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Expression and role of long non-coding RNA H19 in carcinogenesis

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1. ABSTRACT

With the recent advent of whole genome and transcriptome sequencing technologies, long non-coding RNAs have been brought into the spotlight in molecular biology. H19 was one of the first reported long non-coding RNAs; its expression is high in embryonic organs and absent or greatly reduced in most adult tissues. Accumulating evidence suggests that H19 plays crucial roles in embryogenesis. However, its levels are increased in different cancers, including breast, hepato-gastrointestinal, urological, respiratory, and brain tumors. Although there have been several controversial reports as to whether H19 is oncogenic or tumor-suppressive, most studies have indicated that H19 is associated with growth, migration, invasion, and/or metastasis in many cancers; however, its reported functional mechanisms vary among cancer types. Furthermore, serum H19 levels in patients with certain cancers have been suggested to be useful for diagnosis and prognosis. Thus, H19 long non-coding RNA might be a candidate for development of promising therapeutic and diagnostic modalities for several cancers. The purpose of this review is to provide an inclusive report on the functional role of H19 in different cancers.

2. INTRODUCTION

Genome-wide transcriptome studies, based on recently developed microarray and next-generation sequencing technologies, have determined that at least 70% of the mammalian genome is actively transcribed and that most transcripts are derived from non-protein-coding genes (1–4). In the classical central dogma of biology, RNA is only an intermediate between DNA and proteins. Therefore, non-coding RNAs were previously considered useless. However, they have recently gained much importance in molecular biology. Increasing evidence suggests the importance of non-coding RNAs in embryogenesis, several physiological

functions, and various diseases (1, 3, 4). Non-coding RNAs are broadly divided into small and long molecules based on the number of ribonucleotides. The former group includes small interfering RNA (siRNA), microRNA (miRNA), piwi-interacting RNA (piRNA), and small nuclear RNA (snRNA), which consists of a ribonucleotide smaller than 200 nt. In contrast, long non-coding RNAs (lncRNAs) range in length from several hundreds to tens of thousands of ribonucleotides. Many of these are mRNA-like transcripts that are transcribed by RNA polymerase II, but fail to encode an open reading frame.

One of the first reported lncRNAs was H19 (1). Human H19 is a 2.3.-kb RNA molecule encoded by the *H19* gene located on chromosome 11p15.5. It is known as an imprinted gene expressed only from the maternal allele. This gene was originally discovered by different research groups (5). Pachnes *et al.* identified it by screening a murine fetal liver cDNA library for clones containing RNA sequences whose amounts decrease after birth (6). It was also isolated by Davis *et al.* in a screen to identify myogenic differentiation genes in myocytes, and was initially called MyoH (7). Poirier *et al.* also isolated it as a gene activated during embryonic stem cell differentiation (8). H19 is highly expressed during embryonic development and is repressed shortly after birth (9). Therefore, it has been considered that H19 plays a key role in embryogenesis (5). Furthermore, H19 was found to be re-expressed in a wide variety of tumor types (Figure 1A) and was suggested to have oncogenic or tumor suppressor abilities (1, 9). There are many varying reports in the literature discussing the functional mechanism of H19 lncRNA in the development and metastasis of different cancer types. One such function is as a microRNA precursor (10), as exon 1 of H19 encodes two conserved miRNAs: miR-675-3p and miR-675-5p (Figure 1B). Another contention is that H19 functions as a competing endogenous RNA (ceRNA), acting as a microRNA 'sponge' through its miRNA binding sites (Figure 1C) (11). Another mechanism involves its interaction with epigenetic regulatory factors such as polycomb-group proteins (Figure 1D). It is thought that certain lncRNAs might facilitate the recruitment of regulatory factors to the promoter of target genes (12). In the following sections, we describe the profiles of H19 expression in fetal and adult organs and the reported roles and functional mechanisms of H19 based on tumor types.

3. H19 IN FETAL AND ADULT ORGANS

H19 is expressed in most organs during early stages of embryogenesis in humans, mice, cattle, and sheep (5, 13, 14). In human fetal organs, H19 is maximally expressed in the adrenal tissue, muscles, and liver (15). H19 has also been found to be highly expressed in the muscles and kidney in bovine fetuses, and in the liver, skeletal muscle, and heart in sheep fetuses (13, 14). In contrast, no or significantly decreased expression of H19 has been observed in the brain of human and bovine fetuses (9, 13). Prominent expression of H19 occurs in the placenta, including the amnion, chorion, and allantois, at a much higher level than that in fetal organs (9, 13, 15). In particular, H19 expression is most abundant in intermediate trophoblasts and villous cytotrophoblasts in placental tissues (9, 15). H19 has been reported to regulate trophoblast cell differentiation and proliferation via imprinting linkage with Igf2 or miR-675 embedded within H19 (16).

