REVIEW

The long non-coding RNA *H19*: an active player with multiple facets to sustain the hallmarks of cancer

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Abstract

Cancer cells exhibit hallmarks in terms of proliferation, resistance to cell death, angiogenesis, invasion, metastasis, and genomic instability. Despite the progress in cancer research and the comprehension of tumorigenesis mechanisms, cancer remains a major issue in public health. A better understanding of the molecular factors associated with the appearance or progression of cancer may allow the development of therapeutic alternatives. Increasing data highlight the role of long noncoding RNAs in many diseases, including cancer. The long non-coding RNA *H19* was the first discovered riboregulator, and it has been shown to be involved at multiple steps of tumorigenesis. Indeed, this lncRNA exert its action at various molecular scales. Understanding the role of *H19* in cancer progression may allow to set up therapeutic strategies to prevent tumor expansion and metastatic dissemination. In this review, we will summarize the overexpression of the long non-coding RNA *H19* in several types of cancer and the multiple implications of the long non-coding RNA *H19* in the different hallmarks that define human cancer.

Keywords lncRNA · *H19* · Hallmarks of cancer · Proliferation · Metastasis · miRNA

Introduction

Since it is very beginning, the comprehension of molecular and cellular mechanisms that underpin the apparition and evolution of cancer has considerably evolved, and keeps moving. The study of these physiopathological events has been marked in the 1970s by the discovery of the first ''cancer-triggering'' genes, called oncogenes, and then by their opposites named tumor suppressor genes. The conceptual framework of tumorigenesis, thus, involves a random intervention of genes that manage essential biological processes such as proliferation, cell death, senescence, motility, and invasion. During cancer development, cells will acquire specific genetic features, increase their proliferative potential, evade cell death control, and immune system vigilance, but also adapt their own metabolism. In 2000, Hanahan and Weinberg enumerated six cancer cell features that would be considered as hallmarks: sustained proliferative signaling, evasion of growth suppressors, replicative immortality, activation of invasion and metastasis, induction of angiogenesis, and resistance to cell death [1]. With recent progress in the field of cancer research came the proposal that tumors are more than masses of proliferating cancer cells, and are a lot more like hierarchical structures composed of multiple cell types that interact with each other. Accordingly, Hanahan and Weinberg added four more hallmarks in 2011: avoiding of immune destruction, tumor-promoting inflammation, genome instability and mutation, and the deregulation of cell energetics [2]. All these hallmarks are considered as distinctive and complementary capabilities that enable tumor growth and metastatic dissemination.

The Encyclopedia of DNA Elements (ENCODE) consortium exposed that nearly 80% of the human genome is transcribed into functional RNAs, but only 2% of the genome codes for proteins [3–5]. From this analysis, it has been highlighted that RNAs that are not translated are called non-coding RNAs (ncRNAs). These ncRNAs are

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classified according to their length in small ncRNAs (less than 200 nt) and long ncRNAs (more than 200 nt). Small ncRNAs regroup into microRNAs (miRNAs), small interfering RNAs (siRNAs), PIWI-interacting RNAs (piRNAs) that are involved in gene expression regulation, and small nucleolar RNAs (snoRNAs) that act as guides to induce chemical modification of other RNAs [6]. Among long ncRNAs, approximatively 20,000 have been identified as potentially functional and subject to transcriptional regulation by transcription factors and epigenetic modifications [7]. They exhibit classical features of mRNAs such as transcription by RNA polymerase II, 5′ capping, 3′ polyadenylation, and splicing [8, 9]. Long ncRNAs are increasingly described to be involved not only in normal development but also in the development of several pathologies, like neurological disorders [10, 11], diabetes [12], and cancers [13].

Interestingly, embryonic cells and cancer cells share similar features including active proliferation, plasticity, invasive behaviors, and gene expression profiles, all being coordinated by common molecular pathways and epigenetic regulation [14]. One of the common regulators during embryonic development and tumorigenesis is the long non-coding RNA *H19*, encoded by the *H19* gene, which is subjected to genome imprinting and is maternally expressed [15]. The *H19* gene is localized near the telomeric region of chromosome 11p15, within a unique locus shared with the *IGF2* gene. Alterations of gene expression at the *H19*/IGF2 locus are associated with malignancies and developmental disorders [16]. The long non-coding RNA *H19* of 2.3 kb is transcribed by the RNA polymerase II, polyadenylated, capped, and spliced with conserved secondary RNA structure, and was proposed for the first time by Brannan et al. to act as a riboregulator [17].

The aim of this review is to give an overview of the long non-coding RNA *H19* expression in cancer and to highlight its impact on the hallmarks of cancer.

Overexpression of the long non-coding RNA *H19* in cancer

H19 is expressed during embryonic development and repressed after birth, excepted for some tissues like mammary gland and uterus [18]. However, it is expressed de novo in cancers of different tissue origins including breast, liver, lung, and esophageal cancers [19–26]. A meta-analysis using ten studies of various solid cancers showed that patients with high expression of *H19* have a poor prognosis [27]. More recently, *H19* overexpression was reported to be correlated with lower complete remission rate and shorter overall survival of acute myeloid leukemia patients [28]. *H19* overexpression and its known biological effects in cancer cells are summarized in Table 1.

H19 expression in cancer cells is modulated by different stimuli including hypoxia, inflammation, cytokines/growth factors, and therapeutic agents (Table 1). *H19* exerts its diverse actions by interacting with proteins or with miRNAs as a sponge (Table 2) [77]. *H19* is also a precursor of miR-675 [78] that is increasingly found to be involved in physiological processes and cancer development. However, the targets of miR-675 differ according to cancer type, and are listed in Table 3.

Implication of the long non-coding RNA *H19* in the hallmarks of cancer

Sustaining proliferative signaling

Proliferation is considered as the most fundamental trait of cancer cells. In normal cells, the regulation of proliferation is stringent, fully controlled, and involved at multiple levels. Production and signaling of growth-promoting factors that modulate entry into and progression through cell division cycles have to be strictly controlled to ensure tissue homeostasis (cell number, tissue architecture, and function). In cancer cells, this control system is altered. *H19* is found to sustain cell proliferation in different types of cancers (Table 1). For example, *H19* expression is correlated with an increased proliferation of gastric cancer cells, through its association with p53 protein [47]. Moreover, Liu et al. reported that curcumin reduces gastric cancer cells proliferation through inhibiting *H19* expression; accordingly, ectopic overexpression of *H19* or c-Myc-induced *H19* expression impedes the growth inhibitory effect of curcumin [88]. Still in gastric cancer, miR-141 binds to *H19* and suppresses its expression, leading to a reduced cell proliferation [80].

