

***H19*: a long non-coding RNA with different roles in cancer progression**

Review Article

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Summary

Long non-coding RNAs (lncRNAs) are pervasively transcribed and critical RNA molecules with different roles in the cell. The association of some lncRNAs with different diseases especially cancers has been documented. One of these lncRNAs is *H19* which its dysregulation is reported in different cancers. In this review, we describe the molecular function and regulation of *H19* in human cells. We also point to the *H19* dysregulation in different types of cancer.

I. Introduction

Our knowledge suggests that only about 1% of the genome can produce biologically meaningful RNAs encoding proteins. However, it has been revealed that the most of the genomic DNA is transcribed to the RNAs which do not produce any proteins. Human genome encodes thousands of long non-coding RNAs (lncRNAs), which are mRNA-like transcripts that lack protein-coding capacity. These RNAs seem to be responsible for the developmental complexity of the human (Clark MB and Mattick JS,

2011; Hajjari M and Khoshnevisan A, 2013; Khalil AM et al., 2009).

The field of long non-coding RNAs is one of the most popular fields in the biological and medical sciences. Long non-coding RNAs are non-protein coding transcripts longer than 200 nucleotides. These RNAs have been proposed to be key regulators in carcinogenesis or cancer progression. Some examples are maternally expressed gene3 (*MEG3*), *HOTAIR*, and *H19* (Hajjari M and Khoshnevisan A, 2013; Li G et al., 2014; Mercer TR et al., 2009; Yan J et al., 2014).

One of the long non-coding RNAs found in humans is *H19*. This RNA which is transcribed by RNA polymerase II, spliced and poly adenylated, seems to have a role in some forms of cancer. Although the gene encoding the 2.3 kb *H19* lncRNA is expressed from both parental alleles in the early placenta (6–8 weeks gestation), it is expressed exclusively from the maternal allele

on chromosome 11p15.5 after 10 weeks gestation. This is due to a differentially methylated region which is also an imprinting control region. The paternal allele of the *H19* gene is methylated and silent as well. On the other hand, the maternal allele is unmethylated and expressed (**Figure 1**) (Gabory A et al., 2010).

