-PD-L1/PD-1 and BRAF and MEK inhibitors significantly increases the risk of fever, asthenia, myalgia, arthralgia, hypothyroidism, liver injury (with a change in ALT and AST levels) [7]. Therefore, combination of anti-PD-L1/PD-1 and chemotherapy in MN can be related to the risk of complications, which restricts their use. At the same time, anti-PD-L1/PD-1 inhibitors alone are not highly effective. For example, in the treatment of nasopharyngeal carcinoma, the objective response rate (ORR) is 19 % for nivolumab, 23.3 % for JS001, 26.3 % for pembrolizumab, 34.1 % for camrelizumab [8]. For α-PD-1 inhibitors, ORR was 1.33 on average, regardless of tumor type [5]. The meta-analysis of anti-PD-L1/PD-1 use in elderly (older than 75 years) patients with solid tumors did not show their efficacy (except for the treatment of melanoma) when used alone [13]. In this regard, the search for new methods of MN immunotherapy having more specific targets involved in carcinogenesis seems promising.

Retroelements in the immunotherapy of malignant neoplasms

One of the directions in anticancer therapy is the method of viral mimicry, which triggers antiviral response due to activation of retroelements (RE) present in the human genome [14]. Since the formation of 5-methylcytosine is associated with heterochromatization and transcriptional repression [15], DNA methyltransferase inhibitors (DMTi) can be used for this purpose, which unlabel 5-methylcytosine at RE loci and promote their expression. Consequently, this enhances immune transmission of antiviral protection signals and triggers cytosolic recognition of double-stranded RNA (dsRNA) of human endogenous retroviruses (HERV) with subsequent cell apoptosis under the action of interferon. Mitochondrial antiviral-signaling proteins (MAVS) and toll-like receptor 3 (TLR3) can be used as dsRNA sensors [16]. HERV transcription products are also recognized by T-killers that destroy MN cells [17], which may be used for DNA vaccination based on adenoviral or other vectors [18].

Retroelements are mobile genetic elements (transposons), specific DNA regions able to move inside the genome. A thorough analysis of the human DNA sequences has demonstrated that transposons constitute the major part of nucleotide sequences in the human genome (69 %) [19]. In addition to REs, the human genome contains DNA transposons, which are moved using the cut-and-paste mechanism, making up to 3 % of all genome sequence. Retroelements replicate through reverse transcription of their RNA and integration of the cDNA into another locus. REs are subdivided into those containing long terminal repeats (LTR) of HERV (constituting 8 % of genome), and REs non-containing LTR (more than 35 % of genome): autonomous long interspersed nuclear elements (LINE) and non-autonomous short interspersed nuclear elements (SINE) [20].

Viral mimicry can be induced by 5-aza-2-deoxycytidine (5-AZA) and 5-azacytidine (5AC), which were first used in the clinical practice in 1979 for the treatment of chronic myeloleukemia [21]. In 2015, the phenomenon of viral mimicry under the influence of AZA was described in preclinical studies of breast cancer cells [22] and colorectal cancer cells [23]. Non-nucleoside DMTi include such epigenetic regulators as epigallocatechin, curcumin, RG-108, isoxazoline, hydralazine, procaine, which are reversibly binding to the catalytic domain of DMT [24]. Clinical trials conducted in 2017 demonstrated the efficacy of non-nucleoside DMTi of guadecitabine (SGI-110) in patients with acute myeloblastic leukemia [25].

In addition to DMTi, the exposure on histone-modifying enzymes can be used for RE activation in viral mimicry. An example of this is tazemetostat, EZH inhibitor, which is a component of the Polycomb Repressive Complex 2 (PRC2), placing histone H3 lysine 27 methylation marks (H3K27me). The efficacy of tazemetostat in clinical trials for the treatment of mesothelioma, epithelioid sarcoma and large B-cell lymphoma [26] has become the basis for the use of EZH2 inhibitors in the treatment of chemotherapy-resistant breast cancer [27], as well as prostate cancer (in combination with anti-PD-1) [28]. The combination of DMTi and histone deacetylase inhibitors (HDACi) shows the most remarkable antitumor effect. In the experiment with mouse models of non-small cell lung cancer, this method enhanced antigenic presentation through increased dsRNA expression, with stimulation of type I interferon. This also included the activation of CCL5 (a T cell chemoattractant) and inhibition of MYC oncogene. Consequently, the tumors became representative for the immune response, with their infiltration by T-killers [29]. The combination of DMTi and HDAC showed a pronounced antitumor effect in mice with epithelial ovarian cancer, most significantly in combination with anti-PD-1 [30].

