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REVIEW ARTICLE

Long noncoding RNA (lncRNA) *H19*: An essential developmental regulator with expanding roles in cancer, stem cell differentiation, and metabolic diseases

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Abstract Recent advances in deep sequencing technologies have revealed that, while less than 2% of the human genome is transcribed into mRNA for protein synthesis, over 80% of the genome is transcribed, leading to the production of large amounts of noncoding RNAs (ncRNAs). It has been shown that ncRNAs, especially long non-coding RNAs (lncRNAs), may play crucial regulatory roles in gene expression. As one of the first isolated and reported lncRNAs, *H19* has gained much attention due to its essential roles in regulating many physiological and/or pathological processes including embryogenesis, development, tumorigenesis, osteogenesis, and metabolism. Mechanistically, *H19* mediates diverse regulatory functions by serving as competing endogenous RNAs (CeRNAs), *Igf2*/*H19* imprinted tandem gene, modular scaffold, cooperating with *H19* antisense, and acting directly with other mRNAs or lncRNAs. Here, we summarized the current understanding of *H19* in embryogenesis and development, cancer development and progression, mesenchymal stem cell lineage-specific differentiation, and metabolic diseases. We discussed the potential regulatory mechanisms underlying *H19*'s functions in those processes although more in-depth studies are warranted to delineate the exact molecular, cellular, epigenetic, and genomic regulatory mechanisms underlying the physiological and pathological roles of *H19*. Ultimately, these lines of investigation may lead to the development of novel therapeutics for human diseases by exploiting *H19* functions.

Introduction

Gene expression is the core process of all aspects of life. The process begins in the cell nucleus with genomic DNA, the template for transcription of messenger RNAs (mRNAs), after transcription, mRNAs translocate to the cytoplasm and act as blueprints for translation into proteins. In addition to mRNAs, there are many non-protein coding RNAs (ncRNAs), such as transfer RNAs, ribosomal RNAs, and small nuclear RNAs that are also essential for gene expression. Since the completion of the Human Genomic Project, it has been estimated that while over 80% of human genomic DNA is transcribed, only about 2% of the human genome is transcribed into mRNA and translation to proteins, indicating the pervasiveness of ncRNAs.[1–5] Recently, ncRNAs have been characterized as having regulatory functions in many physiological and/or pathological processes and are regarded as the therapeutic targets for disease.[2,6–11] In particular, long non-coding RNAs (lncRNAs), non-protein coding transcripts longer than 200 nucleotides, are rapidly being identified as having crucial roles in regulatory control of gene expression,[2,3,7,10,12] such as promoter-specific gene regulation,[13–15] acting as competing endogenous RNAs (CeRNAs),[15,16] X-chromosome inactivation,[17–20] imprinting,[21–24] maintenance of nuclear architecture,[25–27] *etc*.

LncRNA *H19*, first isolated and reported in the 1980s by 4 different laboratories, is one of the first identified imprinted genes and lncRNAs.[21–23,28–31] In 1990, Brannan et al found that the *H19* gene did not code for any protein even though it is transcribed by RNA polymerase II, spliced, and polyadenylated.[29] In mice, *H19* contains three reading frames, however, multiple translation termination signals were found in all three reading frames.[29] In 1991, Bartolomei et al confirmed that *H19* is only transcribed from the maternally inherited allele, the paternal *H19* allele is not expressed in mice. Meanwhile, *H19* and *Igf2* genes are tightly linked and imprinted in opposite directions.[21] The following year, Zhang et al identified that *H19* is also maternally expressed in humans.[32] Then, H19 was certified as a lncRNA since it does not contain the short introns that are characteristic of imprinted coding genes, complete absence of transcribed peptide, form secondary RNA structures and hairpin loops, localize in a cytoplasmic ribonucleoprotein particle, and may function as a riboregulator.[23,29,33,34] In the past few decades, the regulatory functions of *H19* have been increasingly clarified. The expression patterns of *H19*, *H19* encoded-microRNAs and anti-sense, the interlinking expression of *H19* and *Igf2*, *etc*. are characterized. Here, we summarize these diverse regulatory functions in numerous physiological and pathological processes.

Critical roles of H19 in embryogenesis and development

H19 is highly expressed in developing embryos, especially in mesoderm- and endoderm-derived tissues. However, *H19* is strongly down-regulated after birth in all tissues including skeletal and cardiac muscle tissues,[28,30] although not entirely turned off in skeletal and cardiac muscle tissues.[35] Loss of *H19* function in the liver and a few other endodermal tissues did not influence the survival of mice and instead resulted in an overgrowth phenotype similar to babies with Beckwith-Wiedemann syndrome, which may have been caused by overexpression of *Igf2*.[34] However, the overexpression of *H19* in the mouse zygote causes lethal effects between embryonic day 14 and birth, which

indicates the importance of strict control of *H19* during embryogenesis.[36] On the other hand, mice lacking *H19* showed an overgrowth phenotype, while mice with *H19* enhancer overexpression had reduced postnatal growth.[37] In addition, human imprinting control region 1 (IC1) can functionally replace mouse IC1on the maternal allele, but not paternally, which indicated the paternal imprinting at IC1 between mice and humans.[38] These results indicated the fine-tuning role of *H19* during both embryogenesis and development.