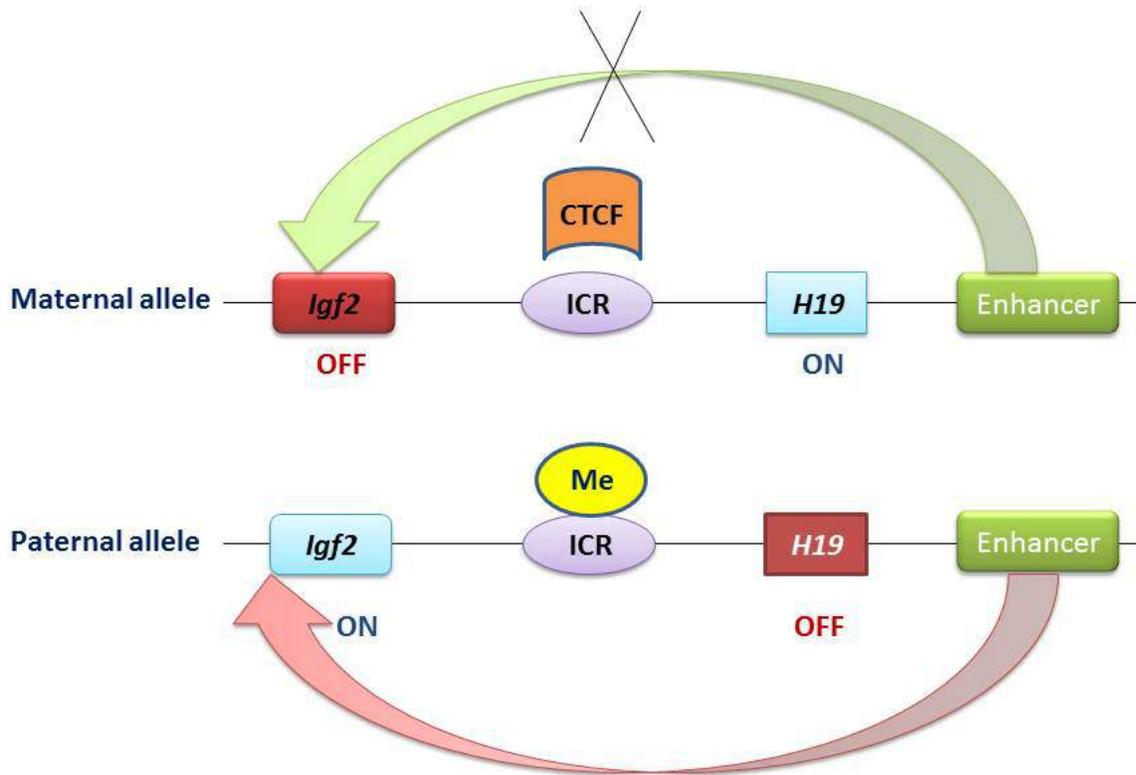


Figure 1: *H19* and *Igf2* expression are expressed from only one parental chromosome. *H19* is exclusively expressed from maternal allele while *Igf2* is expressed from paternal one. These two genes have an enhancer and an ICR (imprinting control region) region as well. The paternal ICR is methylated and this prevents the binding of CTCF protein to the ICR. Finally, the enhancer can interact with the promoter of the paternal *Igf2* and then *Igf2* can be transcribed. On the other hand, the CTCF protein can bind to the un-methylated maternal ICR and this event does not allow the *Igf2* promoter interaction with the enhancers. In this allele, the *H19* can be exclusively transcribed.

The paternal *H19* allele also replicates in the early S phase while the maternal allele replicates later (Bergström R et al., 2007). The expression shifting from biallelic to monoallelic may be essential for the growth of embryonic and extra-embryonic tissues. The *H19* expression decreases significantly in all tissues except skeletal muscles after the birth (Arima T et al., 1997).

II. Regulation of *H19* gene

It seems that the *H19* gene promoter has different sites for various transcription factors such as c-Myc oncogene. It has been reported that c-Myc induces the *H19* lncRNA and so the *H19* may be an intermediate functionary between c-Myc and downstream pathways (Baryte-Lovejoy D et al., 2006). The induction of *H19* has also been confirmed in gastric cancer and the Bcr-Abl expressing cells (Zhang et al., 2014, Guo et al., 2014). It is of note that *H19* can effect let-7-mediated regulation of some metastasis-promoting genes, including c-Myc (Yan et al., 2014). On the other hand *H19* has multiple Sp1 binding sites. However these Sp1 binding sites are not expected to contribute much to the regulation of *H19* gene transcription (Baryte-Lovejoy D et al., 2006). The family of C/EBP transcription factor has also binding sites in the *H19* promoter. Based on this, C/EBP transcription factors could induce the expression of *H19* lncRNA (Jinno Y et al., 1995).

Berteaux et al. have reported that a peptidic hormone (PRL: prolactin) upregulates the *H19* expression in LNCaP cells by the JAK2-STAT5 transduction pathway. They found that *H19* expression is regulated by both a peptidic and a male steroid hormone (Berteaux et al. 2004).

Adriaenssens et al. observed that the regulation of the *H19* gene might be influenced by steroid hormones. They indicated that *H19* promoter activation is both

ligand-dependent and ligand-independent. They found that *H19* gene expression is controlled by steroid hormones. So, they resulted that *H19* is highly expressed in hormone-sensitive organs when the hormonal stimulation is accompanied with a morphological repair. It was demonstrated that 17- β -estradiol and corticosterone can individually induce the *H19* transcription and the progesterone inhibited this effect (Adriaenssens E et al., 1999). Furthermore, the *H19* gene expression has also been demonstrated to be activated by the activation of the E2F1 transcription factor (Berteaux N et al., 2005b).

It has been reported that *H19* is activated under hypoxia and inhibited by TP53. So TP53, as an important tumor suppressor protein, can inhibit the *H19* expression (Dugimont T et al., 1998; Farnebo M et al., 2010). Matouk et al. found that HIF1- α is responsible for *H19* elevation upon hypoxia. They showed that the P53 inhibition effect on *H19* could at least partly involve interfering with HIF1- α activity (Matouk I et al., 2013; Matouk IJ et al., 2014). Matouk et al. found that a functional link exists between P53, HIF1-alpha and *H19* that determines the *H19* elevation in hypoxic cancer cells (Matouk et al., 2010).

