Roles of PEG10 in cancer and neurodegenerative disorder (Review)

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Abstract. Paternally expressed gene 10 (PEG10) is an imprinting gene. In addition to its known roles in placental development, as well as mouse embryonic stem cell and trophoblast stem cell differentiation, PEG10 has recently been shown to have significance in cancers. High expression of PEG10 is observed in various cancer types and is associated with poor prognosis. Of note, disruption of PEG10 expression leads to increased apoptosis, as well as decreased proliferation, invasion and migration of cancer cells. PEG10 is expected to become a target for cancer and neurodegenerative disorder therapy. This article reviewed the latest progress in the role of PEG10 in cancers.

Contents

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1. Introduction

In tumors, certain genes related to proliferation and invasion are upregulated in expression (1). In neurodegenerative diseases, there are also a bulk of genes with abnormal expression, including genes related to the autophagy-lysosomal pathway (2). These abnormally expressed genes may not only serve as biomarkers for disease diagnosis, but also as targets for treatment. Human endogenous retroviruses (HERVs) are derived from ancient retroviruses, which infect and insert viral genes into germline cells. HERVs constitute an estimated 8% of the human genome (3). In general, a complete HERV includes 5' long terminal repeats (5' LTR), a primer-binding site, group-specific antigen gene (gag), a protease gene, a polymerase gene (pol), an envelope gene and 3' LTR elements (4). Paternally expressed imprinted gene 10 (PEG10) is an evolutionarily conserved HERV gene (5) belonging to the Ty3/Gypsy family of retrotransposons. Evolutionarily, PEG10 is a therian-specific gene (6,7), and differentially methylated regions of PEG10 have emerged in the therian ancestor at least 160 million years ago (8). During the evolution of the placenta in mammals, PEG10 was inserted into the genome, as it exists in marsupials but not in egg-laying monotreme species (9). PEG10 is a paternally expressed imprinting gene, which was reported to be located at human chromosome 7q21 in 2001 for the first time (7). Importantly, PEG10 can be used for RNA delivery (10-13). As an imprinting gene, PEG10 is crucial for placental development and plays a key role in mouse embryonic stem cell and trophoblast stem cell differentiation (14-16).

Ono *et al* (17) have reported that PEG10 maintains placental function, and deletion of PEG10 in mice can lead to embryonic lethality. Traditionally, PEG10 expression is limited to the testes, adrenal gland and skin after adulthood (18). During the past few years, knowledge of PEG10 being highly expressed in tumors and neurodegenerative diseases has emerged. Thus, the present article reviewed the recent findings on the roles of PEG10 in these diseases.

2. The structural domains of the PEG10 protein

PEG10 contains 2 overlapping open reading frames (RF1 and RF1/2), and the mRNA of PEG10 utilizes a typical retroviral frameshift mechanism to encode two proteins: RF1 (encoding gag-like protein) and RF1/2 (encoding gag-pol-like polyprotein) (19,20). The frameshifting efficiency of PEG10 is ~22% (19) and a study has identified that the frameshift of PEG10 can be suppressed by a small-molecule compound (21). The ribosomal frameshift element of PEG10 consists of 'slippery' and 'pseudoknot'. The slippery sequence is GGGAAAC, while pseudoknot is composed of multiple stem-loop structures. When ribosomes encounter the pseudoknot, the A- and P-site tRNAs detach from the zero frame codons GGA-AAC, shifting back one nucleotide to GGG-AAA, causing the original encoding of glycine-asparagine to change to glycine-lysine (22). PEG10 has multiple evolutionary conserved functional domains, including a coiled-coil domain, retrotransposon-gag domain, retrovirus zinc finger-like domain, retroviral asparytyl protease domain and reverse transcriptase domain (5,7,23-26). The structure of PEG10 is shown in Fig. 1.