Dramatically decreased expression of H19 is detected in most adult tissues (9). Skeletal muscle is the organ with the highest level of H19 expression in adult humans, mice, and cattle (5, 13). Day *et al.* reported that H19 promoted skeletal muscle differentiation and regeneration by giving rise to miR-675-3p and miR-675-5p (17). A fairly high level of H19 expression is maintained in normal adult adrenal tissue (18). In contrast to neoplasms in most other organs, H19 is also highly expressed in adrenocortical adenomas but reduced in carcinomas, suggesting that loss of H19 expression may be associated with malignancy in adrenocortical neoplasms (18).

4. H19 IN CANCER

4.1. H19 in head and neck cancer

Frequent loss of imprinting (LOI) of the *H19* gene has long been identified in head and neck squamous cell carcinoma (HNSCC) (19). A significant correlation has also been demonstrated between H19 expression in HNSCC and recurrence in patients (20). However, in a prediction analysis of microarray data with leave-one-out cross validation, H19 expression was positively correlated with a low risk of recurrence in larynx squamous cell carcinoma (LSCC) (21). Nevertheless, another study indicated that H19 expression in LSCC is inversely correlated with survival in patients (22). The same study also demonstrated that H19 suppressed the activity of miR-148a-3p, thereby enhancing the expression of its target gene, the DNA methyltransferase enzyme DNMT1, which promoted proliferation, migration, and invasion of LSCC cells. In nasopharyngeal carcinoma, H19 lncRNA promoted invasive properties via inhibition of miR-630 and the subsequent regulation of enhancer of zeste homolog 2 (EZH2), which is a target of the miRNA (23). In these cancers, H19 lncRNA acts as an endogenous 'sponge' for microRNA.

4.2. H19 in esophageal cancer

LOI with H19 overexpression was observed frequently in esophageal squamous cell carcinoma