As a maternally imprinted gene, *H19* expression is regulated by methylation during embryogenesis. *H19* methylation regions differ according to parental inheritance, the paternal copy of *H19* is methylated and silent while the maternal copy is either hypomethylated or unmethylated, resulting in different maternal *H19* allele expression in offspring.[39–43] Meanwhile, methylation of the *H19* promoter is negatively correlated with *H19* expression and *H19* expression is negatively correlated with the neighboring gene *Igf2* expression.[42–45] Han et al recently characterized that disruption of *Igf2*/*H19* expression in parthenogenetic fetuses and placentas contributes to implantation failure and/or abortion in swine parthenogenesis, which might be associated with differential methylation patterns in the imprinting control region of imprinted genes.[46] *H19* and *Igf2* shared several enhancers, which are tissue-specific.[47] In other words, the mutual regulation of *Igf2* and *H19* could not be ignored during embryogenesis.[41,48]

Although *H19* is strongly down-regulated after birth in most tissues, it still plays an important role in development. Since it was known that *H19* was highly expressed in muscles after birth, the biological function of *H19* was first explored in motor system development.[37,49,50] *H19*-deficient mice displayed hyperplasia in the late fetal stage, hypertrophy at the postnatal stage in skeletal muscles, and had decreased number of mutant satellite cells.[51] On the other hand, Martinet et al found that *H19* deficiency decreased the number of mutant satellite cells; however, the self-renewing capacity of these cells was not affected, which may be due to the up-regulation of other genes in the imprinted gene network.[51] During the myogenic differentiation process, *H19* is highly activated by the key transcription factor *MyoD*, which is highly expressed during myoblast differentiation and muscle regeneration. What is more, *H19* and *Igf2* misexpression work separately, cooperatively, and antagonistically to establish the developmental phenotype through different signaling pathways.[52] These results indicated the essential role of *H19* in muscle development.[49]

As for osteogenic differentiation, *H19* showed an increased expression pattern in mesenchymal stem cells (MSCs) during the initial period. *H19* regulates several signaling pathways involved in MSC osteogenic differentiation.[49,53–57] Similar to the function of *H19* in embryogenesis, we found that adenovirus-mediated overexpression of *H19* inhibited osteogenic differentiation of MSCs, while down-regulation of *H19* alleviates MSC osteogenic differentiation.[58,59] Meanwhile, it has been reported that *H19* regulated chondrogenic differentiation by potentiating Sox9-mediated collagen type II formation, which indicates the regulatory function of *H19* in cartilage formation.[49,60] In addition, *H19* was found to promote tenogenic differentiation and suppress adipogenic differentiation of MSCs.[61–63] Overall, these results suggest that *H19* plays an important role in motor system development.

Molecular mechanisms underlying H19 functions

Imprinted tandem gene Igf2-H19

As one of the firstly identified maternal imprinted genes, *H19* and *Igf2* belong to the same locus and are separated only by 90 kb which is located on chromosome 7 in mice and chromosome 11 in human.[21,29,64,65] Most imprinted genes are methylated on maternally derived chromosomes; however, *Igf2-H19* is methylated on paternally derived chromosomes. The expression balance of *Igf2-H19* is one of the most important mechanisms underlying *H19* functions.[66–68] Loss of function of *H19* and overexpression of *Igf2* were associated with overgrowth syndrome called Beckwith-Wiedemann syndrome, on the contrary, will result in fetal and postnatal growth failure called Silver-Russell syndrome.[52,69,70]

The imprinted tandem gene *Igf2-H19* participates in several physiological and pathological processes, such as embryogenesis, tumorigenesis, and guardian of the proliferation of pluripotent stem cells, *etc*.[48,71,72] The regulation of *Igf2-H19* gene expression is one of the essential mechanisms. When the 3′ gene enhancer shared between *H19* and *Igf2* is deleted, both *H19* and *Ifg2* expression are down-regulated. The 3′ enhancer has a more robust effect on the expression of *H19* since *H19* has a stronger promoter in this area than *Igf2* and is physically closer to the 3′ enhancer.[41,48,67,73] On the other hand, tissue-specific and parent-of-origin enhancers were also identified and proved to regulate the expression of *Igf2-H19*[47] (Fig. 1A).

The gap between *H19 and Ifg2* contains differentially methylated regions (DMRs) in the chromosome, whose methylation state regulates the expression of *H19 and Ifg2*. Generally, DMRs are methylated in paternal chromosomes and unmethylated in the maternal chromosome. Methylated DMRs block the binding of DNA-binding zinc finger insulator protein, CTCF, which prevents the transcription of downstream *H19* in the paternal chromosome.[66–68] On the contrary, unmethylated DMRs bind with CTCF and prevent transcription of *Igf2*, and in this situation, only *H19* is transcribed to RNA. This process ensures the maternal imprinted expression of *H19* and maintains a proper balance of *H19* and *Igf2* genes.[48,66–68,73] When the methylation of DMRs within the *Igf2-H19* locus is erased, the expression of *H19* increased and blocked the expression of *Igf2*, which prevents the uncontrolled proliferation and teratoma formation of cells.[73–75] In contrast, loss of imprinting induces hypermethylation of DMRs within *Igf2-H19* on both maternally and paternally derived chromosomes, which is associated with several malignancies and results in high expression of *Igf2*[48,73] (Fig. 1A).