PEG10 as a long non-coding (lnc)RNA. LncRNA is a type of ncRNA with a length exceeding 200 nucleotides. LncRNAs are involved in the occurrence, development and progression of cancer. PEG10 is an upregulated lncRNA in patients with lymphoma (27). In diffuse large B-cell lymphoma (DLBCL), lncRNA PEG10 inhibits microRNA (miR)-101-3p, while miR-101-3p inhibits kinesin family member 2A (KIF2A). Therefore, overexpression of PEG10 leads to an increase in KIF2A expression, promoting DLBCL growth (28,29). LncRNA PEG10 inhibits miR-449a, increases ribosomal protein S2 expression and increases the proliferation, invasion and migration of neuroblastoma cells (30). LncRNA PEG10 and H19 are mutual upstream and downstream regulatory factors, and PEG10 levels are constitutively associated with a high lymph node ratio in gastric cancer (31). Furthermore, knockout of PEG10 causes an increase in miR-3200 and inhibits the proliferation, migration and invasion of gastric cancer cells (32) and glioma cells (33). LncRNA PEG10 inhibits miR-33a in melanoma, thus inhibiting the PI3K/AKT and mTOR pathways (34). Furthermore, overexpression of lncRNA PEG10 also has an essential role in promoting proliferation and invasion in esophageal cancer cells (35) and hypopharyngeal squamous cell carcinoma (36).

PEG10 subcellular localization. PEG10 contains 2 overlapping open reading frames, RF1 and RF2. During embryonic development, PEG10-RF1 and PEG10-RF1/2 proteins are expressed at different stages, suggesting that PEG10-RF1 and PEG10-RF1/2 may have different functions. PEG10-RF1/2 have an aspartate protease domain and new fragments can be generated through self-cutting (19,22). PEG10 is found in multiple cellular components, including the nucleus (24), extracellular vesicles and stress granules (25). PEG10-RF1 has nuclear and cytoplasmic localization and does not enter stress granules under stress conditions. However, PEG10-RF1/2 is only localized in the cytoplasm and enters stress granules under stress conditions (25). PEG10-RF1 contains a retroviral zinc finger domain and is considered a transcription factor, regulates the transcription of genes participates in the progression of cancers and neurodegenerative diseases; these genes include C9orf72-SMCR8 complex subunit, doublecortin like kinase 1, plexin A4, semaphorin 5B, slit guidance ligand 3 and Wnt family member 3A (24).

In addition, PEG10 is a secreted protein produced by Dental-derived mesenchymal stem cells and bone marrow stem cells, which is associated with adipose differentiation. PEG10 expression is generally observed at the immediate early stage of adipocyte differentiation (37).

3. Mechanisms leading to PEG10 activation and inactivation

The increase in PEG10 protein may be caused by various ways, including DNA demethylation, gene duplication, extended RNA half-life, transcriptional activation and inhibition of protein degradation (Fig. 2).

Epigenetic regulation. In the mammalian genome, DNA methylation is an important approach to govern gene expression (38,39). DNA methylation usually inhibits gene expression by recruiting repression proteins or inhibiting transcription factors to DNA. In human parthenogenetic embryonic stem cells, activating transcription factor 7 interacting protein increases PEG10 methylation and inhibits its transcription (40). In $Kras^{G12D}$-induced T-cell neoplasms, imprinting control regions (ICRs) of PEG10 are significantly hypermethylated. Increased DNA methylation at the ICRs of PEG10 is the earliest detectable change in lymphocytic T-cell thymic lymphoma (41). Tet methylcytosine dioxygenase 1 (TET1) is a maintenance DNA demethylase, which promotes PEG10 expression by inhibiting DNA methylation, and deleting TET1 results in an increase of 5-hydroxymethylcytosine in PEG10, leading to a decrease in PEG10 expression (42). Histone methylation is another way to regulate PEG10 expression, and in hepatocellular carcinoma (HCC), menin/mixed-lineage leukemia 1 (MLL) interaction inhibitor MI-503 prevents the display of the menin-MLL1 complex from binding to the PEG10 promoter, reduces the modification of trimethylated H3 lysine 4 in the promoter region and inhibits PEG10 transcription (43).

Gene amplification. Traditionally, gene amplification was identified as one aspect of the genetic instability strongly associated with malignantly transformed cells. Cancer cells use this mechanism to mediate overexpression of certain oncogenes to promote proliferation, anti-apoptosis and resistance to anticancer drugs (44). For instance, genomic amplification of PEG10 at the 7q21.3 locus was found in HCC samples (45,46). In hepatitis B virus-associated HCC, the increase in DNA copy number leads to an increased expression of PEG10 (47).