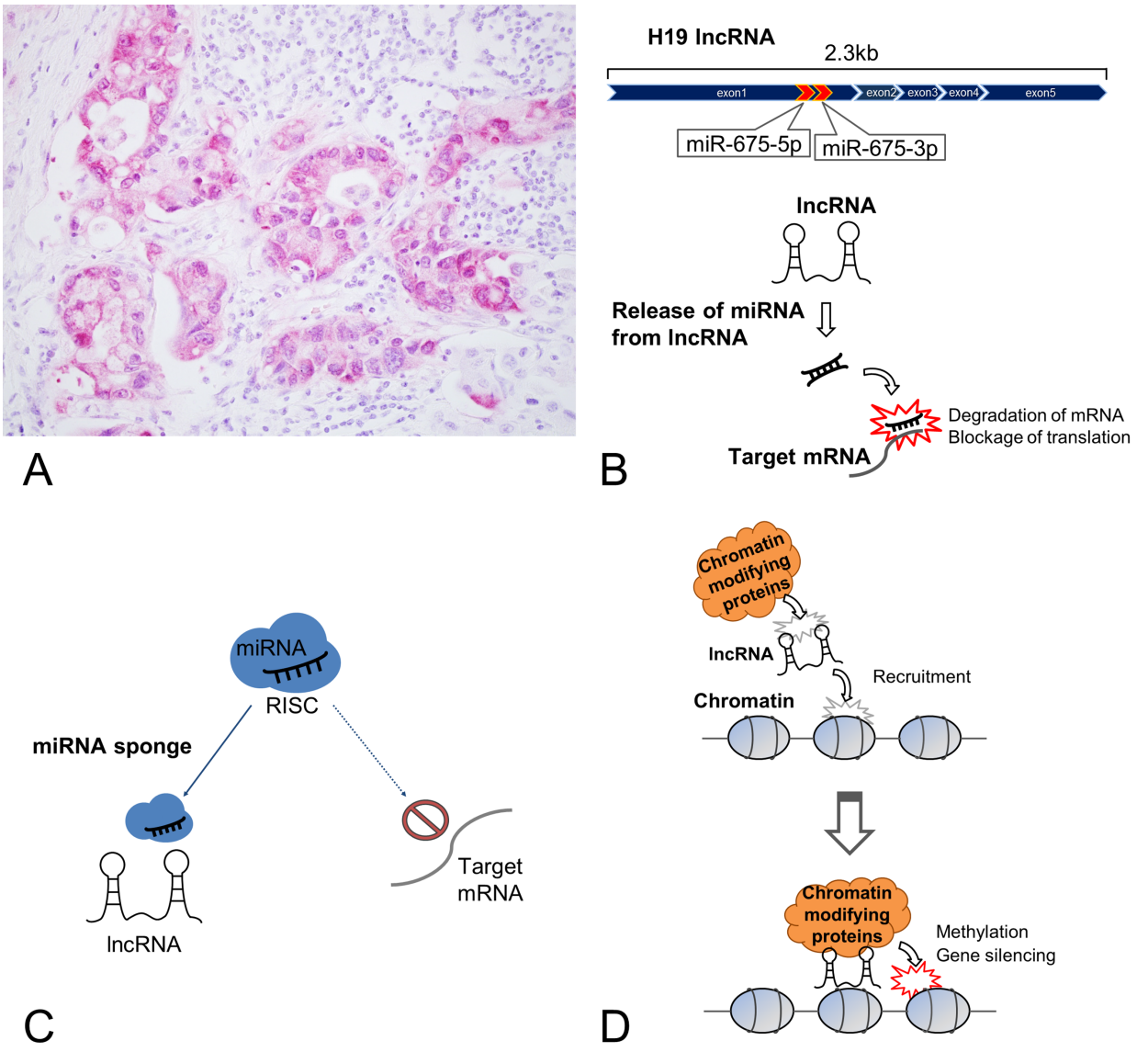

Figure 1. A. H19 lncRNA expressed in human pancreatic carcinoma cells. *In situ* hybridization. B. Some lncRNAs give rise to miRNAs that degrade target mRNAs or block translation. H19 exon1 also encodes two conserved microRNAs, miR-675-3p and miR-675-5p. C. Some lncRNAs share the same miRNA binding sequence with mRNAs. These lncRNAs are considered to act as competing endogenous RNAs (ceRNAs). D. Some lncRNAs can interact with chromatin-modifying proteins such as Polycom-Repressive Complex 2 (PRC2) that are involved in gene silencing. These lncRNAs are considered to facilitate the recruitment of chromatin modifying proteins to promoter of target genes.

(ESCC) (24). A marked correlation was evident between the expression of H19 and tumor invasion depth, tumor stage, and metastasis (25, 26). H19 lncRNA promoted cell proliferation, migration, invasion, and G0/G1 phase arrest, and induced the epithelial-to-mesenchymal transition (EMT), as indicated by downregulation of the epithelial marker E-cadherin with upregulation of the mesenchymal markers vimentin and fibronectin and metastasis-associated protein MMP-9 in ESCC cells (25, 26). Regarding the functional mechanism of H19 in ESCC tumorigenesis, Zhou *et al.* demonstrated that miR-675-5p encoded within the *H19* gene plays a key role by targeting REPS2 via the RalBP1/RAC1/CDC42 signaling pathway (27). In addition, it was reported that H19 DMR methylation might play crucial roles in ESCC progression via IGF2 imprinting (28).

4.3. H19 in gastric cancer

Increased levels of H19 in gastric carcinoma (GC) tissues and cells have been reported (29–31). Among the 135 studied lncRNAs, H19 was the most highly upregulated in GC tissue compared to in paired non-tumorous tissues (32). Enhanced H19 expression in GC tissues correlated significantly with poor overall patient survival (29, 30). Surprisingly, H19 levels in gastric juice from GC patients were significantly higher than those from normal subjects (30). Furthermore,

when the levels of lncRNAs were examined in the plasma of GC patients, H19 was found to be significantly upregulated in patients compared to in healthy controls and significantly downregulated in post-operative samples (33–35). Thus, H19 lncRNA might be useful as a diagnostic biomarker for GC.