It has been shown that *H19* can sustain cancer cell growth through several mechanisms (Fig. 1). *H19* can promote cell cycle progression through G1/S transition. Knockdown of *H19* in esophageal squamous cell carcinoma results in the inhibition of cell growth in vitro and in vivo by the induction of a G0/G1 arrest [32]. Our team showed that *H19*, activated by the transcription factor E2F1, promotes cell proliferation by facilitating G1/S transition in breast cancer cells [40] (Fig. 1a). Knockdown of *H19* induces cell accumulation in G0/G1 in pancreatic ductal adenocarcinoma, resulting in a slower tumor growth in mice. Interestingly, in this model, *H19* knockdown downregulates E2F1 levels, and E2F1 knockdown reduces *H19* expression, indicating an activation loop of cell cycle progression [62]. *H19* can also stimulate cell cycle progression through the sequestration of eIF4A3, which controls pre-mRNA splicing, in colorectal cancer cells (Fig. 1a). This leads to a reduced expression of cell cycle regulatory genes, including *CCND1*, *CCNE1*, and *CDK4* [67].

Table 1 Overexpression of the long non-coding RNA *H19* in several cancer

Type of cancer	Known inducers of H19 overexpression	Biological consequences and/or clinical values	References
Glioma	/	• Increase of cell proliferation • Enhancement of pro-angiogenic factors • Inverse correlation with patient's survival rate	[29] [30] [31]
Oral squamous cell carcinoma	/	• Increase of cell proliferation • Promotion of migration and invasion through epithelial-to-mesenchymal (EMT)-associated protein expression regulation • Immune escape through modulation of pro- and anti-immune factors expression	[32] [33, 34] [35]
Lung adenocarcinoma	• Cisplatin treatment • Benzo[α]pyrene treatment • HGF/SF	• Acquisition of chemoresistance • Disruption of genomic stability by increased mutation frequency. • Association with patients' clinical resistance to cisplatin-based chemotherapy • Serological marker for patients' auxiliary diagnosis • Activation of migration and invasion	[36] [37] [38] [39]
Breast cancer	• E2F1 • ERα/17β-estradiol • *91H* • HGF • TGF- β • Hypoxia	• Increase of cell proliferation • Paclitaxel resistance through epigenetic silencing of pro-apoptotic genes • Enhancing of cell migratory potential • Potential biomarker for early screening and prognosis monitor • Induction of epithelial-to-mesenchymal transition	[29, 40–42] [43] [44] [45] [46] [39]
Gastric cancer	• c-Myc • PEG10	• Inhibition of growth suppressors activity • Inhibition of pro-apoptotic genes expression • Promotion of cell migration, invasion, and metastasis • Correlation with poor prognosis and clinical stage • Potential biomarker for diagnosis and early tumor screening	[47, 48] [49] [50] [51] [52]
Liver cancer	• Cyclin D/*CUDR* • EGR1/PKM2 • Bcl2 • TNF-α • TGF-β	• Inhibition of growth suppressors expression • Modulation of telomerase activity • Activation of pro-angiogenic factors expression • Regulation of immunological response • Association with bile acid homeostasis deregulation • Enhancement of obstructive cholestatic liver fibrosis development • Induction of epithelial-to-mesenchymal transition	[53] [54] [55, 56] [57] [58] [59] [39]
Cholangiocarcinoma	• Oxidative stress	• Activation of invasion and metastasis through regulation of EMT-associated proteins expression • Enhancement of chronic inflammation response to the tumor microenvironment • Correlation with tumor size, TNM stage, post-operative recurrence, and poor prognosis	[60] [60] [61]
Pancreatic cancer	/	• Inhibition of apoptosis through inhibition of caspase 3 cleavage	[62]
Renal cell carcinoma	/	• Promotion of migration and invasion	[63]
Bladder cancer	• TGF-β	• Increase of cell proliferation • Increase of blood vessel density • Activation of invasion and metastasis through epigenetic silencing of EMT-associated proteins • Induction of epithelial-to-mesenchymal transition	[64] [65] [66] [39]
Colorectal cancer	/	• Increase of cell proliferation through enhanced cell cycle progression • Inhibition of growth suppressors expression • Enhancing of tumor migration and invasion	[67] [68] [69]
Cervical cancer	/	• Inhibition of apoptosis	[70]

Table 1 (continued)

Type of cancer	Known inducers of H19 overexpression	Biological consequences and/or clinical values	References
Ovarian cancer	• Cisplatin resistance	• Inhibition of pro-apoptotic factors • Activation of invasion and metastasis through regulation of EMT-associated proteins expression • Induction of cisplatin resistance through regulation of cell metabolism	[71] [39] [72]
Leukemia	• Bcr-Abl kinase • c-Myc • ATRA treatment	• Enhancement of drug resistance • Modulation of telomerase activity	[73] [74]
Osteosarcoma	/	• Promotion of cell migration and invasion	[75]
Melanoma	/	• Promotion of glucose metabolism and cell growth	[76]

Table 2 Mediators of lncRNA *H19* action in cancer

Type of cancer	Mediators of *H19* action	Impact on hallmarks of cancer	References
Glioma	• miR-152 • miR-29a	• Evading growth suppressors • Inducing angiogenesis	[79] [30]
Tongue squamous cell carcinoma	• EZH2	• Activating invasion and metastasis	[33]
Lung adenocarcinoma	• SAHH	• Genomic instability and mutation	[37]
Breast cancer	• E2F1 • ERα • miR-152	• Sustaining proliferative signaling	[40] [41] [29]
Gastric cancer	• p53 • miR-141 • PEG10	• Evading growth suppressors • Sustaining proliferative signaling • Activating invasion and metastasis	[47] [80] [51]
Liver cancer	• Telomerase complex	• Enabling replicative immortality	[54]
Cholangiocarcinoma	• let-7	• Tumor-promoting inflammation	[61]
Pancreatic cancer	• E2F1	• Sustaining proliferative signaling • Resisting cell death	[62]
Renal cell carcinoma	• miR-29b-3p	• Activating invasion and metastasis	[63]
Bladder cancer	• miR-29b-3p • EZH2	• Sustaining proliferative signaling • Resisting cell death • Activating invasion and metastasis	[64] [43] [66]
Colorectal cancer	• eIF4A3 • miR-200a	• Sustaining proliferative signaling	[67] [68]
Cervical cancer	• miR-138-5p	• Resisting cell death	[70]
Leukemia	• Telomerase complex	• Enabling replicative immortality	[74]
Osteosarcoma	• miR-200	• Activating invasion and metastasis	[75]
Melanoma	• miR-106a-5p	• Deregulating cell energetics	[76]