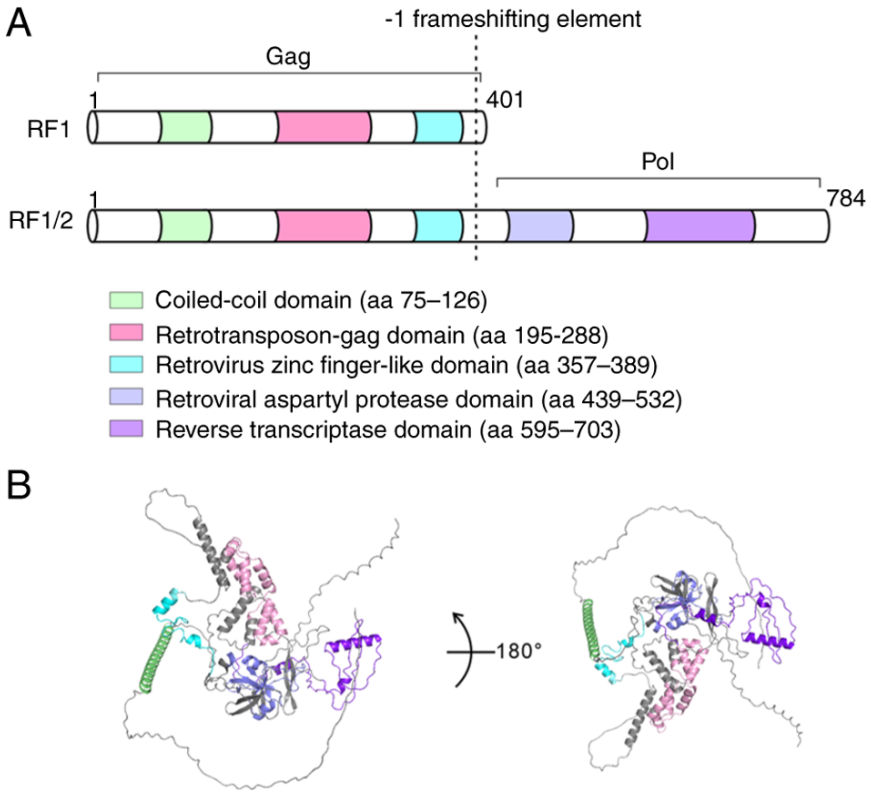

Figure 1. Structure of PEG10. (A) Domain organization of PEG10. PEG10 mRNA produces two proteins, a PEG10-RF1 and a full-length PEG10-RF1/2. (B) Cartoon representation of PEG10-RF1/2 (AlphaFold: AF-I3NHH4-F1). Function of these domains: Coiled-coil domain (homomorphic and heteromorphic protein interaction), retrotransposon-gag domain (RNA binding), retroviruses zinc finger-like domain (DNA binding), retroviral aspartyl protease domain (self-cleavage) and reverse transcriptase domain (RNA binding). Brown ribbons represent the linker domain. RF, reading frame; PEG10, paternally expressed gene 10; pol, polymerase gene; gag, group-specific antigen gene.

RNA stability. The stability of mRNA plays an important role in the control of gene expression (48). PEG10 is a direct target of miRNA-574-5p (30). MiR-138-5p binds to the 3'UTR of PEG10 mRNA, shortening the half-life of PEG10 mRNA (49). In regulating retinoblastoma (RB), the circular RNA Circ:0075804 promotes PEG10 expression by inhibiting miR-138-5p (49). N6-methyladenosine residues on the PEG10 3'UTR are recognized and bind by insulin like growth factor 2 mRNA binding protein 1 to recruit poly (A) Binding Protein Cytoplasmic 1 and enhance the stability of PEG10 mRNA, thereby increasing the protein content of PEG10 (50). In neural progenitor cells, TET3 increases the DNA methylation levels of PEG10 and maintains neural stem cell identity (51). In HCC, miR-122 binds to the PEG10 3'UTR and inhibits PEG10 expression (52). LncRNA SNAI3 antisense RNA 1 increases PEG10 expression through competing endogenous RNA spreading of miR-27a-3p and miR-34a-5p, thereby promoting cancer cell proliferation (53). In human colon cancer cells, miR-491 binds to the 3'UTR of PEG10 mRNA and inhibits PEG10 expression (54). In colorectal cancer, NOTCH1-associated lncRNA in T-cell acute lymphoblastic leukemia 1 increases PEG10 expression to promote tumor progression by sponging miR-574-5p (55).

