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Review

H19 in Endocrine System Tumours

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Abstract. *Long non-coding RNAs (lncRNAs) are over 200 nucleotides long recently discovered RNA molecules that are not involved in the translation process. Accumulating evidence shows that H19 lncRNA is an important regulator of gene expression and its altered expression contributes to carcinogenesis. The aim of this review was to reveal current knowledge about H19 lncRNA and its impact on tumours of the endocrine system. We present findings about H19 altered regulation and its association with tumorigenesis, cancer progression and differentiation, and its potential use in diagnostics, prognostics and therapy. The mechanism and molecular pathways involved in these processes are discussed.*

Non-coding RNAs (ncRNAs) are recently discovered molecules, which do not participate in the translation process and do not have their own protein product (1-3). Approximately 80% of human genome is transcribed into functional RNA, but less than 2% is involved in translation and has protein-coding capacity (4). Therefore, ncRNAs are an abundant group of transcripts that can be divided according to their length or function. According to their length, we can distinguish them into small ncRNAs (less than 200 nucleotides long) and long non-coding RNAs (lncRNAs) (1-3). ncRNAs are divided according to their function into housekeeping ncRNAs and regulatory ncRNAs (2, 5). Ribosomal (r-), transfer (t-), small nuclear (sn-) and small nucleolar (sno-) ncRNAs are housekeeping, whereas micro (mi-), small interfering (si-), piwi-interacting (pi-) and long non-coding (lnc-) ncRNAs are regulatory (2, 5). Up to November 2020, over 260,000 types of human lncRNAs had been identified (6). LncRNAs can be located in the nucleus or cytoplasm (5). Their function is still poorly understood, but their biological roles seem to be more crucial than it was initially hypothesized (1, 3, 5). Accumulating evidence shows that lncRNAs are important regulators of gene expression (3). They play roles in regulation and modification of transcription, post-transcription and epigenetic processes (2, 3). Evidence has revealed that they are involved in the development of diabetes (7, 8) and neurological diseases (9-11). Recent studies have shown that aberrant expression of lncRNAs may also contribute to carcinogenesis (2, 3, 12, 13).

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H19 RNA

H19 lncRNA was the first discovered lncRNA; it was initially classified as an mRNA with unknown protein product and was extracted from a mouse liver (14). A few years later, Brannan *et al*. isolated *H19* gene from human tissues and stated that the only final product of *H19* gene may be an mRNA transcript, located in the cytoplasm (15). The full length of *H19* RNA chain is 2.3 kb (16). In human, the gene is mapped on chromosome 11p15.5 (17). The expression of *H19* is high during embryonic development (14, 18), mainly in the endoderm and mesoderm (19), and maximum expression has been observed in the liver, muscles and adrenals (19, 20). After birth, it is down-regulated in most tissues, but its expression is still detectable in inter alia, skeletal muscle, myocardium and mammary gland tissues (19, 21).

H19 – Contribution to Carcinogenesis

The linkage between *H19* and cancer development was the subject of many studies since the 1990s (18, 22, 23). Bartolomei *et al*. first discovered that *H19* is expressed exclusively from the maternal allele, due to the imprinting process (24). Knowledge about the influence of imprinting alterations on carcinogenesis led to search for an association between *H19* gene and its

potential role in cancer development (18). Probable mechanisms are loss of imprinting (LOI) – an epigenetic event resulting in biallelic gene expression, and changes in the methylation pattern of promoters sequences, which regulate the levels of gene expression (25). It has been proposed that these two mechanisms are strongly related, due to the involvement of methylation in the inactivation of the paternal allele (26). It is important to note that *H19* and *IGF2* genes are commonly imprinted interdependently due to their close location on 11p15.5 (27). Association between LOI of *H19* gene and tumorigenesis was described inter alia, for oesophageal (28), colorectal (28) and lung cancers (29). Additionally, in Wilms' tumour, LOI of *IGF2* gene contributes to methylation of *H19* promoter, resulting in the down-regulation of *H19* expression (30). Nevertheless, LOI does not always directly correspond to a methylation pattern and level of gene expression, as it has been shown by Byun *et al.* in a study on bladder cancer (25). In contrast to the above studies, Yballe *et al.* have shown no connection between LOI of *H19* gene and the occurrence of breast cancer (31). Similar results were obtained for neuroblastoma by Wada *et al.* (32). Further studies have been performed on the mechanisms of *H19* contribution in carcinogenesis. *H19* has been proposed as an oncogene (33, 34), tumour suppressor (35, 36) or as an oncofoetal RNA, associated with germ cell tumours (18, 19, 37).

