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The long Non-coding RNA Orchestrator of Cancer Axis of Evil Insights into the Multiple Modes of Action of the H19 Gene

REVIEW

Imad Matouk

Department of Life Sciences, College of Science & Technology, Al-Quds University, Jerusalem, Palestine

A B S T R A C T

Increasing evidence has indicated that the non-coding RNA molecules play central roles in almost all biological processes and many pathological conditions including carcinogenesis. This review focuses on the pathological tumorigenic role of the first discovered long non-coding RNA gene called H19 and its pivotal contribution to the cancer axis of evil. H19 RNA utilizes a variety of mechanisms to perform its pathological function. Some key unanswered questions are presented by the end. Understanding the H19 RNA mechanisms of action will shed light into the class of long non-coding RNA which contains contains thousands of members mostly with unknown functionn and will help in delineating the pathological role played by at least some of them

Keywords: Long non-coding RNA, Competing endogenous RNA, Epigenetic regulation, microRNA sponge Epithelial to mesenchymal transition, Cancer stemness, Drug resistant, Exosome

After realizing that our DNA is a transcription machine, with a little protein coding potential, the past decade has witnessed an explosion in scientific researches reporting the identifications, characterizations and exploration of the modes of action of the non-coding RNA (ncRNA) genes. Currently, the ncRNA research field is one of the most popular fields in biological and medical sciences. An ncRNA is an RNA molecule that is not translated into a protein product and is classified according to its size into a long (more than 200 nucleotide) and a short (less than 200 nucleotide) ncRNA. The vast knowledge accumulated during the past decade was sufficient for the scientific community to announce the entry into the fascinating ncRNA era which was and still dominated by the microRNAs (miRNA) researches. The miRNAs are small ncRNA mediating regulation of gene expression and their discovery has changed vastly the way we used to think about gene regulation.

The functions and mechanisms of action of the long non-coding RNAs (lncRNAs) are the least understood aspect of the ncRNA biology. Many thousands of lncRNAs are produced from our genome, yet relatively very few have well documented roles. This review will handle a gene called H19, which transcribes to an lncRNA.. Being the first imprinted lncRNA discovered, our knowledge on H19 is relatively high compared to the others. This is especially reflected by the steep increase in the scientific reports handling the H19 lncRNA functions and its modes of action that occurred in the past few years after decades of relative dormancy. H19 is expressed in the placenta and in the embryonic stage but shut down in most tissues after birth and re-expressed again in almost all cancer types.

The roles of H19 in cancer are diverse and

Correspondance: Department of Life Sciences, College of Science & Technology, Jerusalem, Palestine.
E-mail: imatook@staff.alquds.edu

touches almost every aspect of the tumorigenesic process. This review focuses into the well-established mechanistic roles of the H19 lncRNA in the epithelial to mesenchymal transition (EMT), cancer stem cells, and drug resistance, collectively called "cancer axis of evil" (Singh and Settleman, 2010), as they are responsible for the tumor metastasis and the failure of the chemotherapeutic drugs. This dictates indeed the cancer deadly signature. EMT is a reversible trans-differentiation process through which the non-motile epithelial cells are converted to motile mesenchymal cells, a step that is essential for tumor invasion and subsequent metastasis. Cancer stem cells are rare cancer cell population within the tumor that have stem-cell like properties and is greatly believed among the scientific community that these cells are responsible for fueling tumor growth, tumor heterogeneity, drug resistance and invasion. Some examples into other physiological and pathological roles for H19 are presented when needed for clarifications. It is astonishing how H19 can employs diverse mechanisms to perform its specific functions. An illustration of three (among others) well documented modes of action for H19 lncRNA is presented.

H19 lncRNA functions as a scavenger through sponging miRNAs.

One of the well-established modes of action through which the H19 lncRNA performs its function is by acting as a competing endogenous RNA (ceRNA) for the purpose of "sponging" appropriate candidate miRNAs. By this H19 relieves the sponged miRNA inhibitory effect on its downstream targets and thus acts as a scavenger.

One of the earliest reports showed a conserved role for H19 in modulation the major let-7 family availability by acting as a molecular sponge. Consequently, H19 affects expression of endogenous Let-7 targets including Dicer and Hmga2 (Kallen et al., 2013), a multifunctional proteins with broad activities. A double negative feedback loop between H19, let-7 miRNA and the pluripotency factor LIN28 has a critical role in the maintenance of breast cancer stem cell properties (Peng et al., 2018). Additional report indicates that oestrogen induction symmetric division in breast cancer stem-like cells is regulated by H19 through antagonizing Let-7c(Wang et al., 2019). We were the first to document that H19 is induced by hypoxic stress through the Hypoxia-inducible factor 1α (HIF1-α) pathway (Matouk et al., 2010). An interesting recent report indicated that H19 is responsible for glycolysis and breast cancer stem cells (BCSC) maintenance. Mechanistically H19 acting as ceRNA sequesters miRNA let-7 miRNA to release HIF1-α, leading to an increase in pyruvate dehydrogenase kinase 1 (PDK1) expression. PDK1 enhances BCSC properties and is correlated with poor overall survival (Peng et al., 2018).