H19 can also promote cancer cell proliferation by sponging miRNAs. In colorectal cancer, miR-200a decreases cell proliferation by inhibiting β-catenin expression. *H19* is able to sponge miR-200a (Fig. 1b), and thereby enhance β-catenin expression and activity to promote cell proliferation [68]. DNMTs are critical for de novo DNA methylation that ensures a main epigenetic code controlling the transcription profile. Notably, DNMTs allow the expression of growth-promoting genes. DNMT1 is downregulated by miR-152 in breast cancer cells. *H19* sponges miR-152 (Fig. 1b), allowing DNMT1 expression and function to enhance cell proliferation [29]. Similarly, DNMT3B is transcriptionally

repressed by miR-29b-3p in bladder cancer cells. *H19* can sponge miR-29b-3p, leading to the re-expression of DNMT3B and the stimulation of cell proliferation [64].

Evading growth suppressors

In addition to the presence of positive regulators, cancer cells have to override mechanisms that curb cell proliferation. Many of these control systems are based on molecular actors such as tumor suppressors (like p53 and RB), or other elements with an antiproliferative effect. In this context, *H19* can physically interact with p53 protein to

Table 3 Validated targets of *H19*-derived miR-675 in cancer

Type of cancer	Targets of miR-675	Target function	References
Glioma	● Cadherin 13	● Atypical cadherin lacking the cytoplasmic domain	[81]
Breast cancer	● Cbl-b, c-Cbl	● Ubiquitin ligases E3	[45, 82]
Lung cancer	● GPR55	● G protein-coupled receptor	[83]
Esophageal squamous cell carcinoma	● REPS2	● Repressor of cell proliferation and migration	[84]
Gastric cancer	● FADD	● Apoptotic adaptator that recruits caspase 8 or 10	[49]
	● RUNX1	● Transcription factor	[48]
	● CALN1	● Calcium-binding protein	[50]
Liver cancer	● HP1	● Heterochromatin assembler and regulator	[56]
	● RB	● Tumor suppressor	[85]
	● TWIST1	● Transcription factor involved in EMT	[85]
Colorectal cancer	● RB	● Tumor suppressor	[69]
	● DDB2	● Transcriptional repressor	[86]
Ovarian cancer	● Slug	● Transcriptional factor involved in EMT	[39]
Osteosarcoma	● CALN1	● Calcium-binding protein	[87]
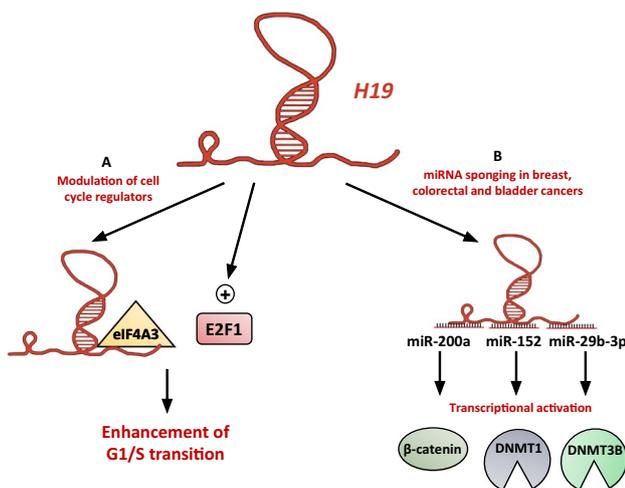
Fig. 1 The long non-coding RNA *H19* promotes cancer cell proliferation. **a** *H19* promotes the G1/S transition in breast and colorectal cancer cells, in esophageal squamous cell carcinoma and in pancreatic ductal adenocarcinoma [32, 40, 62, 67]. **b** *H19* sponges several miRNAs to allow β-catenin and DNMTs expression in colorectal, breast, and bladder cancer, respectively [29, 64, 68]

suppress its activation (Fig. 2a), thus increasing proliferation of gastric cancer cells [47]. On the other hand, PHB1, a mitochondrial chaperone with diverse functions including cell proliferation, apoptosis, and mitochondrial homeostasis has been reported as a negative regulator of hepatocellular carcinoma [53]. It was found that the expression level of *H19* negatively correlates with that of *PHB1* in human hepatocellular carcinoma [53]. *H19* silencing induces *PHB1* expression and prevents *PHB1* knockdown-mediated growth, whereas *H19* overexpression induces the reverse effect, indicating the ability of *H19* to override the tumor suppressing activity of PHB1

(Fig. 2b). In human glioma cell lines, *H19* is able to sponge miR-152 (which is known as a tumor suppressor by targeting proliferation and invasion factors such as DNMT1 or PIK3R3 [29, 89]) to downregulate its activity and promote glioma cells proliferation (Fig. 2c) [79].

H19 can also favor the evasion from growth suppressors via its product miR-675 (Fig. 2d), which downregulates RB protein expression in colorectal cancer cells and hepatocellular carcinoma cells [69, 85]. Moreover, miR-675 is able to negatively regulate RUNX1 expression in gastric cancer cells, leading to the activation of AKT/mTOR pathway and the progression of gastric cancer [48].

Resisting cell death

Programmed cell death by apoptosis is a natural multistep process that plays an important role in the development and life of multicellular organisms, by eliminating damaged cells through a fine-tuned regulatory mechanism. Cancer cells exhibit enhanced tolerance to both environmental and genomic stresses, resulting in resistance to apoptosis and tumor progression.