Transcriptional regulation. Transcription factors can bind to the promoter region of PEG10 and activate its transcription. Myc promotes tumor-cell proliferation by activating PEG10 transcription (56,57). In addition, the E2F family of transcription factors (E2Fs) are transcription factors that promote the transcription of PEG10 and thereby enhance the proliferation of HCC cells (58). Glycogen synthase kinase 3β can phosphorylate and activate E2F transcriptional factor 1 (E2F1). Phosphorylated E2F1 binds to ubiquitin specific peptidase 11, leading to reduced degradation of E2F1 due to deubiquitination. E2F-1 has also been recently shown to be crucial for PEG10 activation in pancreatic cancer, and to further promote cell proliferation, migration and invasion (59). Similarly, in HCC, the expression of PEG10 is positively correlated with lymph node metastasis. Overexpression of PEG10 promotes epithelial-mesenchymal transition, and the expression of PEG10 is influenced by the transforming growth factor β (TGF-β) signaling (60). Furthermore, transcription factor CTR9 homolog, Paf1/RNA polymerase II complex component promotes PEG10 transcription (61).

Although TGF-β promotes PEG10 expression in HCC tissues, in other cancer tissues, the expression of PEG10 is inhibited by TGF-β, e.g. in chondrosarcoma cells (62). Furthermore, the upregulated PEG10 activity in turn inhibits TGF-β and bone morphogenetic protein signaling (63). The transcription factor one cut homeobox 2 binds to the PEG10 promoter and increases the mRNA levels of PEG10 in lethal prostate cancer (64,65), and recent studies demonstrated that androgen receptor (AR) inhibits the transcription of PEG10 (66-68). RB inhibits PEG10 transcription by inhibiting E2F1 activity (26,58). Interestingly, the expression of PEG10 can be regulated by small molecule compounds. For instance,