We have provided several evidences for H19 central role in epithelial to mesenchymal transition (EMT) process (Matouk et al., 2014) and suggested that H19 can also act as an orchestrator for the EMT-MET processes (Matouk et al., 2016). Multiple reports have indicated that this can be performed at least in part through the sponging activity of H19 lncRNA. For instance, by derepressing let-7's suppression on its target HMGA2, H19 promotes EMT and metastasis in pancreatic cancer model (Ma et al., 2013). Additionally, in colorectal cancer it was demonstrated that H19 sponges miR-138 and miR-200a that led to the de-repression of their endogenous targets Vimentin, ZEB1, and ZEB2, all are well established marker genes for mesenchymal cells (Liang et al., 2015) Furthermore it was shown that through differentially sponging miR-200b/c and let-7b, H19 mediates breast cancer cell plasticity during EMT and MET processes (Zhou et al., 2017). In glioma, H19 could compete with SOX4 via sponging miR-130a-3p and thus regulating EMT (Hu et al., 2018). H19 sponges miR-29b-3p and relieve the suppression for DNMT3B, which led to EMT and metastasis of bladder cancer (Lv et al., 2017).

By acting as ceRNA, several reports have indicated that H19 confer cancer chemoresistance in various models. H19 sponges miR-194–5p thus confers 5-Fu resistance in colorectal cancer by promoting SIRT1-mediated autophagy (Wang et al., 2018). Additionally, H19 acts as a miRNA-

106b-5p sponge and thus impairs the function of miRNA-106b-5p on its target gene, TDRG1. By this, H19 facilitate cell survival in cisplatin-based chemotherapeutic conditions in seminoma (Wei et al., 2018). Bortezomib resistance in multiple myeloma is also enhanced by H19 by acting as a miRNA sponge to inhibit the expression of miR-29b-3p, enhance MCL-1 transcriptional translation and inhibit apoptosis (Pan et al., 2019). A recent study indicates that H19 confers resistance to gefitinib via miR-148b/dimethylarginine dimethylaminohydrolase-1 (DDAH1) axis in lung adenocarcinoma. Mechanistically, RNA H19 positively regulated DDAH1 expression via sponging miR-148b-3p (Huang et al., 2020).

H19 is a precursor for miR-675-5p and miR-675-3p

Discovered in 2007 miR-675 processed from the first and longest H19 exon (Cai and Cullen. 2007). MiR-675 was reported to target the "retinoplastoma gatekeeper of DNA replication" (Tsang et al., 2010) and the "p53 Guardian of the genome" (Zheng et al., 2019) both were among the best characterized and well established tumor suppressor genes. The inhibitory effect of miR-675 on p53 could have a myriad consequences given hundreds of targets that p53 has the ability to modulate. We were the first to report that p53 suppress H19 induction upon hypoxic stress (Matouk et al,. 2010) and the upregulation of miR-675 in response to hypoxia (Matouk et al,. 2014). So the possibility of feedback loops between H19-miR-675-P53 by which miR-675b elevate the inhibitory effect of p53 on H19 upon hypoxic stress could be the case. Among other well-known tumor suppressor genes targeted by miR-675 is RUNX1 (Zhuang et al., 2014), and PTEN (Lv et al., 2018) though the latter was not tested in the context of tumorigenicity. Thus it is not astonishing that at least part of the pathological role of H19 is mediated by miR-675. MiR-675 targets a myriad of transcripts in a cellular-context-dependent manner involved in proliferation, apoptosis, EMT, invasion, migration, drug resistance, angiogenesis, and cancer stemness. Although some conflicting data have been reported in different research models, the prevailing view is that miR-675 is functioning as an onco-miR in most models. Physiologically, miR-675 is expressed exclusively in the placenta from the gestational time point when placental growth normally ceases. When lacking H19, the placentas continue to grow suggesting that the physiological role of H19 is to limit placental growth through its microRNA tool. Results indicate that miR-675 slows cell proliferation through at least in part targeting insulin like growth factor receptor 1 (Igf1r), the key receptor through which Igf2 signal to promote growth during fetal development (Keniry et al., 2012).