It has been shown that *H19* knockdown upregulates expression of pro-apoptotic genes (*DDIT3*, *CASP3*) [90], and leads to cholangiocarcinoma cells apoptosis [60]. Furthermore, *H19* decreases caspase 3 cleavage in pancreatic ductal carcinoma cell lines (Fig. 3a), thus avoiding apoptosis [62]. SIRT1, the histone deacetylase that mediates heterochromatin formation and reduces tumor suppressors expression, is targeted by miR-138-5p in cervical cancer cells to enhance apoptosis (Fig. 3b). *H19* will serve as an endogenous sponge to downregulate miR-138-5p and attenuate its suppressive effect [70]. The expression levels of *H19* and
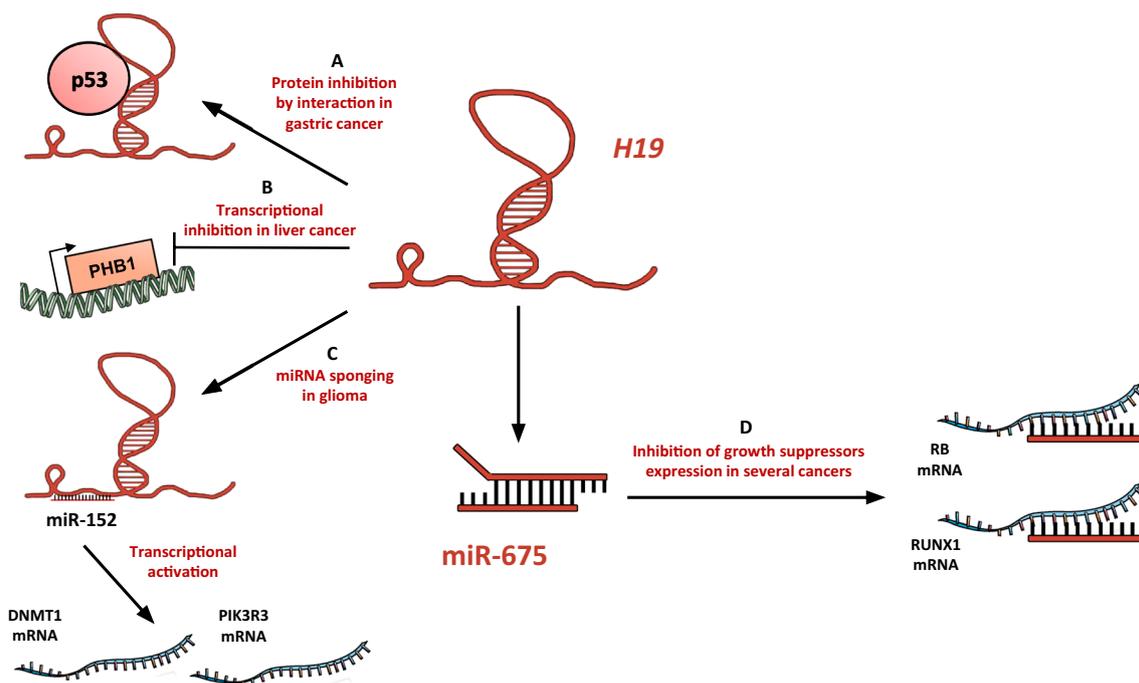
Fig. 2 *H19* downregulates growth suppressors. **a** In gastric cancer, *H19* interacts physically with p53 to inhibit its antiproliferative activity [47]. **b** *H19* induces the transcriptional inhibition of *PHB1* in liver cancer cells [53]. **c** *H19* is able to sponge miR-152 and so enhance glioma cells proliferation [79]. **d** *H19*-derived miR-675 inhibits the expression of well-known growth suppressors such as RB and RUNX1 in colorectal and hepatocellular cancers, and in gastric cancer, respectively [48, 69, 85]
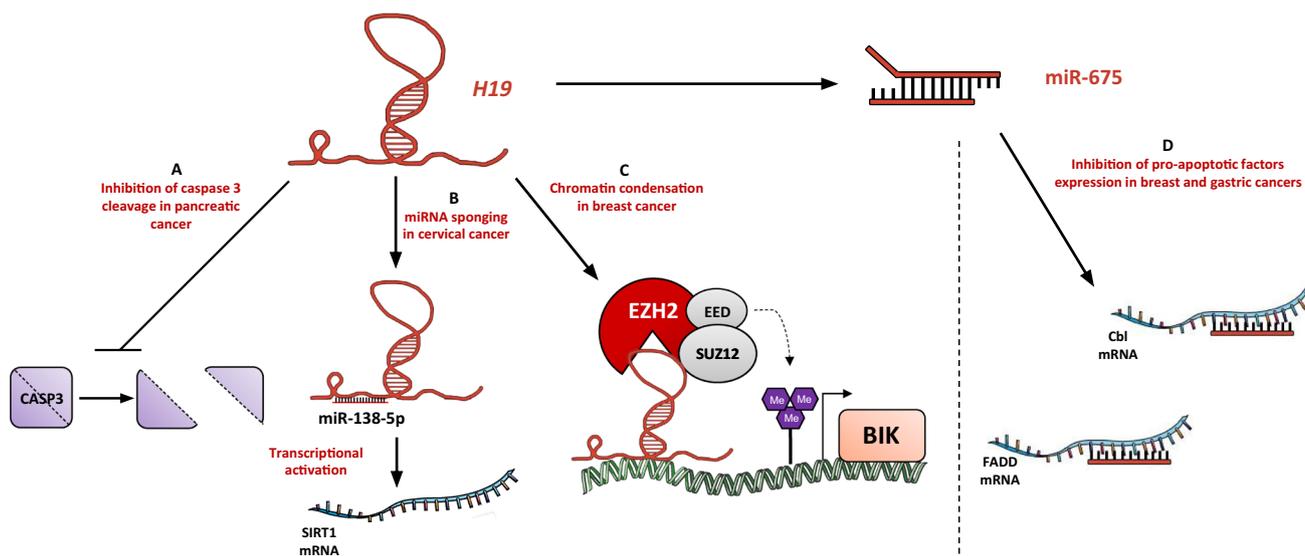

Fig. 3 *H19* impedes cancer cell death. **a** In pancreatic cancer cells, *H19* prevents caspase 3 cleavage [62]. **b** *H19* sponges miR-138-5p in cervical cancer to allow the transcription of SIRT1 [70]. **c** *H19* is able to physically interact with PRC2 complex to catalyze the trimethylation of H3K27, that will lead to chromatin condensation and repression of pro-apoptotic factor *BIK* in breast cancer cells [43]. **d** miR-675 is able to inhibit the expression of pro-apoptotic factors such as Cbl and FADD in breast and gastric cancers, respectively [49, 82]

miR-675 are negatively correlated with FADD expression level in gastric cancer. miR-675 targets FADD (Fig. 3d) and inhibits caspases 8 and 3 [49].