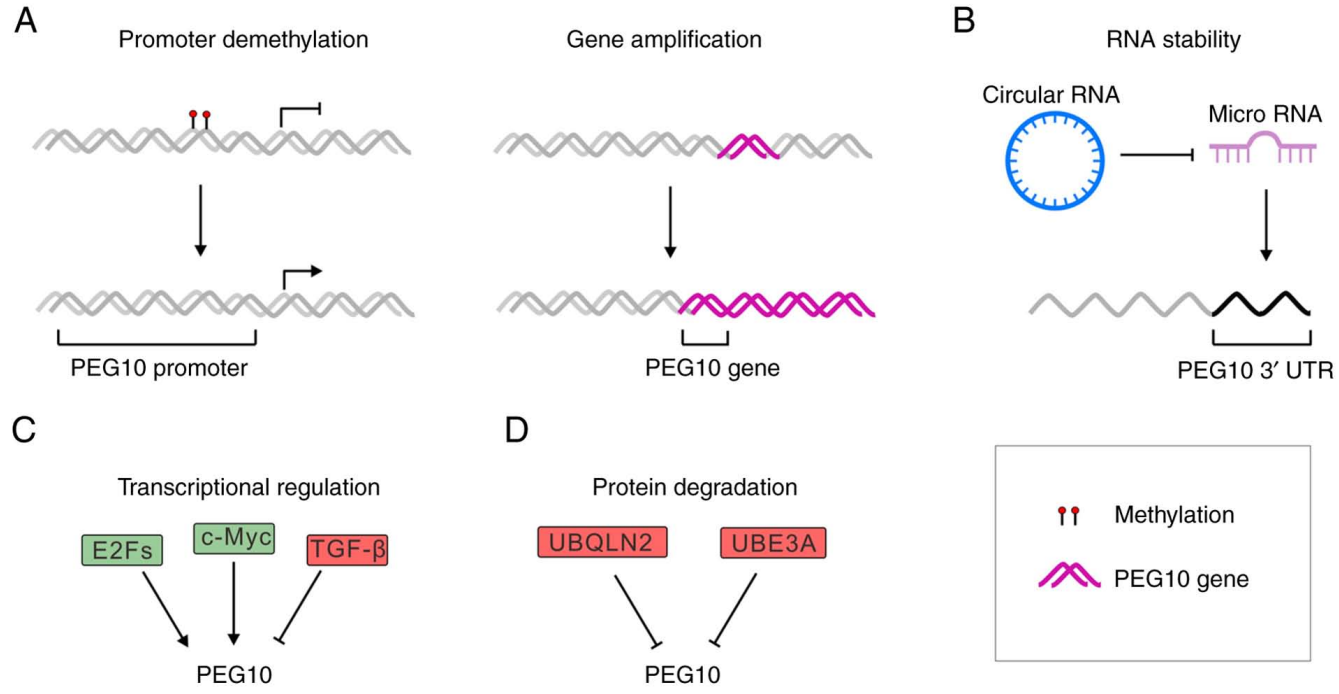

Figure 2. Factors that regulate PEG10 expression. (A) Genetic regulation. (B) miRNAs bind to the 3'UTR of PEG10, which decreases mRNA stability. Circular RNA acts as a sponge for miRNA. (C) Transcriptional regulation of PEG10. (D) Degradation of PEG10 proteins. PEG10, paternally expressed gene 10; miRNA, microRNA; UBE3A, ubiquitin protein ligase E3A; UBQLN2, ubiquilin 2.

curcumin inhibits the expression of PEG10 in an unknown mechanism, thereby inhibiting the growth of breast cancer cells (69). Exposure to cadmium (Cd) can cause a decrease in the expression of Cd-exposed placentas PEG10 (70).

Protein stability. PEG10 has a C-terminal polyproline repeat domain, which may be recognized by human ubiquilin 2 (UBQLN2) and facilitates its proteasomal degradation (24,71). The deficiency of UBQLN2 leads to an increase in PEG10 protein. Furthermore, the ubiquitin protein ligase E3A (UBE3A) is another PEG10 regulating gene. UBE3A inhibits the expression of PEG10 via the proteasome (25)

4. Downstream of PEG10

Nuclear localized PEG10 functions as a transcription factor, mediating the transcription of numerous downstream target genes. Kruppel-like factor 2 (KLF2) is an inhibitory factor of NF-κB and PEG10 activates NF-κB signaling by inhibiting KLF2 expression (23). Upregulated PEG10 expression activates NOTCH signaling and promotes metastatic cancer stem cell self-renewal (72). PEG10 was reported to bind to TGF-β receptor ALK1 and to inhibit ALK1 as well as ALK5 signaling (73). In HCC, TSG101 binds to PEG10 to prevent its degradation, thereby enhancing PEG10 expression and downstream target genes p53, p21 and matrix metalloproteinases (MMPs), leading to cell proliferation, invasion and migration (74). After overexpression of PEG10 in human colon cancer cells, the Wnt1/β-catenin pathway is activated, promoting cell proliferation and inhibiting cell apoptosis (54). In Burkitt's lymphoma cells, PEG10 promotes tumor cell invasion and metastasis by upregulating the expression of MMP-2 and -9 (18,26,59,75). PEG10 promotes the proliferation of endometrial cancer cells by inhibiting the transcription of p16 and p18 genes. PEG10 tends to bind to the TGGGAYTACA and CTCNGCCTCC motifs (50). Of note, it was recently found that PEG10 is an RNA binding protein, promoting trophoblast stem cell differentiation into placental lineages (14).

5. PEG10 in cancer

PEG10 is considered an oncogene and PEG10 protein has been found to be significantly increased in various cancer types to date. Exogenous PEG10 expression leads to increased cellular proliferation and increased cell viability (76).