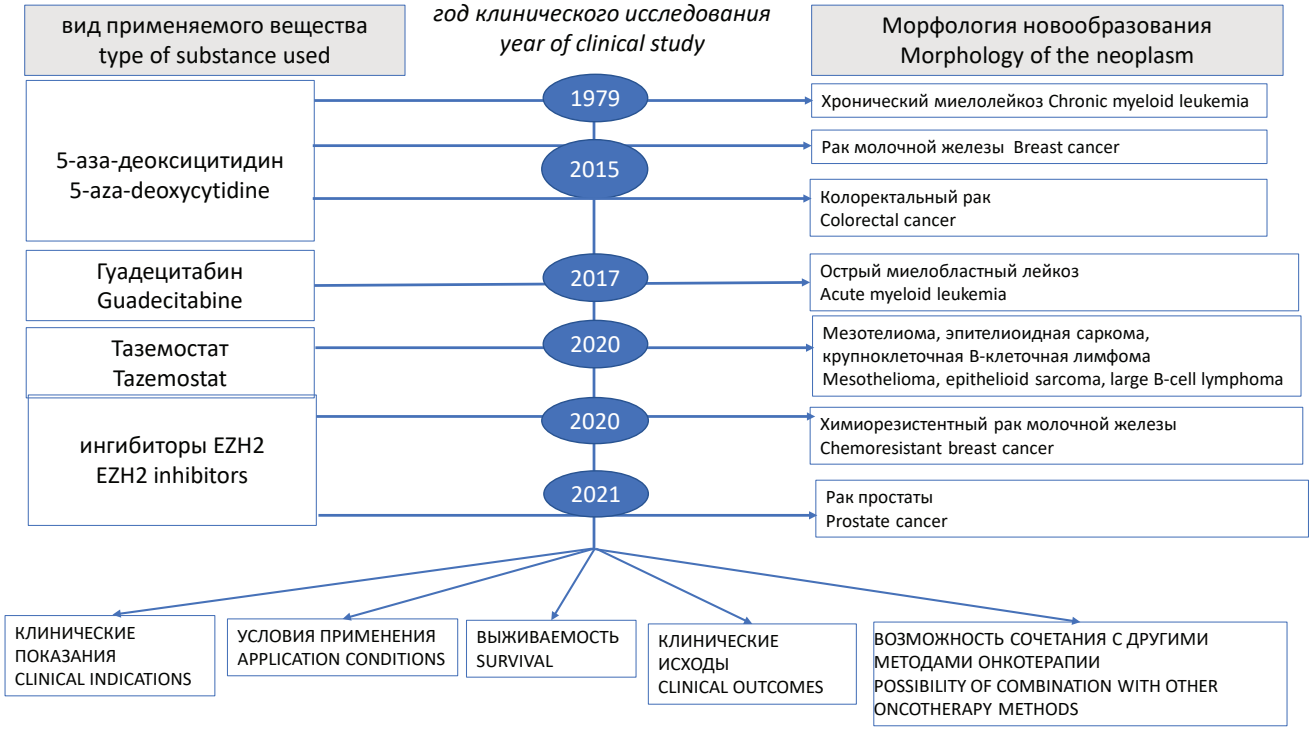

Figure 1. *Algorithm for applying the method of viral mimicry in oncology with examples*

The effect of viral mimicry may be achieved by inhibition of histone methyltransferase (trimethylation of H3K9me3, a RE repressive mark). An example of this is the use of SENDB1 histone methyltransferase inhibitors in the treatment of acute myeloblastic leukemia, which causes the formation of heterochromatin in RE loci using KAP1 or human silencing hub complex (HUSH) [31]. G9a histone methyltransferase inhibitors demonstrated their efficacy against ovarian cancer cells [32]. A promising target for viral mimicry in anticancer treatment is SUV39H1 histone methyltransferase, which is recruited by FBXO44 in the RE locus [20]. Depletion of another SETDB1 histone methyltransferase causes RE activation, inducing expression of viral response genes and SETDB1-medicated death of acute myeloblastic leukemia cells [33]. Figure 1 shows an algorithm for virus-mimicking drugs in the oncology with examples.