The role of H19 lncRNA in gastric carcinogenesis has been addressed in several studies. Yang *et al.* reported that H19 was associated with p53 inactivation, which was followed by suppression of apoptosis and increased cell proliferation (31). Zhang *et al.* reported that H19 lncRNA was induced by the oncogene c-Myc and regulated proliferation in GC cells (29). Zhuang *et al.* demonstrated that H19 modulates GC cell proliferation via its mature product miR-675 by targeting the tumor suppressor runt domain transcription factor 1 (RUNX1) (36). Liu *et al.* also confirmed that RUNX1 is a downstream molecule of the H19/miR-675 axis and that inhibition of RUNX1 stimulates activation of the Akt/mTOR pathway to enhance GC cell proliferation and invasion (37). In contrast, Li *et al.* found that H19 promoted proliferation, migration, invasion, and metastasis in GC cells and identified CALN1 as a target gene of H19-derived miR-675. In addition, H19 was suggested to likely play an additional role through direct binding to ISM1 (38). Furthermore, Zhou *et al.* reported that miR-141 could bind to a sequence in H19 and suppress H19 expression in GC cells (39).

4.4. H19 in colorectal cancer

Enhanced expression of H19 has long been known to occur in colorectal carcinomas (CRCs) and has been suggested to result from LOI (40). High H19 expression levels in CRC tissues were significantly correlated with worse overall survival and disease-free survival in patients (11). A recent evaluation of single nucleotide polymorphisms of *H19* provided evidence that *H19* rs2839689 is positively associated with susceptibility to CRC in the Chinese population (41).

Some researchers have proposed a mechanism for the effect of H19 in the progression of CRC. Tsang *et al.* confirmed an inverse expression pattern between H19/miR-675 and the tumor suppressor Rb in human CRC tissues and cell lines. Furthermore, they identified that H19-derived miR-675 targets Rb to increase cell growth and soft-agar colony formation in colon carcinoma cells (10). Liang *et al.* found that overexpression of H19 promoted EMT and tumor growth in colon carcinoma cells (42), and they focused on the function of H19 as a ceRNA in this process. H19 was found to serve as a molecular 'sponge' for miR-138 and miR-200a, targeting mesenchymal marker genes including vimentin, ZEB1, and ZEB2. In contrast, Han *et al.* confirmed that an RNA-binding protein, eukaryotic translation initiation factor 4A3 (eIF4A3), could bind to H19 lncRNA (11). Combining eIF4A3 with H19 prevented the recruitment of eIF4A3 to cell-cycle-associated mRNA and consequently led to aberrant proliferation of CRC cells.

4.5. H19 in liver cancer

There is contradictory evidence indicating that *H19* can act as an oncogene or a tumor suppressor in hepatocellular carcinoma (HCC). In support of its role as an oncogene, Matouk *et al.* reported that in the Hep3B HCC cell line, H19 expression was elicited in response to hypoxic stress and that knockdown of H19 inhibited tumorigenicity after the cells were subcutaneously injected into nude mice (43). In addition, microarray analysis of H19 knockdown in Hep3B cells after hypoxic stress revealed modulation of the expression of genes involved in angiogenesis, survival, and tumorigenesis. Furthermore, Yang *et al.* demonstrated that high H19 levels in resected HCC tissues were associated with shorter disease-free survival in patients (44).

In contrast, a tumor suppressor role has also been proposed for H19; the results of Zhang *et al.* appeared to directly contrast with the results of the reports described above (45). In particular, Zhang *et al.* showed that H19 expression was lower in intratumoral tissues (T) than in peritumoral tissues (L) and that a low T/L ratio for H19 was an independent predictor of poor outcome in HCC patients. In addition, suppression of H19 expression increased *in vitro* invasion in HCC cells; in addition, intrahepatic metastasis in orthotopic xenograft tumors with reduced H19 expression was greater compared to that in controls. H19 was found to bind to the protein complex hnRNP U/PCAF/RNAPol II to activate the miR-200 family, which consists of EMT suppressive miRNAs, by promoting histone acetylation. Therefore, H19 lncRNA could upregulate the miR-200 family and suppress EMT in HCC cells.

Hernandez *et al.* attempted to solve this paradox (46). They demonstrated that α-fetoprotein-secreting HCCs that are often associated with poor prognosis displayed elevated expression of H19 and its product miR-675. The increased expression of miR-675 led to reduced expression of the tumor suppressor Rb, and therefore stimulated proliferation in HCC cell lines. Furthermore, miR-675 dramatically increased anchorage-independent growth. miR-675 also directly inhibited the expression of a well-known EMT mediator, Twist1, and consequently induced downregulation of the mesenchymal phenotype. This included reduced expression of the mesenchymal cytoskeleton protein vimentin, enhanced expression of the adhesion protein E-cadherin, transformation of cell morphology from a spindle to an epithelioid shape, and reduction of invasive capacity in HCC cells. Although these results were apparently contradictory, the authors concluded

that the epithelial phenotype provided an advantage for cell proliferation and that metastasizing carcinoma cells implanted in secondary organs might induce a mesenchymal-to-epithelial transition (MET) program, required for secondary tumor formation, through the H19/miR-675 pathway.