Additional physiological roles for miR-675 have been described in promoting skeletal muscle differentiation and regeneration (Dey et al., 2014) and the regulation of intestinal epithelial barrier (Zou et al., 2016).

H19 lncRNA epigenetically modulate gene expression

Since H19's discovery in 1984, its locus has been used as a dogma to study epigenetic regulation of the imprinted genes where H19 also act in *cis* modulating and fine tuning the imprinting of other genes within the imprinted cluster where it resides. In this section the emerging role of H19 in epigenetic regulation of gene expression in *Trans* is handled which was uncovered in the past few years. H19 lncRNA interacts with transcription-repressors functioning epigenetically and guide them to specific loci. For example H19 binds the methyl-CpG–binding domain protein 1 (MBD1) and recruits it to some of its targets, by doing so H19 enables the maintaining of repressive H3K9me3 histone marks in their loci (Monnier et al., 2013). Enhancer of zeste homolog 2 (EZH2) is a critical component of Polycomb-Repressive Complex 2 (PRC2). EZH2 is responsible for generating histone H3 lysine 27 trimethylation, a modification that always correlates with transcriptionally repressed chromatin. Several reports uncover a "partnership" between H19 and EZH2. Even more dramatic are reports covering that H19 regulate EZH2 expression itself. EZH2 is regulated by H19, through sponging

of miR-630 (Li et al., 2016). Additionally, and through sponging miR-130, it was reported that H19 regulate EZH2 expression (Hong et al. 2018). The functional outputs of H19-EZH2 association have been reported in a number of studies and using different models. Upregulated H19 enhances bladder cancer metastasis by associating with EZH2 and inhibiting E-cadherin expression. The authors showed that this association resulted in directly suppressing *Ecadherin* transcription and indirectly activating the *Wnt* signaling pathway (Luo et al., 2013). In tongue squamous cell carcinoma, it was shown that H19 promotes carcinoma progression through β-catenin / GSK3β/EMT signaling via association with EZH2 (Zhang et al., 2017). Additionally, in esophageal cancer H19 facilitates EMT and metastasis through let-7c/STAT3/EZH2/β-catenin axis (Chen et al., 2019). Furthermore, in glioblastoma cells H19 regulate NKD1 transcription via EZH2-induced H3K27 trimethylation of its promoter resulting in the repression of Nkd1-a negative regulator of *Wnt* pathway (Fazi et al/. 2018). In diabetic cardiomyopathy model, H19 inhibits autophagy by epigenetically silencing of DIRAS3. H19 knockdown could reduce EZH2 occupancy and H3K27me3 binding in the promoter of DIRAS3 (Zhuo et al., 2017). Perhaps the most dramatic finding of the large scale (genome wide) epigenetic effect of H19 was reported by Zhou et al. (Zhou et al., 2015). In this report, it was shown that H19 binds to and inhibits S-adenosylhomocysteine hydrolase (SAHH), the only mammalian enzyme capable of hydrolysing S-adenosylhomocysteine (SAH). This enzyme is a potent feedback inhibitor of S-adenosylmethionine (SAM)-dependent methyltransferases that methylate nucleic acids, proteins and lipids. SAHH modulation by H19 thus exerts global effects by causing methylation changes at numerous gene loci genome-wide. This represents the first case in which H19 acts in trans to alter the epigenetic landscape genome-wide.

The influence of H19 lncRNA extends beyond the cells transcribing it

With the discovery that RNA could be secreted outside the cells through exosomal vesicles, and cause phenotypic change in the cells receiving them, major changes about the local (cells transcribing it) phenotypic effect of these transcripts have been challenged with a very long believe that this function is only attributed to proteins. Cells communicated through RNA exosomes is relatively novel and could happen between normal cells, between cancer cells, and between normal and cancer cells. H19 lncRNA has functions far outside the cells transcribing it.Multiple reports indicate that exosomal H19 can induce drug resistant. For example exosomal H19 facilitated erlotinib and gefitinib resistance in non-small cell lung cancer (NSCLC) (Pan et al., 2020, Lei et al., 2020), H19 is delivered by exosomes to sensitive cells, leading to the dissemination of doxorubicin resistance in breast cancer (Wang et al.,2020). Carcinoma-associated fibroblasts promote the stemness and chemoresistance of colorectal carcinoma by transferring exosomal H19 (Ren et al., 2018). Additional reports have indicated that exosomal H19 induce other phenotypes related to tumorigenesis including stemness, angiogenesis, cell invasion and migration and proliferation. Interestingly many of those phenotypes are induced in recipient cells with similar H19 scenarios of action to those described in the previous sections. In summation, it is increasingly clear that the H19 lncRNA is a major player and a corner stone of many facets of the tumorigenic processes. It's an ideal target for therapeutic intervention. It uses diverse tools embedded in its primary RNA sequences to act as a sponger or a producer of microRNA (Figure 1).