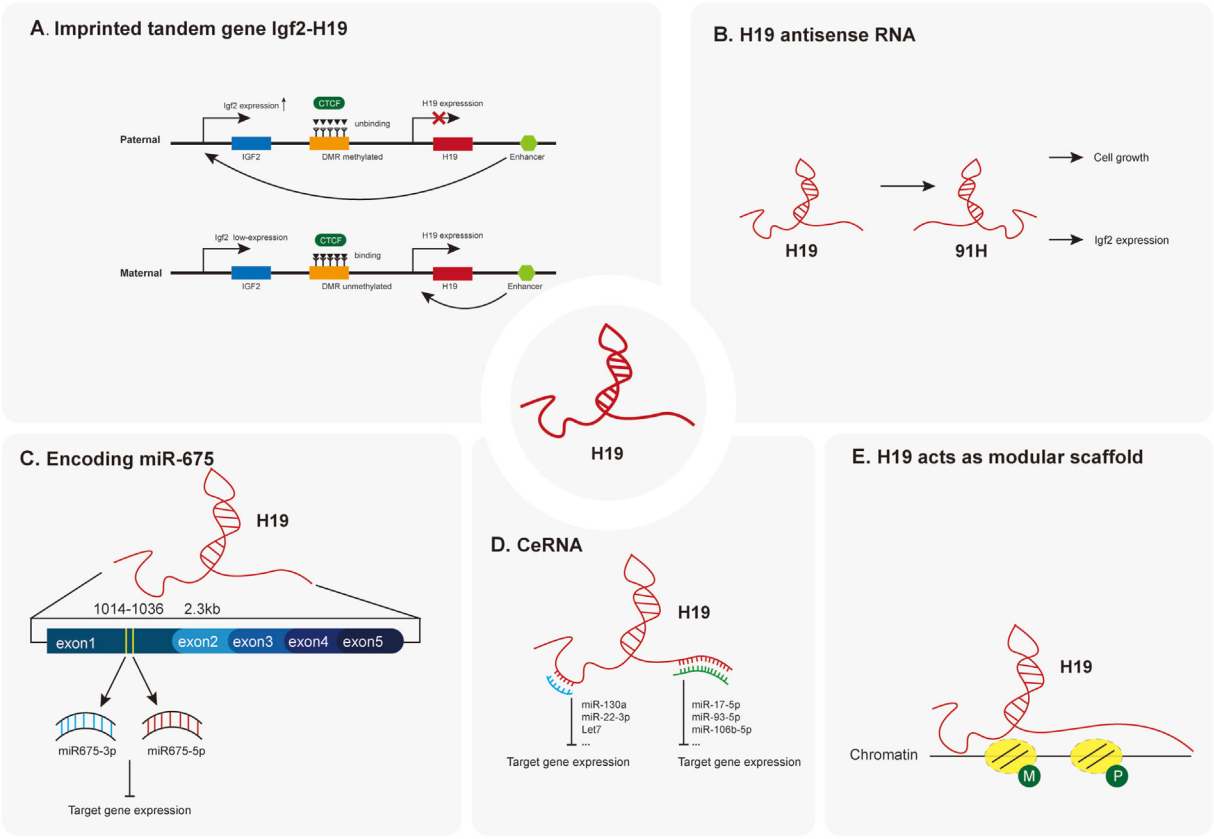

Figure 1 Current models of action for *H19*. **(A)** The imprinted *Igf2-H19* tandem gene participates in several physiological and pathological processes. **(B)** The antisense RNA *91H* can regulate *H19-Igf2* expression and hence impacts cell growth. **(C)** *H19* can encode *miR-675* which regulates gene expression. **(D)** *H19* can act as CeRNA and regulate gene expressions. **(E)** *H19* can act as modular scaffolds for epigenetic modifications.

H19 antisense RNA

Since noncoding antisense transcripts have been suggested to constitute a new epigenetic regulatory system, *H19* antisense (*91H* RNA) was identified with varying levels of expression in both the estrogen-sensitive T47D and the estrogen-insensitive BT20 breast cancer cell lines.[76] These results indicate the existence and regulatory function of *91H*. In addition, through nucleic acid analysis, Berteaux et al[76] confirmed *91H* is a single 120-kb transcript generated from the *H19/Igf2* locus. Next, it was confirmed that, rather than affecting *H19* expression, 91H influence *Igf2* expression.[76] Moreover, although 91H, *H19*, and *Igf2* are overexpressed in breast tumors, *91H* was demonstrated to promote breast tumor cell growth, migration, and invasion by preventing histone and DNA methylation on the maternal allele at the *H19/Igf2* locus.[77]

In most tumor cells except breast tumor cells, *91H* was identified to promote *Ifg2* transcription by activating the *Igf2* promoter in mouse myoblast.[78] Gao et al[79] found that 91H was down-regulated in esophageal squamous cell carcinoma with higher depth of invasion, neoplastic grading, and TNM. Lower *91H* expression was associated with an increased risk for the occurrence, progression, and prognosis of esophageal squamous cell carcinoma. Recently, the regulatory function of 91H was also reported in colorectal cancer, osteosarcoma, and hepatocellular carcinoma, *etc.*[80–83] On the other hand, H19 antisense encodes a protein, H19 opposite tumor suppressor, and could inhibit Wilms, rhabdoid, rhabdomyosarcoma, and choriocarcinoma tumor cell growth, which indicates that H19 locus harbors an imprinted gene encoding a tumor suppressor protein.[84] Taken together, these results suggested a new mechanism of *H19/Igf2*-associated regulation (Fig. 1B).

H19: encoding miR-675

Exon 1 of *H19* encodes two distinct miRNAs, *miR-675-5p* and *miR-675-3p*, which are highly conserved and confer functionality to *H19*[85,86]. *MiR-675-5p* and *miR-675-3p* could synergistically regulate the same or different physiological or pathologic processes with different mechanisms[87–89] (Fig. 1C). To prove *H19* encodes *miR-675*, Cai et al[90] first identified the sequence in *H19* located from 1014 to 1036 that encoded *miR-675*. They then identified that *miR-675* was generated from longer pri-miRNA precursors by the RNase III enzymes Drosha and Dicer in the 293 T cell line, which does not normally express *H19*. In addition, the 293 T cell line readily expressed *miR-675* at high levels after

being transfected with human or mouse *H19* plasmid, but not in mock-transfected cells. These results indicated that *miR-675* is encoded by *H19* and positively correlated with the expression of *H19*.[41,49,90,91]