In a recent study, it was reported that inducers of EMT pathway can induce *H19*. This provides novel insight into the involvement of *H19* in the EMT pathway and tumor growth (Matouk IJ et al., 2014). On the other hand, Ma et al., in a recent study, have revealed that *H19* can promote HMGA2-mediated epithelial-mesenchymal transition (EMT) through antagonizing let-7 (Ma et al., 2014).

H19 gene is epigenetically controlled by methylation. Banet et al. demonstrated that the *H19* imprinting occurs in early placenta development (Banet G et al., 2000). This leads to exclusive expression of *H19* from the

maternal allele. It is of note that due to a genomic imprinting event, when the *H19* expression is silent on one allele, the expression of IGF2 (the neighboring gene) is active and vice versa (Banet G et al., 2000). Zimmermann et al. reported that Oct4/Sox2 binding sites contribute to maintaining hypomethylation of the maternal *Igf2/H19* Imprinting Control Region (Zimmerman et al., 2013).

Liu et al. in a recent study have indicated that CTCF regulates the imprinted genes *Igf2* and *H19* by organizing chromatin at the *Igf2/H19* locus. They identified vigilin, a multi-KH-domain protein, as a new partner of CTCF, and showed that the CTCF-vigilin complex contributes to regulation of *Igf2/H19* (Liu et al., 2014). Furthermore, Chan et al. found that long non-coding RNA *H19* is aberrantly expressed and induced by upregulated Hh signaling and Yap1 overexpression (Chan et al., 2013).

Collectively, by considering all of the proposed mechanisms for the regulation of *H19*, it seems that *H19* is under the regulation of different pathways controlling important cellular and molecular functions in the cell (**Figure 2**).

III. Downstream pathways for the *H19*

Different cellular functions are influenced by *H19* activation (**Figure 2**). These include cell cycle progression, angiogenesis, migration and etc. It seems that *H19* is especially involved in the transition from G1- to S-phase of cell cycle. Furthermore, *H19* can increase the Inhibitor of DNA binding/differentiation 2 (ID2) expression which in turn up-regulates the transcription of nuclear factor- κ B and cyclin (Luo M et al., 2013). It is concluded that upregulated *H19* increases bladder cancer growth by regulating ID2 expression (Luo M et al., 2013).

There are different other genes, involved in various pathways, which are reported to be regulated by *H19*. (Ayesh S et al., 2002; Matouk I et al., 2013). Also, Lottin et al. showed that the overexpression of *H19* up-regulates post-transcriptionally thioredoxin which is an important factor for the reduction-oxidation reactions in cell metabolisms (Lottin S et al., 2002).

Thioredoxin is a key protein of the oxidative stress response and in the reduction of ribonucleotides to deoxyribonucleotides as well. It enables the DNA synthesis and the passing of the cells through the S-phase (Lottin S et al., 2002). This protein accumulates in many cancerous tissues such as breast carcinomas. There are different evidences that Trx modulates the expression of various kinds of genes in regulating the DNA binding of several transcription factors (Hayashi et al., 1997). Altogether, it seems that *H19* transcript could be included in the abiotic and biotic stress response RNA categories providing a new overview of the *H19* gene function (Lottin S et al., 2002).

As indicated in above, the *H19* expression is regulated by p53 protein (Dugimont T et al., 1998). On the other hand, *H19* can interestingly regulate the P53 activity (Dugimont T et al., 1998). Yang et al., found that *H19* RNA can interact physically with the p53 protein and regulates negatively the p53 protein (Yang F et al., 2012).

Based on the above mentioned pathways, it appears that *H19* harbors pro-tumorigenic properties, thus the *H19* gene behaves as an oncogene. *H19* RNA shows the promoting cellular migration, angiogenesis and metastasis. It is of note that several of those genes up-regulated by the *H19* RNA are also induced by hypoxia. However there are different findings indicating the *H19* as a tumor suppressor RNA. Hao et al. showed that *H19* overexpression decreased the tumorigenic

properties of cells derived from kidney tumor (Hao Y et al., 1993). Furthermore Moulton et al. found that the *H19* gene is frequently inactivated in Wilms tumor (Moulton T et al., 1994). Knocking-down of *H19* RNA results in attenuation of p57kip2 induction. P57kip2 is a KIP family cyclin-dependent kinase (Cdk) inhibitor which blocks the cell. So, one of the factors seems to be involved in tumor suppressor role of *H19* might be P57kip2 (Matouk IJ et al., 2007).