There are evidences that *H19* is involved in drug resistance. Overexpression of *H19* in lung adenocarcinoma is associated with acquired resistance to cisplatin and

correlated with the patients' clinical response to cisplatin-based chemotherapy [36]. Knockdown of *H19* in glioblastoma leads to increased apoptosis due to temolozomide treatment, suggesting the role of *H19* in the anti-apoptotic process of glioblastoma cells [91]. In Bcr-Abl-positive leukemic cells, c-Myc-induced expression of *H19* enhances cell survival. Silencing of *H19* results in the imatinib-induced apoptosis of leukemic cells and the inhibition of tumor growth induced by Bcr-Abl [73]. *H19* silencing in ovarian cancer cell lines induces cell apoptosis characterized by an enhanced expression of the pro-apoptotic protein Bax and a decreased expression of the anti-apoptotic protein Bcl2, as well as the activation of caspases 9 and 3 [71]. In ERα+ breast cancer cells, *H19* expression is linked to paclitaxel resistance (Fig. 3c). *H19* is involved in the epigenetic silencing of *BIK*, and contributes to attenuate the apoptosis response [43]. The expression of *H19* is suppressed in breast cancer cells by Huaier extract (aqueous extract of *Trametes robiniophila murr*, used in China for cancer complementary therapy) to promote anti-tumor effects. Interestingly, Huaier extract enhances Cbl expression, that our team previously demonstrated as a miR-675-5p direct target (Fig. 3d) [82].

Enabling replicative immortality

Linked to their proliferative potential, cancer cells require to replicate endlessly to generate macroscopic tumors. This goes against normal cells standards, which divides a limited number of times before undergoing senescence and/or cell death.

It is now known that the protection of chromosomes' ends by telomeres plays a major role in the unlimited replicative potential [92]. Telomeres are constituted by the repetition of multiple tandem hexamers and have an outward 3′ strand that presents a loop structure to protect them from nucleases. In normal (non-immortalized) cells, telomeres are shortened through cycles of replication. The number of cell generations is thereby dictated by the length of telomeric DNA. Telomeres erosion triggers entrance into replicative senescence and potentially cell death. Telomerase is a RNA-dependent DNA polymerase specific for telomeres. This enzyme adds telomere repeats segments to the ends of telomeric DNA. It is absent from non-immortalized cells but found at significant levels in immortalized cells, including cancer cells. The extension of telomeres length by telomerase is, thus, a ''counter-attack'' of cancer cells to avoid induction of senescence and/or apoptosis. Telomerase is composed of two major subunits: TERT (telomerase reverse transcriptase) that carries the DNA polymerase activity, and TERC (telomerase RNA component) that serves as a matrix for telomeric sequences.

Recent studies highlighted the role of *H19* in the regulation of telomerase activity, but opposite models have been proposed. In liver cancer, the non-coding RNA *CUDR* (Cancer Up-regulated Drug Resistant) associates with cyclin D1 and PTEN in an inactive trimeric complex. The decrease of PTEN leads to increase the binding capacity of *CUDR* to cyclin D1, thus, forming an active dimer. *CUDR* and cyclin D1 accelerate the proliferation of liver cancer stem cells by demethylating *H19* promoter. *H19* expression allows the enhancement of telomerase activity by promoting TERT/TERC complex formation and inhibiting TERT/TERRA (Telomeric repeat-containing RNA, a telomeric long non-coding RNA) complex formation [54]. El Hajj et al. studied, for their part, the effects of All-trans retinoic acid (ATRA) treatment in acute promyelocytic leukemic cell lines resistant to retinoids. ATRA is associated with TERT repression, and induces *H19* expression. *H19*, thus, induces the inhibition of telomerase activity by disassembling the telomerase complex TERT/TERC. According to El Hajj et al., *H19* would function as a molecular chaperone able to promote either the association or the dissociation of TERT to TERC, and thereby telomerase activity, depending on the cellular context [74].

Inducing angiogenesis

As long as tumor size remains small, cancer growth does not depend on blood supply, as cells can be sufficiently supplied with oxygen and nutrients via diffusion. However, when tumor grows beyond a few millimeters, it triggers an angiogenic switch to form blood vessels within the tumor, allowing for supplies of nutrients and oxygen, as well as an evacuating arrangement for metabolic wastes. Tumor angiogenesis is driven by numerous cytokines, chemokines, and growth factors such as VASH 2 (vasohibin 2).

Stable overexpression of *H19* promotes tumor formation of glioblastoma cells in mice [31]. CD90+ liver cancer cells are cancer stem cells like and show a mesenchymal phenotype. Conigliaro et al. have shown that CD90+ cells express *H19* and release it via active production of exosomes. *H19* will stimulate angiogenesis and promote cell adhesion to endothelial cell monolayer [55]. *H19* can also enhance tumor angiogenesis by sponging miRNAs. *H19* sponges miR-29a, resulting in an overexpression of VASH2 in glioma microvessels and glioma-associated endothelial cells, to favor tumor-induced endothelial cell proliferation and tube formation in vitro [30].

Halofuginone, a quinazolinone alkaloid isolated from the plant *Dichroa febrifuga*, can be used in bladder carcinoma cells to suppress extracellular matrix deposition and cell proliferation. This negative effect is accompanied by a marked decrease in blood vessel density and in *H19* gene expression, suggesting a role for *H19* in bladder carcinoma angiogenesis [65].

Activating invasion and metastasis

Metastasis is a multi-step process including (i) invasion of tissues surrounding the primary tumor, (ii) escape of the tumor site via the lymphatic circulation of blood vessels, (iii) extravasation from the blood vessels to colonize distant organs, and (iv) formation of secondary tumors. During this process, cancer cells modify their microenvironment to make it permissive and conducive to their growth. In return, tumor microenvironment contributes to cancer cells migration and invasion. Our team previously showed that in response to HGF/SF, *H19* is able to modify cell morphology and enhance their migratory potential [93]. *H19* expression correlates with metastatic potential of breast cancer cells and is found in common metastatic sites according to primary tumor localization [39]. We also demonstrated that the lncRNA *91H*, the *H19* antisense RNA, is able to increase oncogenic properties of breast cancer cells by enhancing migration and invasion in vitro and metastasis in xenografted mouse model [44].