As an indispensable part of the *H19*-miR-*675* axis, *miR*-675 has been reported to regulate myogenesis, chondrogenesis, adipogenesis, tenogenesis, and osteogenesis, *etc*.[41,49,60,92] Dudek et al identified that *miR675* expression level was positively correlated with the expression level of *Sox9* and regulated type II collagen expression in human articular chondrocytes.[60] Dey[93] et al found that *H19* encoded-*miR-675-3p* and *miR-675-5p*, which promoted skeletal muscle differentiation and regeneration by directly targeting and down-regulating the anti-differentiation *Smad* transcription factors. Similarly, *miR-675* was reported to down-regulate some functional genes and regulate signaling pathways during tumor progression.[86,94,95]

H19: competing endogenous RNA (CeRNA)

MicroRNAs (miRNAs) have important regulatory functions in many physiological and pathological processes. One of the most essential roles of miRNAs is post-transcriptional regulation, in which miRNAs bind to specific recognition sequences ("seed sequences") located in the 3′ untranslated regions (3′ UTRs) of target mRNAs. In this event, miRNAs inhibit the expression of target proteins by enhancing mRNA degradation and/or by directly interfering with protein translation.[7,96,97] As mentioned above, lncRNA can generate miRNAs, simultaneously, lncRNA can act as CeRNA, in which specific lncRNA can impair miRNA activity through sequestration and finally up-regulate miRNA target gene expression.[7,98–100]

It is reported that *H19* contains functional miRNAs *let-7* interaction sites and can inhibit *let-7* function by acting as a molecular sponge. In addition, this competitive binding can accelerate muscle differentiation and regulate muscle glucose metabolism in muscle cells, which indicates that *H19*'s function as CeRNA is one of its essential mechanisms of the regulatory function of *H19*.[101,102] By preventing H19 from interacting with miR-let-7, Park et al identified cardiac phenotypes were associated with the interaction between H19 and miR-let-7.[35] At the same time, *H19* can bind with miR-17–5p,[103] miR-93–5p,[104] miRNA-106 b-5p,[105] miR-130a,[106] miR-22–3p,[107] *etc*. respectively, and regulates the specific biological process. Significantly, *H19* may regulate a specific biological process by simultaneously binding with several miRNAs. These results indicate the flexibility and diversity of *H19* in regulating gene expression by acting as a CeRNA[58,108,109] (Fig. 1D).

H19 acts as a modular scaffold

It was known that lncRNAs regulate chromatin states and epigenetic inheritance. Tsai et al identified that lnRNA *HOTAIR* serves as a modular scaffold for two histone modification complexes, in which the 5′ domain of HOTAIR binds to the polycomb repressive complex 2 and the 3′ domain binds to the LSD1/CoREST/REST complex.[110] Different from *HOTAIR*, it is reported that hypoxia regulates *H19* expression and function by regulating allele-specific histone modification.[111] On the other hand, we found that *H19* could act as a modular scaffold in the cytoplasm and promote specific protein phosphorylation, then it can regulate the activation of the protein and downstream signaling pathway[112,113] (Fig. 1E). The main mechanisms of *H19* mediated regulation are shown in Figure 1.

Complex roles of *H19* in cancer development and progression

Abnormal expression of *H19* has been demonstrated in a variety of different types of cancer cells.[85] As *H19*-mediated regulatory function can occur through several different mechanisms, *H19* was found to be associated with different types of cancer and played different roles in cancer development and cancer progression.[85,114]

H19 in osteosarcoma (OS)

The disruption of *H19* and *Igf2* expression was associated with the development of rhabdomyosarcoma, which was identified in 1997, and *H19* was regarded as the tumor suppressor of rhabdomyosarcoma.[115,116] Recently, defective osteogenic differentiation has been characterized to play an important role in the development of OS.[117] With the use of induced pluripotent stem cells, Lee[118] et al found that impaired osteoblast osteogenic differentiation resulted in Li-Fraumeni syndrome -associated OS. The mechanism underlying this is the low expression of *H19* and dysregulation of *H19* IGN. Aside from participating in the development of OS, *H19* also regulates the migration and invasion of OS. It was reported that *H19* has higher expression in OS tumor tissue than in adjacent healthy tissue.[119] Furthermore, *H19* expression level in OS is positively associated with tumor migration and invasion, which is mediated by the down-regulation of the nuclear factor-κB pathway (NF κB).[120,121] By acting as a CeRNA, *H19* can regulate OS development, invasion, and migration by suppressing functional miRNA expression.[85,122] Taken together, the down-regulation of *H19* increases the risk of OS development and up-regulated *H19* is associated with a poor prognosis of OS.

H19 in breast cancer

Breast cancer is one of the most common cancers among women worldwide. Since *H19* is an estrogen-regulated transcript and regulates cell proliferation and differentiation, several studies have been carried out to clarify the effects and mechanisms of *H19* in regulating breast cancer development, progression, and metastasis.[85,123] Firstly, *H19* expression levels were positively associated with breast cancer cell proliferation, invasion, and angiogenesis, and ectopic overexpression of *H19* promotes tumorigenic properties of breast cancer cells.[124–126] Secondly, a recent clinical case-control study showed that *H19*-associated single nucleotide polymorphisms were associated with breast cancer risk and have the potential for breast cancer diagnosis and estimating prognosis.[127,128] In addition, it was identified that *H19* can lead to breast tumorigenesis by

altering DNA methylation.[126] Simultaneously, as mentioned above, *H19* antisense *91H* also regulates breast cancer development by epigenetic modifications.[76–78] In summary, it can be concluded that *H19* is an oncogene in breast tumorigenesis.