Role of virus-mimicking targets in carcinogenesis

Since DMTi, HDACi, and methyltransferase inhibitors used in the clinical practice and developed in viral mimicry are not selective towards activation of specific REs, possible consequences caused by their effects should be considered, since REs are drivers of carcinogenesis (Figure 2). The role of abnormal activation of LINE-1 in tumor initiation in MN is confirmed [34, 35]. In meta-analyses, reliable activation of Alu elements [36] and LINE-1 [37] has been identified in the tissues of various MN. In large-scale trials, RE insertions in the genomes were demonstrated in 35 % [38] to 87 % (for certain MN types) of tumor samples with activation of proto-oncogenes under the influence of integrated promoters HERV and LINE-1 [39]. The grade of RE activation also influences the survival rate of patients with MN, which is indicative of RE significance in tumor progression mechanisms [40]. Therefore, it may be safer to use the methods that affect strictly defined REs, carrying no potential risk of secondary tumors in humans. This strategy may be implemented with specific guides: synthetic oligonucleotides or non-coding RNA, that is complementary to RE. Since most long non-coding RNA (lncRNA) genes [41] and microRNAs [42] evolved from transposons, an analysis of their relationships may be promising for the development of targeted therapy for MN using viral mimicry.

The data on the involvement of specific ncRNAs derived from RE in carcinogenesis are in favor of the proposed approach to the use of guides. LncRNA TROJAN evolved from HERV is used in the mechanisms of triple negative breast cancer (TNBC) progression [43]. HERVs have proven to be sources of HCP5 [44], PRLH1 [45], and lncMER52A [46] lncRNAs involved in carcinogenesis. LncRNA processing can lead to the development of specific microRNA involved in carcinogenesis: in breast cancer, lncRNA LOC554202 is expressed, processing in