During the first steps of metastasis, carcinoma cells are induced to suppress their epithelial features and upregulate mesenchymal gene expression programs to acquire a new fibroblastic-like phenotype. This phenotypic plasticity, named epithelial-to-mesenchymal transition (EMT), enables cancer cells to invade and disseminate. Several well-known EMT inducers like TGF-β, hypoxia, HGF/SF, or muti-drug

resistance were reported to increase *H19* gene expression [39, 45, 93]. Xu et al. showed that inhibition of *H19* in cholangiocarcinoma reverses EMT and represses cell migration and invasion in vitro [60]. *H19* can promote EMT by modulating factors like cell adhesion molecules. In bladder cancer, *H19* associates with EZH2, the catalytic subunit of PRC2 complex, to induce chromatin condensation at the promoter of *CDH1*, and a decrease of E-cadherin expression (Fig. 4a). This leads to the promotion of bladder cancer cell metastasis [66]. Zhang et al. showed that *H19* promotes tumor growth and metastasis of tongue squamous cell carcinoma through its association with EZH2. Downregulation of *H19* impedes β-catenin/GSK-3β activation, and modulates the expression of mesenchymal/epithelial markers to reverse EMT [33]. *H19* also represses E-cadherin expression in human esophageal cancer cell lines, and enhances vimentin and fibronectin expression [34] (Fig. 4c). Knockdown of *H19* in this model suppresses cell migration and invasion [32]. *H19* acts as a ceRNA in osteosarcoma cells to suppress miR-200 family and increase the expression of ZEB1 and ZEB2 (Fig. 4b) and, thereby, promoting cell migration and invasion [75]. *H19* can also regulate expression of DNMT3B and EMT-associated proteins by sponging miR-29b-3p. This repression enhances migration and invasion of bladder cancer cells [64]. miR-29b-3p is also targeted by *H19* in clear cell renal cell carcinoma to upregulate E2F1 (Fig. 4b), and thus promoting migration and invasion [63].
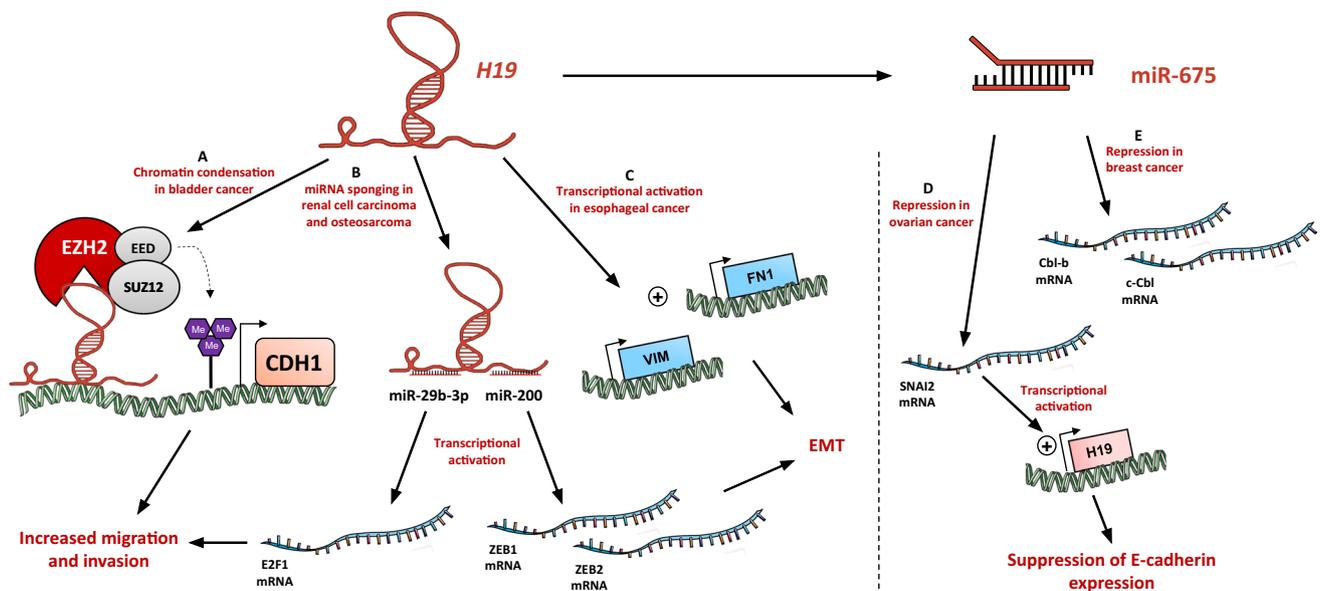

Fig. 4 *H19* promotes the migration, invasion, and metastasis of cancer cells. **a** In bladder cancer, *H19* is able to interact with PRC2 complex to induce chromatin condensation at the *CDH1* promoter, leading to the repression of E-cadherin [66]. **b** *H19* sponges miR-29b-3p and miR-200 in renal cell carcinoma and osteosarcoma, respectively, to activate the transcription of E2F1, ZEB1, and ZEB2

[63, 75]. **c** *H19* acts as a transcriptional activator in esophageal cancer to enhance the expression of vimentin and fibronectin [34]. **d** miR-675 represses the expression of SNAI2 in ovarian cancer to create an activation loop of the *H19* expression and repress E-cadherin expression [39]. **e** miR-675 inhibits Cbl-b and c-Cbl expression to induce the activation of AKT and ERK pathways in breast cancer cells [45]

The expression of miR-675 in ovarian carcinoma cells downregulates the slug transcription factor expression (Fig. 4d), creating a *H19*-slug positive loop involved in the suppression of E-cadherin expression [39]. Similarly, *H19*/miR-675 upregulation promotes gastric cancer cell migration and invasion in vitro [50]. *H19* is also able to cooperate with PEG10 (paternally expressed gene 10) to promote gastric cancer cells transformation, invasion, and anchorage-independent growth [51]. c-Cbl and Cbl-b are involved in the degradation of tyrosine kinase receptors after their activation by growth factors. Our team showed that in breast cancer cells, miR-675 targets c-Cbl and Cbl-b expression to induce the activation of AKT and ERK pathways (Fig. 4e), which in turn increase metastatic potential of breast cancer cells [45].