Globally, H19 modify gene expression through epigenetic regulation genome wide. Despite this impressive progress made in the past decade, still we have many points need to be addressed for better understanding.We have highlighted the importance of H19 lncRNA during many stages of tumorigenesis. We are aware that the vast scenarios presented above are collected from different models and situations. So what dictates the mode of action? For instance, E-cadherin is suppressed by H19 by at least three modes of action as a sponger and a producer of microRNA, and also through epigenetic regulation.

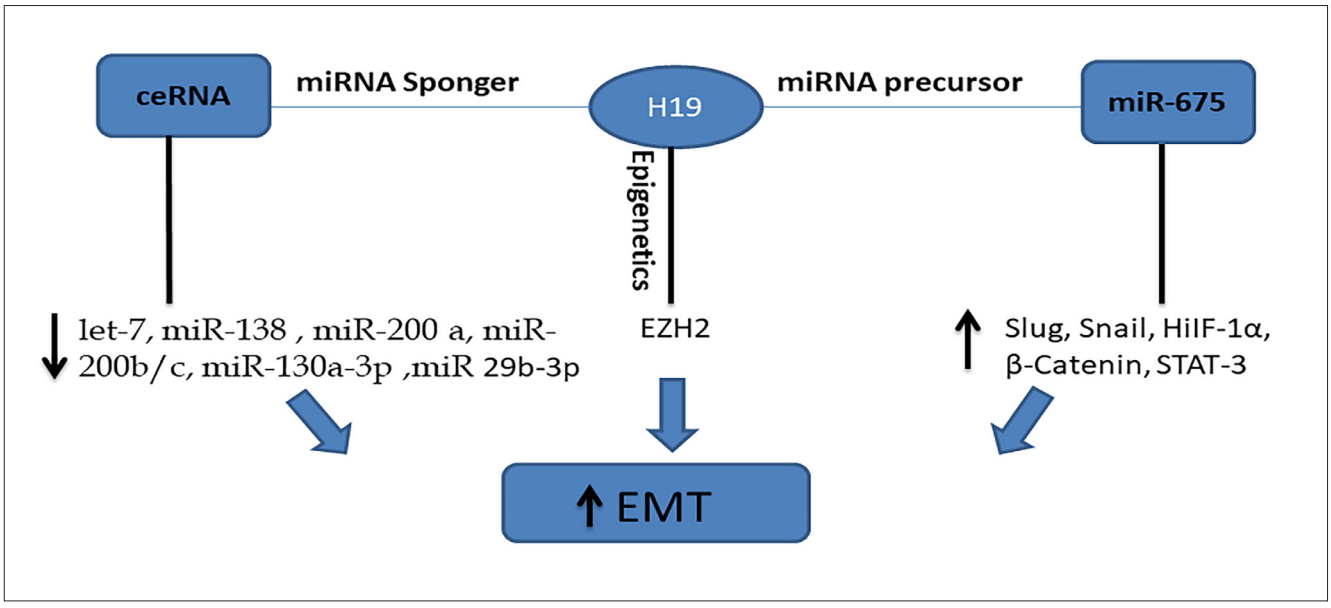

Figure 3: H19 lncRNA induces EMT via multiple mechanisms of action
By acting as competing endogenous RNA, miRNA precursor, and epigenetic regulator, H19 lncRNA induces EMT. Shown are some of the validated targets of H19 and its miRNA miR-675.

Are these scenarios happening concurrently in the same cancer cells to assure E-cadherin suppression or each scenario is happening in a tissue-specific manner? What triggers the release of H19 through the exosomes? Do H19 and miR-675 have different regulatory sequences, taking into consideration that they are both upregulated in many cancer types and it seems that miR-675 is not produced an the expense of H19. Why are still some reports arguing for a tumor suppressor function of H19 and its miR-675- Is H19 gene locus playing a dual role? If yes what triggers each role. Another question that needs to be addressed is whether H19 lncRNA is also acting as an antisense transcript given that its locus also transcribed in antisense direction.

Certainly, understanding the different mode of actions performed by H19 lncRNA will foster our thoughts towards delineating the possible roles and the mechanism of action of so many lncRNA with unknown function. It is not odd to speculate that the mechanistic mode of action of H19 is shared by other lncRNAs.

Competing interest

The author declares no competing interest to disclose.

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