Additionally, as the precursor of *miR-675*, it was reported that *miR-675* expression was significantly higher in breast cancer tissue compared with the control group, which demonstrates regulation of *H19*-miR576 axis.[123,129] Further studies identified that ectopic expression of *H19*-miR675 reinforced breast cancer cell proliferation, migration, metastasis, and drug resistance.[85,95,123,125,129] As for the ceRNA network of *H19*, by differently sponging *miR-200b/c* and *let-7b*, *H19* regulates the epithelial-to-mesenchymal transition in breast cancer cells. Similarly, *H19* can bind with *miR-152*, *miR-93-5p*, *let-7a/b*, *miR-324-5p*, *miR-29b-3p*, *etc.* in breast cancer progression.[85,123,130]

H19 in gastrointestinal cancers

The digestive system includes the gastrointestinal tract (the esophagus, stomach, intestine, and colorectum) and the accessory organs of digestion (the pancreas, liver, and gallbladder). Recently, *H19* has been reported to regulate digestive system cancers on multiple levels, both as an oncogene or regulating tumor-suppressing gene expression.[93,129,131–134]

Firstly, *H19* is found to be up-regulated in gastric cancers,[135–137] pancreatic cancers,[138–140] hepatocellular carcinoma,[141–143] esophageal squamous cell carcinoma,[144,145] colorectal cancer,[132,146–148] *etc.*, which indicates that *H19* may act as an oncogene in digestive system cancers. Simultaneously, *H19* polymorphisms were identified to be a potential marker for the diagnosis of digestive system cancers,[149–151] and *H19* expression levels were reported to have a positive correlation with the proliferation, invasion, and metastasis of digestive cancer cells.[131,137–139,152] In addition, Wang et al found that *H19* could function as CeRNA, bind with miR-194–5p and influence SIRT1-mediated autophagy, and finally promote 5-Fu resistance in colorectal cancer.[153] Wu et al demonstrated that *H19* promotes methotrexate resistance in colorectal cancer by activating *Wnt/beta-catenin* signaling.[154] In hepatocellular carcinoma, Xu et al[155] identified that *H19* participated in sorafenib resistance by the *H19-miR675* axis. In summary, *H19* may act as an oncogene in digestive system cancers and hold the potential for early diagnosis, acting as a target of treatment and working as prognosis markers.[135,140,146,156,157]

H19 in lung cancer

There are two main types of lung cancer, non-small cell lung cancer, which occupies 80%–84% of all lung cancer cases, and small cell lung cancer, which occupies 10%–15%. Although these two types of lung cancer are treated very differently, *H19* was found to be up-regulated in both non-small and small cell lung cancer with different mechanisms.[158–161] Studies conducted on ethnic Chinese populations showed that the polymorphism *rs2107425* in the *H19* gene was associated with the risk of lung cancer among females whom never smoked,[162] and the single nucleotide polymorphism *rs217727* in lncRNA *H19* was significantly associated with susceptibility to lung cancer, particularly in squamous cell carcinoma and adenocarcinoma in smokers.[163] In non-small cell lung cancer, Zheng et al[164] identified that up-regulated *H19/miR675* promoted hypoxia-induced cancer progression by inhibiting *p53* signaling. Ren et al[165] reported that *H19* sponged *miR-196b*, which targeted a conserved RNA binding protein LIN28B, and accelerated lung cancer growth. Simultaneously, by acting as a CeRNA, *H19* was found to sponge *miR-200a*,[166] *miR-107*,[161] *miR-17*,[167] *miR-6515-3p*,[168] *miR-138*,[169] *miR-203*, *etc*, and promoted lung cancer cell proliferation, invasion, metastasis, or epithelial-mesenchymal transition. In small cell lung cancer, Li et al[170] found that *H19* promoted small cell lung cancer tumorigenesis by regulating the *miR-140-5p/FGF9* axis by acting as CeRNA.

In addition, several studies identified that *H19* expression was associated with lung cancer drug resistance.[171–174] Zhou et al[174] characterized that inhibition of *H19* could enhance gefitinib sensitivity and the effectiveness of chemotherapy, which indicated the function of *H19* in lung cancer drug resistance. Pan et al[173] found that *H19* was highly expressed in erlotinib resistance lung cancer cell lines via exosomes and regulated drug resistance via targeting *miR-615-3p* to regulate *ATG7* expression. Lei et al[171] also proved that *H19* packaged into exosomes and mediated lung cancer cell resistance to gefitinib. In human lung adenocarcinoma cells, *H19*-mediated cisplatin resistance potentially serves as a molecular marker to predict the prognosis of lung adenocarcinoma.[172]

In summary, *H19* gene acts as an oncogene in lung cancer and participates in tumorigenesis, progression, metastasis, and drug resistance, which indicates that *H19* can be a molecular marker or target for lung cancer diagnosis and treatment.

H19 in genitourinary cancer

By the function of *H19* in other systems, *H19* participates in tumorigenesis in genitourinary cancer.[71,129,175,176] As a rare kidney cancer, Wilms tumor primarily affects children, *H19* was identified to be an imprinted tumor-suppressor gene of Wilms tumor.[177] Meanwhile, *H19* could interact with another anti-oncogene to suppress Wilms tumor development.[177–180] Except for breast cancer,[181] genomic variants with *H19* were identified to hold the potential to be diagnosis markers in bladder cancer,[182,183] epithelial ovarian cancer,[184] Wilms tumor,[185] *etc*. In prostate cancer, *H19* is regarded as the essential regulator of cell fate, plasticity, and treatment resistance and holds the potential to be a diagnosis marker.[186] Meanwhile, *H19* acts as an estrogen- and hypoxia-response regulator and promotes prostate cancer invasion through the epithelial-to-mesenchymal transition to a β integrin pathway.[187] By acting as CeRNA, *H19* was reported to regulate prostate cancer, bladder cancer,[188] ovarian cancer,[189] seminoma,[105] *etc*. In addition, impaired *Igf2-H19* imprinting was found in prostate cancer,[190] ovarian cancer,[184,191] bladder cancer,[192] Wilm's disease,[193] malignant endometrium,[194] *etc*. Simultaneously, *H19* regulates several genitourinary cancer cell

proliferation, invasion, metastasis, and drug resistance through different mechanisms.[184,186,188,189]