Collectively, like some other molecules such as miR-17-92(Xiang J and Wu J, 2010), the *H19* RNA might not be considered alone as an RNA molecule with a direct effect on tumorigenesis. This non-coding RNA, which has a complex secondary structure, needs

further investigations.

Another twist to the *H19* activity is the fact that a microRNA named *miR-675* is derived from *H19* lncRNA. *MiR-675-5p* and *miR-675-3p* are generated by the exon1 of *H19*(Shi Y et al., 2014). Some few targets such as *Rb1*(Tsang WP et al., 2010) have been identified for this microRNA. RB is an important tumor suppressor protein involved in cell cycle progression (Hajjari M et al., 2014). *MiR-675* may also influence on the expression level of Cadherin 13 by directly targeting the binding site within 3'UTR. Thus, *H19* may at least partly act in the cell by its derivative microRNA (Shi Y et al., 2014). By this mechanism, it may post-transcriptionally regulate some target genes.

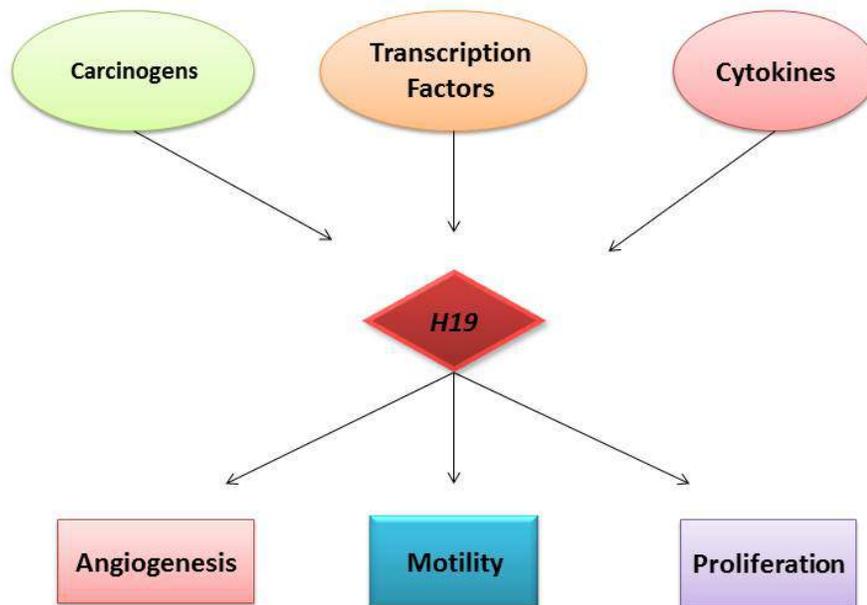


Figure 2: The oncogenic role of *H19* in the human cell. Different pathways and molecules can induce the expression level of *H19* which have different downstream pathways involved in cancer progression.

IV. Role of *H19* as an oncogene factor or tumor suppressor molecule

There are different evidences indicating the loss of imprinting and dysregulation of the *H19* locus in different cancers such as bladder, gastric cancer, breast carcinomas, and HCC. These reports provide the supporting findings for the role of *H19* in cancer progression. Different types of cells with induced expressing of *H19* are able to form larger colonies in soft agar in anchorage-independent growth assays as compared to the control (Lottin S et al., 2002). So, the oncogenic role of *H19* has been demonstrated by different studies (Figure 2). However there are different findings indicating the *H19* as a tumor suppressor RNA. Herein we point to different reports about the oncogenic and tumor suppressor roles of *H19* in different cancer types:

***H19* is dys-regulated in breast cancer**

Adriaenssens et al. showed that the *H19* expression levels in breast adenocarcinoma tissues are higher compared to normal breast tissue (Adriaenssens E et al., 1999). The *H19* overexpression leads to promoting the proliferation of breast cancer cells (Berteaux N et al., 2005a). This overexpression can be inhibited by tumor suppressor protein pRb and transcription factor E2F6 (Berteaux N et al., 2005a).

The expression of *H19* seems to induce the multidrug resistance of breast cancer cells. Doyle et al. found that MCF-7/AdrVp which is a sub-line of MCF-7 with a multidrug resistance, has up-regulated level of *H19* (Doyle LA et al., 1998).