Liver cancer. The relationship between PEG10 and cancer was first studied in liver cancer. PEG10 is strongly expressed in HCC (77). A machine learning study found that PEG10 is highly expressed in patients unresponsive to transarterial chemotherapy (78). Expression of PEG10 is significantly correlated with poor survival and tumor recurrence in HCC, making PEG10 an independent predictor of early recurrence of HCC (79). However, other studies found that PEG10 has an inhibitory effect on tumor cell growth by activating immune response. For instance, transduction of dendritic cells with PEG10 recombinant adenovirus induced anti-tumor immunity against HCC (80). Another study also identified that androgens activate PEG10 (81). Thereby, PEG10 is the potential biomarker of HCC (82,83).

Lung cancer. An increase in PEG10 content is closely related to the prognosis of lung cancer; therefore, PEG10 is a diagnostic and prognostic gene for lung adenocarcinoma and squamous cell carcinoma (84). E2Fs activate MMPs by upregulating PEG10, leading to lung cancer progression, prognosis and

Table I. Selected PEG10-directed therapies.

Process	Disease	Target	Regulator	(Refs.)
Transcription	HCC	H3K4me3	MI-503	(43)
	HCC	CTR9	shRNA	(61)
RNA stability	Diffuse large B-cell lymphoma	PEG10	shRNA	(23)
	Cutaneous T-cell lymphoma	PEG10	shRNA	(23)
	HCC	PEG10	miR-122	(52)
	Colon cancer	PEG10	miR-491	(54)
	Colon cancer	PEG10	Curcumin	(54)
	HCC	PEG10	miR-27a-3p	(53)
	HCC	PEG10	miR-34a-5p	(53)
	Angelman syndrome	PEG10	shRNA	(25)
	Bladder cancer	PEG10	siRNA	(108)
	Breast cancer	PEG10	siRNA	(112)
	Colorectal cancer	PEG10	miR-574-5p	(55)
	Endometrial cancer	PEG10	siRNA	(50)
	Gastric carcinoma	PEG10	miR-3200	(32)
	Lung cancer	PEG10	siRNA	(85)
	Prostate cancer	PEG10	shRNA	(26)
	Prostate cancer	PEG10	siRNA	(94)
Protein stability	Cutaneous T-cell lymphoma	USP9X	WP1130	(98)
Vaccine	HCC	Dendritic cells	PEG10 recombinant adenovirus	(80)

miR, microRNA; shRNA, short hairpin RNA; PEG10, paternally expressed gene 10; USP9X, ubiquitin specific peptidase 9 X-linked; MI-503, Menin-MLL1 inhibitor 503; HCC, hepatocellular carcinoma.

metastasis (85,86). E2F1 activates PEG10 gene transcription, promoting proliferation of lung epithelial cells (87). Furthermore, transcription termination factor 1 activates receptor tyrosine kinase like orphan receptor 1 (ROR1), which activates PEG10 transcription. Inhibition of ROR1 by small inhibitory (si)RNA in the human lung cancer cell line PC-9 leads to a decrease in the transcription level of PEG10 (88). On the contrary, the expression of PEG10 is also inhibited by certain transcription factors. The expression of PEG10 is inhibited by PI3K/AKT, which leads to a decrease in PEG10 protein levels in lung cancer cells (89).

Prostate cancer. The expression of PEG10 in prostate cancer is usually suppressed, as AR inhibits the transcription of PEG10 (26). However, during the treatment of prostate cancer, AR inhibitors drive cancer cells to evolve into neuroendocrine prostate cancer (NEPC) and the expression of PEG10 gradually increases during the transition from adenocarcinoma to NEPC. Therefore, PEG10 can be used as a predictive indicator for biochemical recurrence of prostate cancer (90). As a characteristic gene of NEPC, silencing PEG10 inhibits the *in vitro* growth of prostate cancer cells (91). In AR activated adenocarcinoma type prostate cancer, full-length RF1/2 is the dominant form, while in NEPC cells, RF1 and RF1/2 are both highly expressed (26). Full-length PEG10 (RF1/2) drive the proliferation of NEPC, while short-length PEG10 (RF1) promotes invasion (26). The expression of PEG10 is associated with short survival of patients with prostate adenocarcinoma (92). Importantly, studies have highlighted the crucial role of PEG10 in promoting the malignant transformation of the highly lethal AR-negative phenotype prostate cancer (93). Silencing PEG10 reduced the expression of neuroendocrine markers and inhibited cell proliferation (94).