It is worth mentioning that, as an essential oncogene, targeting *H19*-mediated tumor treatment has been explored in various studies.[195] Sidi et al[196] investigated the effects of intravesical injection of a DNA plasmid that contains *H19* gene regulatory sequences which drive the expression of an intracellular toxin in a phase I/II marker lesion study. They found an ablation effect on the bladder, which indicated the potential of this method. A fragment of diphtheria toxin (DTA) or herpes simplex virus thymidine kinase (HSV-tk), under the control of an 814-bp 5′-flanking region of the *H19* gene, was applied for regulating the expression of *H19*.[195] A phase 1/2a clinical study found that intraperitoneal use of *H19*-DTA was a safe and effective method for recurrent ovarian/peritoneal cancer.[195] A phase 2 b marker lesion trial also confirmed the effect of *H19*-DTA in nonmusical invasive bladder cancer. These results indicated the treatment potential of targeting *H19*.

H19 in MSC lineage-specific differentiation

H19 in osteogenic differentiation

As we mentioned before, *H19* plays an important role in motor system development. As the key process of bone development and regeneration, osteogenic differentiation of MSCs is closely involved in the regulation of *H19*.[53,197–200]

Like the function of *H19* in development, we identified that the expression balance of *H19* is essential for the osteogenic differentiation of MSCs. Our *in vitro* and *in vivo* studies found that overexpression of *H19* blocked BMP9-induced osteogenic differentiation of MSCs and kept MSCs in undifferentiation status. However, down-regulation of *H19* in *BMP9* induced osteogenic differentiation of MSCs inhibited osteogenic differentiation and relatively promoted adipogenic differentiation.[58,109] Wang et al further found that *H19* regulates osteogenic and adipogenic differentiation of BMSCs through ligand-dependent corepressor by sponging miR-188.[201] Furthermore, Huang et al proved that the *H19*-miR *675* axis regulated the balance between osteogenesis and adipogenesis of MSCs by targeting the 3′ UTRs of the histone deacetylase (*HDAC*) 4—6 transcripts.[62] Simultaneously, *H19* was reported to hold the potential to induce stem cell osteogenic differentiation. Li et al[202] found that *H19* promoted osteogenic differentiation of bone marrow MSCs by sponging *miR-149*, which increased the expression of stromal cell-derived factor-1. Huang et al[54] identified that both *H19* and *miR-675* promoted osteogenic differentiation of MSCs by activating the *TGF-beta1/Smad3/HDAC* signaling pathways. In addition, *H19* mediated CeRNA mechanism was proved to regulate several signaling, including the *ERK1/2* and *p38 MAPK* signaling pathways,[203] *Runx2*,[204] focal adhesion protein-tyrosine kinases,[199] *etc*. Meanwhile, as an imprinted gene, *H19-IFG2* also regulated osteogenic differentiation.[205] Loss of imprinting of *Igf2* could improve the osteogenic potential of human deciduous teeth MSCs, which could be the main difference compared with human adipose tissues.[206]

Crosstalk between *H19* and *Wn*t signaling was identified recently. *Wn*t signaling is essential for the osteogenic differentiation of MSCs.[207] As an enhancer of Wnt4, forkhead box C2 (*Foxc2*) binds to the promoter area of Wnt4 and then activates the *Wnt-β-catenin* pathway, and *H19* synergistically promotes this process by directly binding with *Foxc2*.[208] On the other hand, *H19*-encoded *miR675-5p* was proved to be a negative regulator of BMSC osteogenic differentiation, as the *H19-miR675-5p* axis regulates osteogenic differentiation through *Wnt-β-catenin* pathway.[209] However, Ma et al found that *H19*-derived *miR-675* targeted the adenomatous polyposis coli protein and promoted osteogenic differentiation of MSCs by activating *Wnt* signaling.[210] In addition, Liang et al[56] found that *H19* acted as CeRNA and sponged *miR-22* and *miR-141* which targeted *Wnt/beta-catenin* signaling, and then regulated osteogenic differentiation of human MSCs. Similar results were detected by Gong et al[211] in ectomesenchyme stem cells.

Moreover, *H19* was reported to be activated by estrogen and regulated osteogenic differentiation of BMSCs, which could reduce osteoporosis via the *miR-532-30/SIRT1* axis.[197] Simultaneously, *H19* was also identified to regulate different types of body cells including osteoblasts, osteoclasts, and osteocytes in the osteogenic differentiation process which hold the potential to be a target for osteoporosis treatment.[203,212–214]

H19 in endochondral ossification and angiogenesis

H19 was identified to regulate chondrogenic differentiation and maintain the anabolic and catabolic activities of chondrocytes and endochondral ossification.[60,92,215] In mouse limbs, we detected that the expression level of *H19* is high in the proliferation zone and decreases gradually from the prehypertrophic zone to the hypertrophic zone. In addition, we characterized that *H19* is essential for chondrogenic differentiation and maintaining the proliferation of chondrocytes, and down-regulation of *H19* promoted hypertrophic differentiation of chondrocytes and followed endochondral ossification. In mechanism, we proved that *H19* facilitated *Runx2* phosphorylation.[112] In chondrocytes, Steck et al found that *H19* expression levels were not correlated with *Igf2* expression levels, but positively correlated with *miR-675* expression levels; a further study confirmed that *H19* could be an attractive marker for chondrocyte anabolism and be a potential target for cartilage recovery.[92]

Angiogenesis is a key process of endochondral ossification and osteogenesis. Notch signaling regulates both endothelial cell generation and angiogenesis during both bone development and regeneration.[216–222] We characterized that *H19* functions as CeRNA that sponges miRNAs targeted to Notch signaling, which indicated the regulatory function of *H19* in Notch signaling activation.[58] As reported by Shang et al,[223] Notch signaling promoted the hypertrophic differentiation process. Our previous work also proved that the down-regulation of *H19* promoted hypertrophic differentiation of MSCs.[112] Furthermore, our recent work found that *H19* binds with p53 and promotes the phosphorylation of *p53*, phosphorylated *p53* promoted *Notch1* transcription by binding on the promoter area of Notch1, and then the activated Notch1 promoted endothelial cell

generation.[113] These results indicated the regulation axis of *H19-Notch* in endochondral ossification.