Recently, Conigliaro *et al.* found that HCC stem-cell-like cells (indicated by CD90 positivity) released exosomes that had the ability to promote tube formation and cell-cell adhesion in endothelial cells (47). LncRNA profiling revealed that the exosomes derived from CD90+ HCC cells were enriched in H19 lncRNA. After upregulation or downregulation of H19 in endothelial cells, it was clarified that H19 plays a critical role in angiogenesis. Thus, H19 lncRNA can be released by cancer stem-like cells via exosomes to potentially affect the cancer microenvironment.

4.6. H19 in bladder cancer

H19 expression in bladder carcinoma (BC) has long been suggested to be useful as a prognostic marker for early recurrence (48–50). SNP polymorphisms in the *H19* gene have been reported to be associated with an increased or decreased risk of suffering BC (51, 52).

Matouk *et al.* showed that overexpression of H19 in BC cells enhanced tumor growth after the cells were subcutaneously injected into mice (43). Additionally, H19 silencing using siRNA decreased tumor volumes *in vivo*. Luo *et al.* reported that H19 lncRNA increased cell migration through its association with EZH2, which led to activation of the Wnt/β-catenin pathway and subsequent inhibition of E-cadherin expression in BC cells (12). They also demonstrated that H19 increased BC cell proliferation through enhanced expression of the DNA-binding protein inhibitor ID2 (53). Liu *et al.* confirmed that miR-675 derived from H19 lncRNA promoted BC cell proliferation through induction of G1 arrest and suppression of cell apoptosis, which was likely dependent on its negative regulation of the tumor suppressor p53 (54). The Yes-associated protein 1 (YAP1) oncogene was identified by Li *et al.* as an upstream gene that induces H19 lncRNA expression (55).

4.7. H19 in renal cancer

It has been shown that epigenetic H19 silencing occurs as an early event in the tumorigenesis of Wilms tumors (56). Therefore, H19 was originally thought to be a tumor suppressor in renal neoplasms (57). However, Wang *et al.* showed that clear cell renal carcinoma (ccRC) tissues had significantly higher levels of H19 compared to adjacent normal tissues and that silencing of H19 reduced cell proliferation, migration, and invasion of RC cells (58). Furthermore, patients bearing ccRC with higher H19 expression had poorer overall survival.

4.8. H19 in lung cancer

LOI of H19 leading to its overexpression has been described as a frequent event during the development of lung carcinoma (LC) (59). Higher expression of H19 is associated with advanced tumor-node-metastasis stage and poorer survival in LC patients (60, 61). H19 knockdown experiments revealed that H19 is involved in cell proliferation, clonogenicity, and anchorage-independent growth in LC (60, 62). Furthermore, H19 was shown to promote cell cycle progression by downregulating miR-107 (63).

As in BC and GC cells, H19 is known to be directly regulated by c-Myc in LC cells (60, 62, 63). Moreover, mineral dust-induced gene (mdig) was reported to demethylate H3K9me3 on the histone H3 peptide, a key regulator and epigenetic marker of heterochromatin, which was followed by the de-repression of H19 lncRNA (61). In a statistical study of lncRNA genetic polymorphisms, H19 rs2107425 was strongly associated with LC susceptibility in individuals under 50 years of age and H19 rs2839698 showed a relationship with platinum-based chemotherapy response in small-cell LC (64).

4.9. H19 in breast cancer

In human breast carcinomas (BCs), the expression of H19 lncRNA is evident in cancer cells or stromal cells (65). Adriaenssens *et al.* performed *in situ* hybridization (ISH) with 102 BCs and found that the *H19* gene was obviously expressed at a higher level in 74 cases (72.5.%) when compared to expression in normal breast tissue. H19 upregulation in BCs was significantly correlated with T values (TNM classification). However, of these carcinomas, only eight cases (7.8.%) exhibited overexpression of H19 in the carcinoma cells themselves, whereas in 99 cases (97.1.%), expression occurred in stromal cells (66). In BCs, H19 lncRNA might contribute to carcinogenesis through the formation of cancer-associated fibroblasts.