***H19* is involved in progression of gastric cancer**

Yang et al. reported the up-regulated level of *H19* is involved in proliferation of gastric cancer cells. They found that *H19* may inactivate P53 and so can be regarded as a

potential therapeutic target for gastric cancer (Yang F et al., 2012). The role of *H19* in gastric cancer progression was approved by a study of Li et al. who showed that the effect of *H19* might be the direct up-regulation of ISM1 and the indirect suppression of CALN1 expression via *miR-675* (Li H et al., 2014). Furthermore, Zhang et al demonstrated that the *H19* expression in gastric cancer cells is induced by c-Myc (Zhang EB et al., 2014).

***H19* has potential role in hepatocellular carcinoma**

It seems that the imprinted expression of *H19* is usually lost in hepatocellular carcinoma cells. The reports indicate that in hypoxic condition, the *H19* expression is up-regulated (Matouk IJ et al., 2007). Lizuka et al. found that dysregulated *H19* transcripts are correlated with advanced tumor stage and poor outcome in HCC patients. They suggested that *H19* and *IGF2* genes have little or no functional contribution to the progression of HCC. They proposed that changes in transcriptional regulation of these genes are involved in the progression and metastatic potential of HCC. They found that HCCs with high *H19* expression were at more advanced stages than those without (Iizuka N et al., 2004).

However, in a different study by Zhang et al., *H19* was found to be down-regulated in invasive HCC specimens compared with non-invasive tissues. The reduced expression of *H19* induced EMT by regulating the *miR-200* family (Zhang L et al., 2013). The up-regulation of *H19* has also been identified to inhibit the RNA Pol II-mediated transcription through disrupting the hnRNP U-actin complex (Bi HS et al., 2013).

***H19* may act through *miR-675* in colorectal cancer**

It has been found that *H19* and its mature product, *miR-675*, are up-regulated in

colorectal cancer cell lines and tissues. It also seems that the tumor suppressor retinoblastoma (RB) is a direct target of *miR-675* in colorectal cell lines. Thus, *H19* and its derived *miR-675* down-regulate the RB and regulate the CRC development and so may be considered as a potential target for CRC therapy (Tsang WP et al., 2010).

Loss of Imprinting of *H19* has been observed in bladder cancer

The *H19* expression level increases in bladder cancers tissues compared to normal ones (Banet G et al., 2000). There are also some evidences about the loss of imprinting of *H19* gene in bladder carcinomas. The amount of *H19* transcripts is also higher in invasive bladder carcinomas (Ariel I et al., 1995).

Verhaugh et al. analyzed different polymorphisms in the *H19* gene and demonstrated an association between the risk of non-muscle invasive bladder cancer and some polymorphisms (Verhaegh GW et al., 2008).

***H19* has dys-regulated expression in endometrial/ovarian cancer**

In endometrial and ovarian tumors, the *H19* is highly expressed compared to normal tissues (Tanos V et al., 2004). The loss of imprinting of *H19* and *IGF2* is also reported to be involved in the development of ovarian cancer (Chen CL et al., 2000; Dammann RH et al., 2010).

Lottin et al. reported the *H19* overexpression in myometrium and stroma during pathological endometrial proliferative events (Lottin S et al., 2005). Liu et al. has also recently introduced *H19* as one of the lncRNAs which are deregulated in ovarian cancer (Liu SP et al., 2013).

The tumor suppressor role of *H19* in adrenocortical neoplasms

The expression level of *H19* seems to be

down-regulated in adrenocortical neoplasms. Gao et al. found the hypermethylation of *H19* in carcinomas compared to normal, hyperplasia, and adenoma adrenals (Gao ZH et al.). By their results, it seems that *H19* acts as a tumor suppressor molecule in adrenocortical neoplasms. Thus, it seems that the different roles of *H19* depend on the context of tissues. However, the molecular characterization of *H19* in different tissues is remained to be challenging and more studies are needed to find the molecular function and regulation of *H19*.

V. Conclusions:

The differential expression of *H19* lncRNAs seems to be a hallmark feature in different types of cancer; however the exact molecular function of this RNA is still in question. In this review, we described the identified functional role and molecular regulation of *H19* in human cells. We also reviewed the role of *H19* in some types of cancers. Finally, we note that the potential role of *H19* in cancer initiation/progression can be considered for cancer therapy and/or diagnosis.

Conflict of Interest

The authors declare no conflict of interest.

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