Roles of *H19* in metabolic cardiovascular diseases

H19 and its variant expression alteration were associated with cardiovascular diseases, endocrine system disease, liver disease, nephrotic syndrome, *etc.*, which indicated the functional effects of *H19* in metabolism.[224–226]

H19 in atherosclerosis and cardiovascular diseases

Atherosclerosis is one of the main cardiometabolic diseases and drives cardiovascular disease, which is one of the main causes of mortality worldwide.[225] Atherosclerosis is mechanistically involved in numerous biological processes including lipid metabolism, adipogenesis, angiogenesis, inflammatory response, cellular proliferation, and apoptosis, *etc*.[225,227] Foam cell-mediated lipid accumulation and inflammatory response occupy an important position in the progression of atherosclerosis. It was reported that *H19* was highly expressed in atherosclerosis foam cells, and down-regulation of *H19* counteracted the increase of triglycerides/total cholesterol/low-density lipoprotein-cholesterol and down-regulated the level of high-density lipoprotein-cholesterol.[228] Meanwhile, down-regulation of *H19* decreased the expression of pro-inflammatory factors (*TNF-*α and *IL-*β) and increased the expression of anti-inflammatory factors (*IL-4* and *IL-10*).[228] In mechanism, these effects were mediated by the *H19*-miR-130 b axis. In addition, the expression level of *miR-130b* was correlated with the expression levels of triglycerides, LDL, serum creatinine, and blood urea nitrogen and inflammatory response in diabetic nephropathy, which also indicated the regulation of *miR-130b* in lipid metabolism.[229]

H19 has also been identified to regulate the proliferation and apoptosis of vascular smooth muscle cells and endothelial cells, which contribute to the development of atherosclerosis. Park et al identified that H19 interacting with *miR-let-7* and regulating the expression of *Igf2* were associated with cardiac phenotypes.[35] Huang et al found that *H19* promoted the proliferation of vascular smooth muscle cells and endothelial cells and suppressed apoptosis through acid phosphatase 5, which promoted the development of atherosclerosis.[230] Sun et al identified that *H19* sponging *miR-let-7a*, which targets cyclin D1, promoted vascular remodeling by regulating the cell cycle.[231] Meanwhile, it is reported that *H19* regulates vascular smooth muscle cell proliferation by miR-148b/Wnt/beta-catenin singling. Overall, *H19* regulates atherosclerosis development through lipid metabolism, inflammatory response, cell proliferation, apoptosis, *etc*. Meanwhile, in myocardial infarction, *H19* was found to ameliorate myocardial infarction-induced myocardial injury and maladaptive cardiac remodeling by acting as CeRNA, which sponges *miRNA-22-3p* and promotes the expression of *KDM3A*.[232] Moreover, by acting as CeRNA, *H19* was reported to inhibit myocardial infarction and myocardial ischemia/reperfusion by sponging different miRs.[225] Recently, Viereck et al found that H19 is an anti-hypertrophic lncRNA and represents a promising therapeutic target to combat pathological cardiac remodelling.[233]

H19 in hepatic lipid metabolism, non-alcoholic fatty liver disease, and liver fibrosis

H19 was also proved to play an important role in liver diseases.[234,235] In hepatic stellate cells, *H19* was up-regulated by hypoxia-inducible factor-1alpha through binding to the lncRNA-*H19* promoter at two hypoxia response element sites located at 492—499 and 515—522 bp. Up-regulated *H19* activated hepatic stellate cells and promoted the development of liver fibrosis through the *AMPK*α signaling pathway.[236] Inhibition of *H19-AMPK*α signaling by dihydroartemisinin holds the potential for improving lipid droplet metabolism and the prevention and treatment of liver fibrosis.[237] The liver plays an essential role in lipid metabolism. It was reported that up-regulated *H19* was associated with non-alcoholic fatty liver disease. Mechanistically, *H19* induced lipid accumulation and up-regulated the expression of lipid synthesis-, storage-, and breakdown-associated genes by up-regulating both the mTORC1 signaling axis and MLXIPL transcriptional network.[226] As a lncRNA, *H19* was also identified to promote lipogenesis and triglyceride secretion in hepatocytes by sponging miR130a, which targets PPARγ directly.[106] In addition, the expression level of *H19* was positively associated with the expression levels of lipids, which served as a lipid sensor. By synergizing with the RNA-binding polypyrimidine tract-binding protein 1, *H19* regulated hepatic metabolic homeostasis and exacerbated the development of fatty liver.[238]

H19 in insulin sensitivity, obesity, and diabetes

As *H19* is highly expressed in skeletal muscles, which is essential for glucose and lipid metabolism. It was reported that *H19* was down-regulated in the muscle of both *db/db* mice and high-fat diet-induced obese mice and that overexpression of *H19* ameliorated glucose intolerance and insulin resistance in db/db mice and decreased ectopic lipid accumulation in the skeletal muscle and liver. In terms of mechanism, *H19* promotes the oxidation of fatty acids by targeting heterogeneous nuclear ribonucleoprotein.[239] As a cellular energy sensor, AMPK enhanced muscle insulin sensitivity and whole-body energy metabolism by regulating glucose uptake, lipid oxidation, and mitochondrial biogenesis. Geng et al[240] found that *H19* sponged *miR-let7* and increased the expression of DUSP27, which activated AMPK signaling and enhanced muscle insulin sensitivity. Meanwhile, *H19* variants were identified to have a significant association with T2MD.[241]