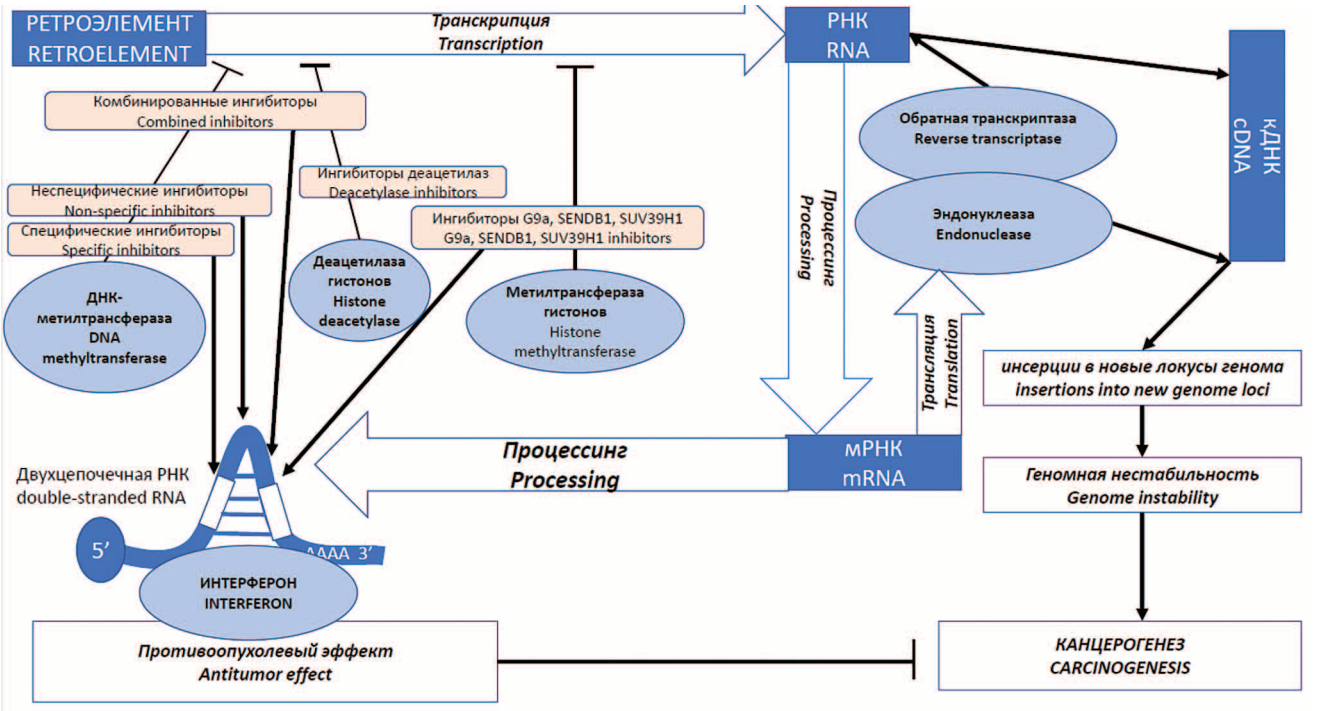

Figure 2. *Scheme of used variants of viral mimicry and the role of retroelements in carcinogenesis*

miR-31 [47], and lncRNA H19 in miR-675 [48]; lncRNA MIR497HG generates pri-miR-497, precursor of miR-195 and miR-497 (binding with ribosomes and producing tumor suppressive peptide miPEP497) [49]. According to the literature data, 94 specific microRNA derived from transposons take part in the development of various MN [42].

Role of retroelements in the spliceosome-targeted therapy of tumors

The viral mimicry phenomenon may be used with regard to the RE genes located in the introns, as well as the sequences of the introns, that evolved from RE [50]. This technique is part of the spliceosome-targeted therapy (STT) of tumors. Inhibition of spliceosome components leads to defective splicing, resulting in the formation of double-chain loops of mRNA molecules (Figure 3) and becoming targets for the body's antiviral systems. The resulting interferon causes tumor cell apoptosis. In STT, various splicing components are affected, including SF3B1 protein that stabilizes binding of small nuclear RNA U2 with branch point sequence; protein U2AF1, recognizing AG dinucleotide in 3'-splice site; SRSF2 binding mRNA exonic splicing enhancer motifs; ZRSR2, spliceosome components, required to recognize 3'-splice sites [51].

Since the immunogenicity of REs is the highest, dsRNAs of SINE transcripts, which are often located in introns, have been proposed as targets for viral mimicry in STT [15]. The efficacy of STT was demonstrated in the experiment on MYC-positive cells of TNBC. In this case, dsRNAs formed from incorrectly spliced mRNA, which were perceived by the body's antiviral defense systems, were used as the targets. For this purpose, agents SD6 and H3B-8800 targeted to SF3B1 spliceosome component were used [52]. Prostate cancer cells are characterized by high sensitivity to the spliceosome inhibitor E7107, which also targets the SF3B complex [53].

It should be noted that mutations of the splicing factors or molecules affecting it can play an important role in the MN etiopathogenesis. For example, mutations in *SF3B1, SRSF2, U2AF1, ZRSR2* genes can be associated with acute myeloblastic leukemia, while a mutation in the *U2AF1* gene is found in hairy cell leukemia [51]. Therefore, one of STT options can be based on a completely opposite principle: restoration of spliceosome component function to eliminate the mechanisms of tumor development. In renal cell carcinoma, microRNA miR-30a-5p and miR-181a-5p suppress expression of SRSF7 (serine/arginine-rich splicing factor 7). Consequently, splicing of apoptosis regulators and tumor suppressors is disrupted, which leads to carcinogenesis [54]. Retinoic acid-induced miR-10a and miR-10b repress SRSF1, leading to differentiation of neuroblastoma cells [55].