Interestingly, Wang et al. showed that miR-675 expression could have opposite effects. The miR-675-5p targets miR-200 expression through an increased expression of ZEB1 and ubiquitin-like UBQLN1 protein. This leads to the inhibition of cell migration and invasion in pancreatic ductal adenocarcinoma [94]. According to the authors, contrary findings about *H19* and miR-675 mechanisms of action in pancreatic cancer may be due to different cell lines used and the respective levels of *H19* expression. However, these results contribute to the complexity and plasticity of *H19* mechanisms of action in cancer.

Genomic instability and mutation

Genomic instability and mutation of cancer cells constitute the first of cancer "emerging hallmarks" defined by Hanahan and Weinberg [2]. It is considered as the triggering element of all previous hallmarks: the induction of genome mutations would confer selective advantage to cancer cells and their progeny, allowing them to multiply and takeover normal cells in a local tissue environment. These modulations can be characterized by the inactivation of tumor suppressor genes, or perturbation of epigenetic mechanisms such as DNA methylation. Genomic instability can also concern chromosomal organization. In somatic cells, chromosomal stability and the number of chromosomes pairs are essential features during cell cycle to prevent DNA damages or flawed replication.

In this context, Wolanin et al. showed that the use of curcumin downregulates survivin expression, leading to polyploid formation and defects in chromosome segregation in Bcr-Abl expressing cells. Curcumin disrupts cell cycle regulation and blocks cells in G2/M phase, resulting in the accumulation of abnormalities of mitosis and cytokinesis, and then in apoptosis. [95]. Moreover, curcumin was proved by Kujundžić et al. to downregulate the transcription of both *H19* and DNA topoisomerase II alpha (TOPO2A) in several tumor cell lines [96]. Ravid et al. showed that adipose-derived mesenchymal stem cells stably retain their diploid state under various culture conditions. This ability is associated with a reduced *H19* expression and a higher basal activity of p53 protein [97]. Shoshani et al. studied, for their part, polyploid mesenchymal stem cells, illustrating that polyploid condition maintains a non-tumorigenic state. They revealed that *H19* expression differs between diploid and polyploid cultured mesenchymal stem cells, and that *H19* suppression is associated with a tetraploidization of diploid cells and a reduced tumorigenic potential.

Benzo[α]pyrene (BαP) is a carcinogen molecule that enhances the interaction between *H19* and SAHH (*S*-adenosyl-L-homocysteine hydrolase, the methyl cycle enzyme). Fu et al. studied the effects of BαP treatment in human lung-derived cells in vitro, and showed that the *H19*/SAHH interaction following the treatment inhibits the methyltransferase activity of SAHH. This leads to the demethylation of long interspersed element-1 (LINE-1), which has a retrotranscription activity. Hypomethylation of LINE-1 leads to chromosomal instability and in several genomic alterations such as deletion, amplification, and translocation, and has been reported as a marker of poor prognosis in lung cancer [98]. Thus, *H19* is able to disrupt the genome stability and induce mutations in cancer cells [37].

In an interesting way, DNA demethylation of rhabdomyosarcoma (RMS) cells due to 5-azacytidine treatment upregulates miR-675 expression. This overexpression has been shown to inhibit cell growth through loss of imprinting at the *H19-IGF2* locus: *H19* is re-expressed and IGF2 is downregulated. Tarnowski et al. show that miR-675 overexpression in RMS cells impairs insulin signaling in repressing IGF1R and insulin receptor expression [99]. However, the authors highlight the putative role of several other genes demethylation that could contribute to this phenomenon.

Tumor-promoting inflammation

The promotion of inflammation would seem paradoxal for a phenomenon like tumorigenesis, but immune cells have been shown to have functionally important effects on tumor progression [100]. Indeed, an immunosuppressive microenvironment will be generated by the tumor, thereby preventing its infiltration by immune effector cells. However, cancer cells promote the recruitment of macrophages and regulatory T cells that inhibit antitumoral immune response. These cells will release mutagenic factors (such as ROS) or other inflammatory factors (like TNF-α) that enhance the malignancy evolution of surrounding cells [101].

There are few data available about the link between *H19* and cancer inflammation. *H19* has been shown to influence inflammation-associated pathways initiated by oxidative stress in cholangiocarcinoma cells. Indeed, *H19* sponges let-7a/let-7b miRNAs to upregulate IL-6 expression and enhances chronic inflammation response to the tumor

microenvironment [61]. However, the existence of inflammation processes involving *H19* in other models (pathological or not) can bring us to think that there could exist similar mechanisms in cancer.

Deregulating cellular energetics

In normal cells, the oxygen availability conditions the process of glucose: under aerobic context, glucose is processed via glycolysis in pyruvate and then in carbon dioxide through Krebs cycle, and is dispatched to the respiratory chain in mitochondria. Under anaerobic context, pyruvate is processed in lactate that characterizes fermentation. Cancer cells energy metabolism does not follow that logic: even in presence of oxygen, cancer cells can reprogram their glucose metabolism, and thus their energy production, by favoring glycolysis, in a state called "aerobic glycolysis". This allows the redirection of glycolysis intermediates into various biosynthetic pathways and facilitates the generation of new cells.

Knockdown of *H19* modulates the expression of several genes involved in lipid, carbohydrate, and polyamine metabolisms (such as *PLA2G4A, MPI, PYGB*) [90]. We previously saw that *H19* expression dowregulates PHB1, the chaperone that maintains the functional integrity of the mitochondria [53]. In addition, it has been shown that *H19* overexpression in high-grade serous ovarian cancer promotes glutathione metabolism that induces cisplatin resistance [72]. Moreover, *H19* enhances pyruvate dehydrogenase kinase 1 (PDK1) expression and, thus, promotes glycolysis in breast cancer stem cells [102].

H19 can also act on miRNAs expression to disrupt cell energetics. *H19* sponges miR-106a-5p to upregulate E2F3 expression and to promote glucose metabolism and growth of melanoma cells [76]. *H19* also modulates lipid metabolic by sponging miR-130b in ox-LDL-treated macrophages from atherosclerotic patients [59].