In addition, an intrauterine hyperinsulinemia environment may cause hepatic *Igf2/H19* epigenetic alteration and induce glucose intolerance in gestational diabetes mellitus. Mechanistically, an intrauterine hyperinsulinemia environment could increase hepatic FoxO1 levels, which subsequently increases the expression of DNMT3A and epigenetic alterations on *Igf2/H19* DMRs.[242] In other words, *H19* may be a potential target for the treatment of type 2 diabetes mellitus.[243,244] The function of *H19* in different diseases, physiological processes, and pathological processes are summarized in Figure 2.

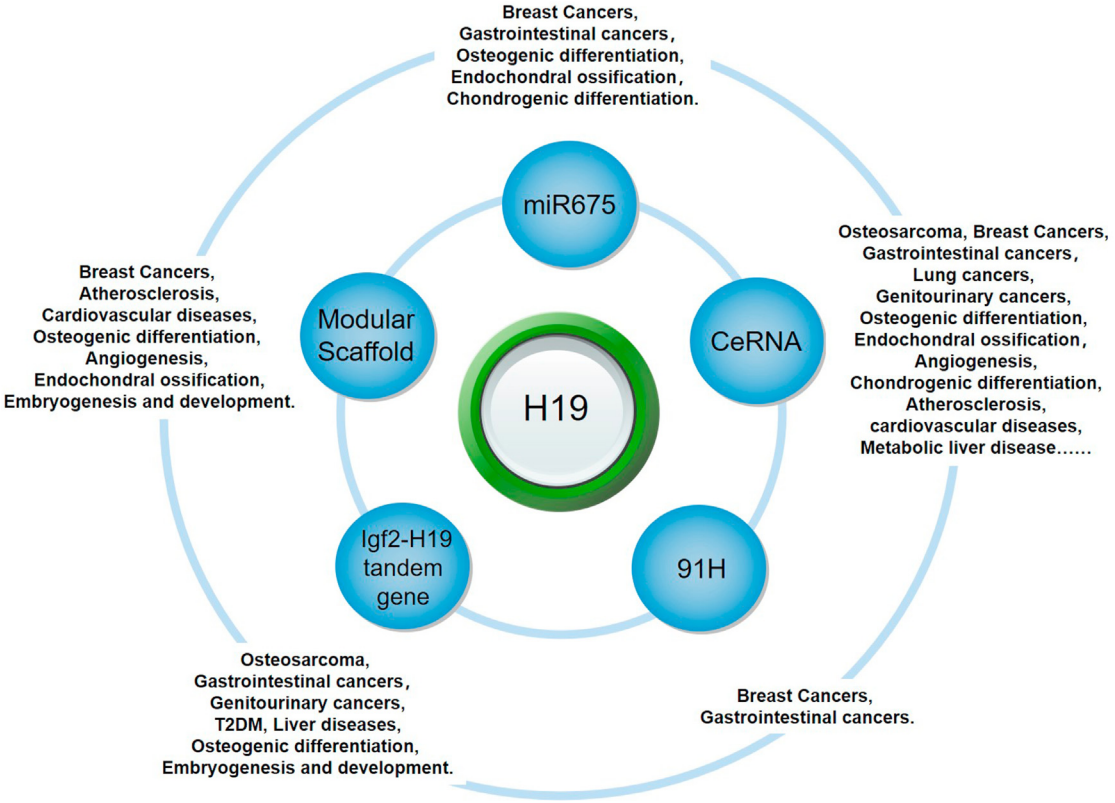

Figure 2 Summary of the functions of *H19* in different physiological and/or pathological processes.

Conclusions and future directions

As one of the first identified noncoding RNAs, *H19* was identified to play essential roles in several physiological and pathological processes. Dandolo et al found that *H19-Igf2* locus interact with *Myod* and regulated diaphragm formation,[245] and they also identified that H19 acted as a trans regulator on imprinted gene network and controlling growth and development.[37,41,51,246–248] On the other hand, Hochberg and Adriaenssens et al found that H19 was associated with cancer development, invasion, and metastasis, and implied that H19 was a potential target for cancer treatment.[77,129,194,249–260] These studies indicated the multiple functions of H19 in different cell types. In mechanism, it has been shown that *H19* mediates diverse regulatory functions by serving as CeRNA, *Igf2/H19* imprinted tandem gene, modular scaffold, cooperating with *H19* antisense, acting directly with other mRNAs or lncRNAs, *etc*. Biologically, H19 participates in embryogenesis, development, tumorigenesis, osteogenesis, and metabolism, which are associated with the development of many diseases. Therefore, *H19* holds the potential for disease diagnosis, tissue regeneration, and the development of targeted therapeutics. Recently, a plasmid DNA encoding the A chain of the diphtheria toxin (DTA-H19) driven by the transcriptional regulatory sequences of human *H19*, was tested as a monotherapy or in combinations with other chemotherapeutics in treating some cancers, such as pancreatic cancer and ovarian cancer, while more clinical trials are being conducted.[261–265] However, *H19* was regarded as a double-edged sword in cancer therapy.[266] Thus, more in-depth studies are warranted to delineate the exact molecular, cellular, and genomic mechanisms underlying the physiological and pathological roles of *H19*. Ultimately, these lines of investigation may lead to the development of novel therapeutics for human diseases by exploiting *H19* functions.

Conflict of interests

The authors declare no conflict of interests.

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