Although H19 overexpression in BC cells was detected at a lower frequency than expected, this phenomenon seemed to be important for cancer progression. Multidrug-resistant MCF-7/AdrVp BC cells display abundant expression of H19 relative to parental MCF-7 cells (67). Moreover, in an *in vitro* study using MDA-MB-231 BC cells, a clone stably transfected with the genomic sequence of the human H19 gene was shown to form more and larger colonies in soft agar during anchorage-independent growth assays and formed more and larger subcutaneous tumors after injection into *scid* mice (68). A follow-up study from the same research group showed that H19

promotes the G1-S transition, as the H19 promoter is activated by E2F1 in BC cells (69). Furthermore, the same research group identified that miR-675, derived from H19 lncRNA, enhanced proliferation and migration in BC cells by downregulating genes of the ubiquitin ligase E3 family (70). Barsyte-Lovejoy *et al.* demonstrated a strong association between c-Myc and H19 expression in samples from BC patients (62). The product of the *MYC* oncogene directly binds to conserved E-boxes at the *H19* promoter and enhances the transcription of the maternal H19 allele. In addition, knockdown of H19 expression significantly decreased clonogenicity and anchorage-independent growth in BC cells.

A relationship between the expression of H19 and hormone receptors has been suggested in BC. H19 overexpression in BCs was significantly correlated with the presence of both estrogen and progesterone receptors (66). H19 expression was shown to depend on the estrogen receptor, and H19 was suggested to mediate estrogen-induced cell proliferation in BC cells (71). H19 was also reported to be associated with luminal progenitor cell differentiation that is regulated by estrogen (72).

Recently, Zhang *et al.* evaluated whether circulating H19 RNA in the plasma could serve as a novel biomarker for the diagnosis and monitoring of BC (73). H19 levels were significantly increased in plasma from BC patients compared to that from healthy volunteers and the value of H19 as a biomarker was higher than that of carcinoembryonic antigen and carbohydrate antigen 153.

4.10. H19 in cervical cancer

According to a previous report, LOI of the *H19* gene occurred in 36% and 100% of informative cervical and endometrial carcinoma cases, respectively (74). When H19 expression was assessed in cervical intraepithelial neoplasia 3 (CIN3) samples by *in situ* hybridization, the signals were present exclusively in areas of CIN3 that were within the cervical epithelium (75). In cervical carcinoma cells, H19 lncRNA was overexpressed and promoted cell proliferation and sphere formation, but did not affect apoptosis and migration (76). H19 expression was regulated by TGF-β1 treatment or the hypoxia inducer $CoCl_2$ in a cell line-specific manner. In addition, extracellular vesicles released from cervical carcinoma cells into the culture medium contained H19 lncRNA.

4.11. H19 in brain neoplasms

Imprinting status varies in different types of brain tumors (77–79). Shi *et al.* discovered high expression of H19 lncRNA in high-grade gliomas and found that H19 stimulated glioblastoma cell invasion by modulating the expression of Cadherin13, which was a direct target of miR-675 derived from H19 (80). Jiang *et al.* reported that H19 expression levels in glioblastoma tissues were associated with patient survival (81). H19 was shown to promote cell invasion in Matrigel assays, angiogenesis in endothelial tube formation assays, and tumorigenicity in a xenograft mouse model. In addition, H19 was suggested to be correlated with stemness based on the enrichment of H19 lncRNA in stem cell marker CD133+ glioblastoma cells and based on the high degree of sphere formation in H19-overexpressing cells. Li *et al.* later observed low cell proliferation and high rates of apoptosis, in addition to downregulation of the stem cell markers CD133, NANOG, Oct4, and Sox2, in H19-deficient glioblastoma cells (82). Jiang *et al.* also demonstrated decreased stemness in H19-deficient glioblastoma cells. In addition, the observed enhancement of the ability of tumor suppressor let-7 miRNA to inhibit the expression of its target HMGA2 oncogene was related to the self-renewal of cancer stem cells (83). The function of H19 as a let-7 'sponge' was responsible for this phenomenon.

5. CONCLUSION

Although the oncogene or tumor suppressor status of H19 remains controversial in some cancers, H19 is highly expressed and correlated with growth, migration, invasion, and/or metastasis in most types of cancer. Restricted expression of H19 has been shown in adult normal tissues of several organs. These findings indicate that this lncRNA might serve as a novel candidate for molecular targeted therapy, using nucleic acid-based medicine, for several cancers. Furthermore, recent studies have suggested that H19 lncRNA is released from a wide variety of cancers and is detectable in the sera of patients as a stable form that is protected from endogenous RNases. Thus, circulating H19 lncRNA could be a promising new biomarker for the early detection or prognosis of cancers.

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