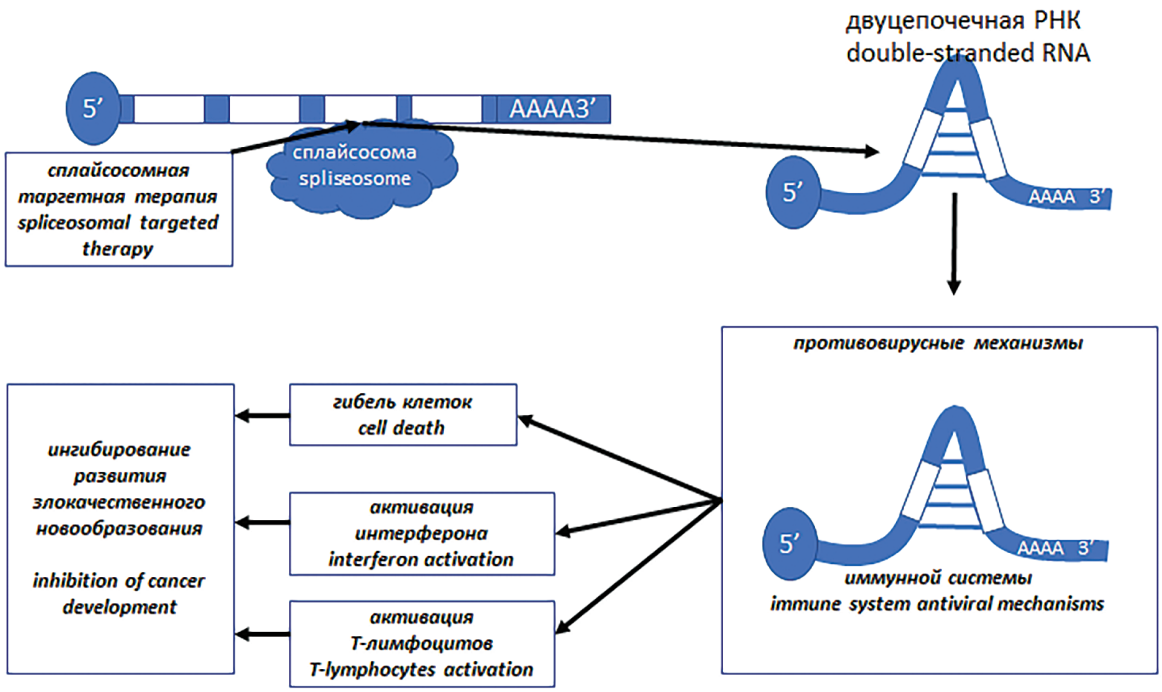

Figure 3. *Scheme of immune response activation against the tumor using spliceosomal targeted therapy*

Inhibition of retroelements in anticancer treatment

It should be taken into account that the use of viral mimicry in anticancer treatment can have negative effects, since MN is characterized by abnormal activation of REs, which cause genomic instability and carcinogenesis. Therefore, similarly to STT, a strategy aimed at suppressing RE expression, which is completely opposite to viral mimicry, can be used in MN treatment with regard to REs. Inhibition of histone demethylases (HDM) characterized by hyperexpression in MN with loss of heterochromatin and RE activation can be used for this purpose. A target for RE inhibition can be HDM KDM1A (LSD1), which suppresses HERV expression and genes containing LTRs in their promoters through demethylation of H3K9 and increased acetylation of H3K27 and methylation of H3K4 [56]. Increased levels of HDM KDM5A/B/C/D subfamily members, JARID1 family, demethylating H3K4me2 and H3K4me3, are also detected in various tumor types. Selective HDM inhibitors include CPI-455 and 1,7-naphthyridines, which are effective against chemotherapy-resistant MNs [57].