Avoiding immune destruction

Immune surveillance is a mechanism in which cells and tissues are checked at any time by an immune system always on alert. It recognizes and eliminates foreign bodies, putative dangers or abnormalities. To keep walking through the multiple steps of tumorigenesis, cancer cells will have to develop strategies that will dissimulate them from the immune system. In that way, solid tumors that could make it through this surveillance have handled to avoid detection or limit immunological elimination and, therefore, prevent cancer destruction. The immunological defecting managed by tumors is observed in some cases of cancer development in immunodeficient individuals [103]. These are generally virus-induced cancers, meaning that this class of cancers

can expand depending on the reduction of viral burden in infected individuals, through eliminating virus-infected cells. Cancer cells can also escape to immune surveillance by impeding its mobilization against the tumor. As we previously said in the tumor-promoting inflammation context, tumors will generate an immunosuppressive microenvironment that prevents its infiltration by immune effector cells. However, macrophages and regulatory T cells recruited by cancer cells inhibit antitumoral immune response: those bypassing strategies will, thus, allow tumor growth.

Few are known about the implication of long non-coding RNAs in the invalidation of the immune system. An emerging theory would involve lncRNAs in cases of virus-caused immunodeficiencies [104]. In other pathologies such as laryngeal squamous cell carcinoma, some immunity-associated molecules like FOXP3 or CD274, that are expressed at the surface of lymphocytes and macrophages, respectively, are enhanced. However, other factors that reduce immune response such as IL-10 are upregulated and negatively associated with patient's survival, meaning that a program leading to the immune response avoidance is set up. Sun et al. showed that a ceRNA network, including several lncRNAs like *H19,* is involved in the regulation of those molecules, thus developing an immune escape mechanism for LSCC cells [35].

Conclusions

In this review, we highlight the upregulation of the long non-coding RNA *H19* and its strong implication in cancer progression. *H19* acts through various mechanisms such as interaction with proteins and/or miRNAs or the action of *H19*-derived miR-675 to sustain the hallmarks of cancer (Fig. 5). The presence of *H19* in exosomes, involved in tumor progression, reinforces its importance in this pathology. Although further studies are needed to deepen our knowledge on the function of *H19* in a more integrative manner, *H19* has already attracted strong interest in terms of clinical application. Thus, plasma levels of *H19* have been proposed as a predictive marker for breast, stomach, and lung cancers and as a tool to monitor the evolution of cancer [38, 46, 52]. Moreover, by using a plasmid approach that allows the expression of diphtheria toxin A-chain gene under the control of *H19* promoter (DTA-H19/BC-819) to selectively kill *H19*-expressing cells, Sorin et al. showed a significant reduction of liver metastasis growth in treated animals [105]. This strategy is currently in phase 2b clinical trial for bladder cancer and in phase 1/2a trial for ovarian and pancreatic cancers [106, 107]. Clearly, a better understanding of the mechanisms of action of *H19* and the molecular pathways altered by *H19* or miR-675 could provide new therapeutic
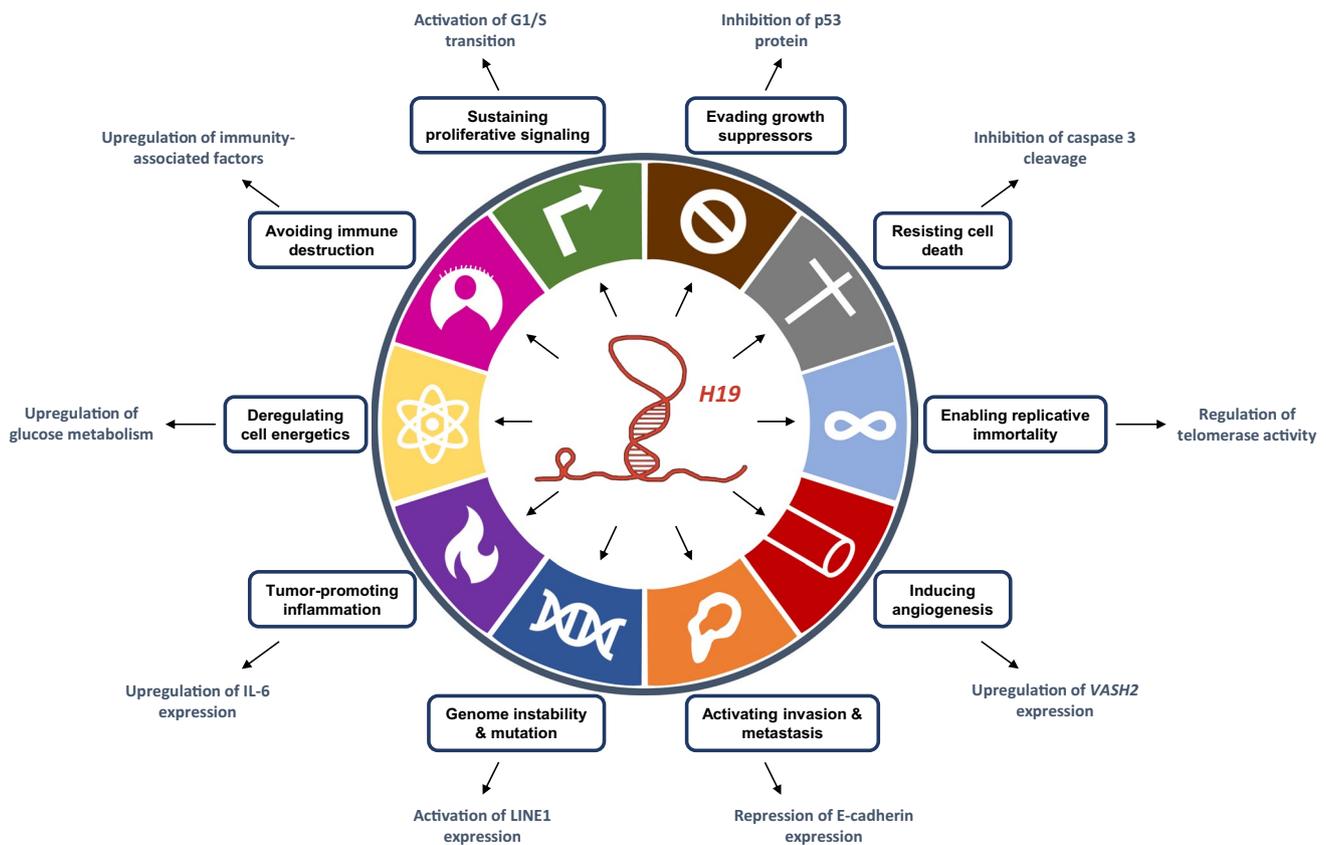
Fig. 5 Implication of the long non-coding RNA *H19* in the hallmarks of cancer. For each hallmark is figured a representative example of *H19* mechanism of action

targets and strategies in the development of personalized management of cancer.

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