Leukemia. Driven by genomic gains and promoter demethylation, PEG10 is highly expressed and is associated with poor patient prognosis in mycosis fungoides-large-cell transformation (23). Furthermore, PEG10 overexpression was observed in B-cell acute lymphoblastic leukemia and B-cell chronic lymphocytic leukemia (95,96). Reducing PEG10 expression leads to a decrease in cell volume and a weakened colony-formation ability in large transformed cutaneous T-cell lymphoma cells; consequently, PEG10 inhibition may be a promising treatment for advanced invasive T-cell lymphoma (23). In thymoma, the DNA methylation level of the promoter region of PEG10 is higher than that of T-cell lymphoblastic leukemia (97,98). Abnormal DNA methylation in PEG10 ICRs is expected to become a prognostic marker for T-cell neoplasm and B-cell chronic lymphocytic leukemia (41,99).

Other cancer types. To date, PEG10 has been shown to be crucial in several types of cancer, such as Ewing sarcoma (ES), esophageal squamous cell carcinoma (ESCC) and metastatic thymic adenocarcinoma. In ES, PEG10 inhibits the TGF-β pathway and reduces cell growth. In the human skin epidermoid carcinoma cell line A431, miR-145, miR-432 and miR-1972 inhibit

PEG10 expression (100). Besides, genetic mutations can also affect PEG10 activity. In metastatic thymic adenocarcinoma, PEG10 was found to have a somatic p.R207H mutation (101). LncRNA PEG10 is elevated in serum exosomes of patients with ESCC (102). Higher PEG10 levels are associated with unfavorable overall and progression-free survival (103). Therefore, PEG10 can serve as a marker of carcinogenesis, progression and poor prognosis, as well as a putative drug target in ovarian cancer (72,104,105), rectal adenocarcinoma (106), early-onset colorectal cancer (107), neuroendocrine muscle-invasive bladder cancer (108), bladder cancer (108), adenosquamous carcinomas (109), gallbladder adenocarcinoma (110), breast cancer (111,112), adenocarcinoma (113), oral squamous cell carcinoma (114) and glioma (115).

6. Neurodegenerative disorder

Amyotrophic lateral sclerosis (ALS). ALS is a chronic neurodegenerative disease that mainly causes damage to upper and lower motor neurons. Mutations in the ubiquitin-adaptor protein UBQLN2 is considered one of the causes of ALS (116,117). PEG10 is a substrate of UBQLN2 (118); UBQLN2 binds to the C-terminus of PEG10 and initiates its degradation (24).

Angelman syndrome. Angelman syndrome is caused by UBE3A defect; patients with Angelman syndrome often experience developmental delay, balance disorders, limb incoordination and gait instability. The UBE3A mutation causes PEG10 aggregation, alters neuronal migration and ultimately leads to Angelman syndrome (25).

7. Therapeutic strategies to target PEG10-driven diseases

Although no targeted small-molecule inhibitors to block PEG10 have been developed, there are still numerous ways to inhibit PEG10, including inhibitors that target its transcription factors, siRNAs, shRNAs or miRNAs that target PEG10 mRNA, as well as using PEG10 as an antigen to develop vaccines (119). PEG10-related treatment methods are listed in Table I. The functional diversity of PEG10 poses multiple challenges to drug development, and ensuring target specificity is key in drug development to avoid unnecessary damage to embryo development or normal tissue function.

8. Conclusions

PEG10 can be used for RNA delivery (10). PEG10 is an imprinting gene expressed in the placenta and tumors. Silencing PEG10 expression in cancer cells slows cell growth, increases apoptosis, and reduces invasion and metastasis. PEG10 is a promising therapeutic target and prognostic marker for cancer. However, due to its nuclear distribution, PEG10 is not suitable for antibody drug development. Synthetic PEG10 siRNA is a potential therapeutic agent. In addition, small molecules targeting the ribosomal frameshift of PEG10 are a promising approach (120,121).

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Availability of data and materials

Not applicable.

Authors' contributions

DM, SB and XB were involved in the conceptualization of the study. SW and YC wrote the original draft. YW and YD prepared the figures. MT and XT reviewed and revised the manuscript. All authors reviewed the manuscript and have read and approved the final version. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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