A specific histone methyltransferase SETDB1 (ESET, KMT1E), acting on H3K9me3 in an HDM-independent manner through interactions with the KRAB-containing zinc-finger protein, could be a promising target for RE inhibition in anticancer treatment [58]. However, the studies show that in addition to RE splicing, SETDB1 prevents functioning of transcription factors CDX2, ELF3, HNF4G (hepatocyte nuclear factor 4 gamma), PPARG (peroxysome proliferator-activated receptor), VDR (vitamin D receptor). Therefore, depletion of SETDB1 in the experiment contributed to the transition of colorectal cancer stem cells into a postmitotic state with restoration of normal morphology and global gene expression profile of differentiated cells [59]. Consequently, SETDB1 activation to inhibit REs abnormally activated in tumors can cause other pathways of carcinogenesis. It is necessary to consider these mechanisms when developing targeted anticancer therapy. Therefore, the effect on specific REs that are carcinogenesis inductors using the microRNA or lncRNA complementary to these REs as molecule guides seems promising (Figure 4). The use of reverse transcriptase as a target can be another alternative option of RE inhibition.

Clinical studies demonstrated a significant efficacy of nucleoside reverse transcriptase inhibitor (NRTI) in patients with colorectal cancer. In addition to eliminating the genomic instability caused by retroelements, NRTI induced DNA damage and antitumor interferon response [35]. Antitumor efficacy of NRTI is determined with regard to hormone resistance prostate cancer [34].

In the breast cancer cell line, the use of NRTIs such as abacavir and stavudine was shown to be associated with a significant increase in the number and rate of cell death and inhibition of their migration ability, especially in combination with paclitaxel [60]. Meta-analyses also demonstrated a reduced risk of hepatocellular carcinoma in patients treated with NRTI tenofovir in patients with chronic viral hepatitis B [61].

The use of non-nucleoside reverse transcriptase inhibitors (NNRTIs) is also promising. They include efavirenz, which showed its antitumor activity in pancreatic cancer cells [62]. NNRTI etravirine, which caused AGR2 degradation (anterior gradient homolog 2 protein), suppressed proliferation, migration and tumor-cell invasion in vitro. In mouse models, the combination of paclitaxel and etravirine demonstrated more effective inhibition of ovarian cancer progression [63]. It should be noted that a pronounced expression of telomerase reverse transcriptase was associated with a poor clinical response to immune checkpoint inhibitors [64], due to which NNRTIs can be recommended in combination with these agents.

Antisense oligonucleotides (ASOs), RNA sequences of 12 to 25 nucleotides long, which inhibit gene expression by binding to cellular mRNAs, as well as microRNAs and long non-coding RNAs, can be used as tools for RE inhibition [65]. Since REs are key evolutionary sources (therefore, they contain identical sequences) of lncRNA [41] and microRNA [42] genes, the use of these ASOs may influence REs. In addition to non-coding RNAs, the targets of ASOs are molecular members of splicing, RNA translation, mRNA degradation, and sequestered protein release [65]. The modern scientific literature contains no information on the use of RE-targeted ASOs in oncology. However, there is evidence of the use of ASO targeting Alu in age-related macular degeneration [66], targeting SVA (SINE-VNTR-Alu) RE in Fukuyama muscular dystrophy [67], targeting HERV HML-2, which participated in the pathogenesis of amyotrophic lateral sclerosis [68].

The design of ASOs targeting specific REs may be based on the existing information on the use of ASOs targeting microRNAs (which may have evolved from REs) [42], oncogenes or oncosupressors (since they are characterized by a close relationship with REs in oncology [69]. For example, there are ASOs targeting exon 11 of *NF2* tumor suppressor gene in type 2 neurofibromatosis [70], FLT3-ITD (FMS-like tyrosine kinase-3) and microRNA miR-125b in acute myeloblastic leukemia [2], microRNA miR-17 (for μ-17-ON), miR-21 (for μ-21-ON) and miR-155 (for μ-155-ON) in lymphosarcoma [71], oncogenes IGF1R (insulin-like growth factor receptor) [72], tumor suppressors Smad7 [73], Stat3 in hepatocellular carcinoma [74], oncogene transforming growth factor TGF-β2 in lung cancer [75] and TNBC [76].

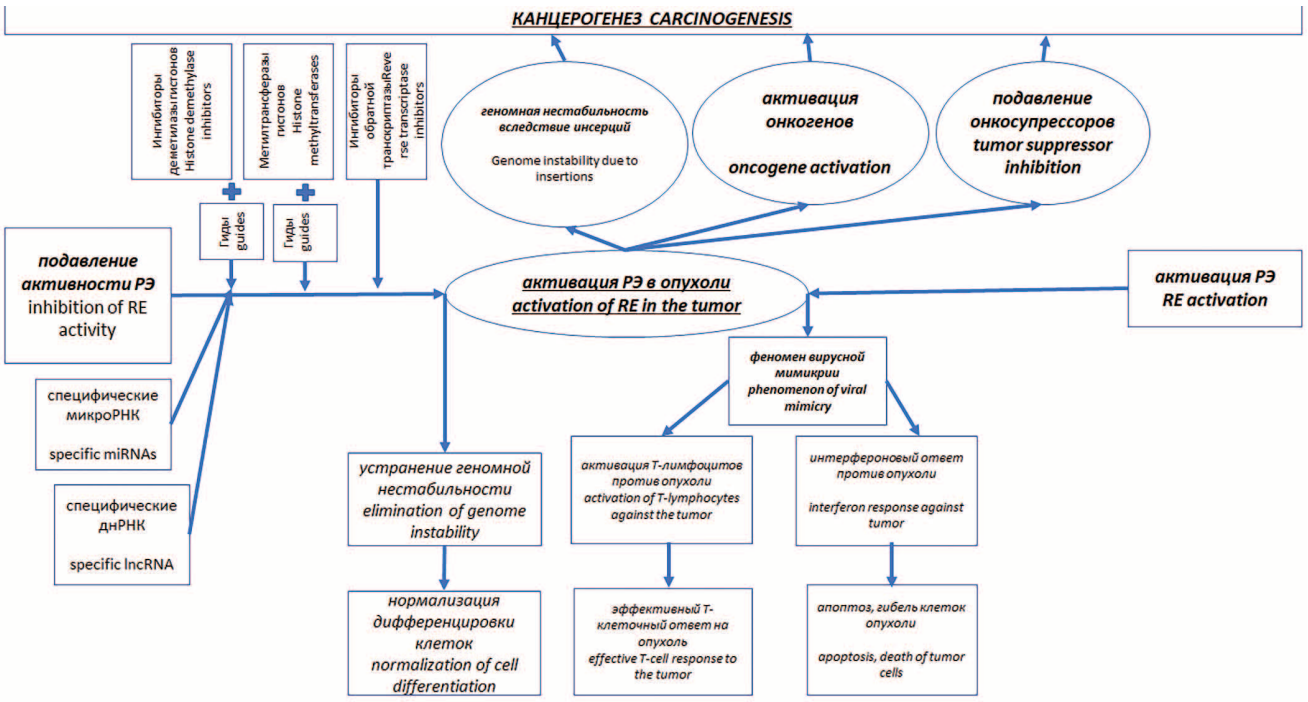

Figure 4. *Scheme of retroelement-targeted antitumor therapy*

Conclusion

Since the anti-PD-1/PD-L1 method is ineffective when used alone, and in combination with anticancer agents, it leads to serious complications, the search for more effective and fewer toxic options is required. The method of viral mimicry is based on activation of RE expression in the tumor, which stimulates the MN immune response. For this purpose, DNA methyltransferase, histone deacetylase and histone methyltransferase inhibitors are used to activate RE and trigger an antitumor interferon response. Splicing targeting therapy is a variant of viral mimicry, in which the targets for the immune response are introns inserted into REs or introns evolved from REs. Since abnormal activation of REs plays a significant role in MN etiopathogenesis, the method of viral mimicry may be most safe when used in combination with agents suppressing the activity of specific REs and their insertion. Reverse transcriptase inhibitors, which are used in clinical practice, can be also used for this purpose. The use of histone demethylase and histone methyltransferase inhibitors, as well as the method of viral mimicry, can be most promising when used in combination with guides (microRNA, lncRNA or ASO) that can recruit histone modification enzyme and DNA into the RE loci playing a certain role in tumor etiopathogenesis (in RE inhibition) or having the greatest clinical significance in the immune response (in RE activation).

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