The oncogenic properties of *H19* may be due to its increased expression in neoplasm tissues. Over-expression of *H19* RNA has been shown to contribute to the carcinogenesis and progression of tumours of the breast (34, 38), lung (39, 40), oesophagus (28, 41), stomach (42-44), colon (28, 45), liver (46), pancreas (47, 48), kidney (49), bladder (46, 50), cervix (51), ovary (52, 53), as well as in glioma (54, 55), leukaemia (56), oral squamous cell carcinoma (57), cholangiocarcinoma (58), osteosarcoma (59, 60) and melanoma (61). On the other hand, in some tumours down-regulation of *H19* expression was observed [inter alia in Wilms' tumour (30, 62)], which means that *H19* may be classified also as a tumour suppressor.

The mechanisms through which *H19* is involved in the process of cancer development include promotion of gene mutations, cell proliferation, invasion, migration and angiogenesis, immune and pro-apoptotic factors modulation and growth suppressor expression regulation (63, 64). Additionally, some studies have shown that *H19* RNA functions through sponging mi-RNAs including miR-675 (45, 48), miR-107 (39, 40), miR-370-3p (65), miR-106a-5p (61), miR-29a (54), miR-29a-3p (49) and miR-138-5p (51).

In recent meta-analyses (64, 66) the prognostic and clinicopathological values of *H19* in different types of cancers were explored. Both studies demonstrated that high levels of *H19* RNA contribute to shorter overall survival and associate with more advanced clinical stage of tumours and lymph node metastasis. Additionally, *H19* RNA positively correlates with poor tumour differentiation, earlier distant metastasis (64), as well as with poorer histological tumour grade and disease-free survival (66). Summarizing, *H19* RNA has been demonstrated as a potential marker for tumour progression and patient's prognosis.

So far, *H19* has been introduced as an intriguing figure in neoplasms' origin and development. But what is its impact on tumours of the endocrine system?

Pituitary Adenomas

In the study by Lu *et al.*, significantly higher expression of *H19* was observed in aggressive growth hormone-secreting pituitary adenomas compared to non-invasive growth hormone-secreting tumours (67). A similar observation was made for oesophageal cancer (*H19* correlated positively with tumours' depth, stage and metastasis) (41), lung cancer (*H19* enhanced cell proliferation, migration, and invasion of a cell line) (68), glioblastoma (in cell line and xenograft mouse model, *H19* promoted invasion, angiogenesis and tumour growth) (55), cholangiocarcinoma (*H19* positively correlated with tumour size, cell migration and invasiveness in tissues and cell lines) (58). Thus, we could hypothesize that in invasive pituitary adenomas *H19* might be a potential marker of malignancy and patients' prognosis.

On the other hand, Wu *et al.* (69) and Zhang *et al.* (70) observed down-regulation of *H19* expression in pituitary tumour tissues and in the plasma obtained from patients with pituitary adenomas in comparison to normal pituitary glands and healthy controls. In *in vitro* and *in vivo* models, an increase in cell proliferation after knockdown of *H19* gene was observed (69). Furthermore, in mouse models injection of *H19* lentivirus led to shrinkage of tumour volumes. *H19* expression levels negatively correlated with tumour volumes. Antitumor effects were induced by inhibiting 4E-BP1 phosphorylation in the mTORC1/4E-BP1 pathway. Moreover, in xenograft experiments *H19* overexpression was more effective than cabergoline in suppressing tumour growth (69). Additionally, the investigators revealed that cabergoline stimulated *H19* expression and *H19* and dopamine agonists exerted a synergistic therapeutic effect. These results indicate that increasing *H19* expression can be a potential therapy for pituitary adenomas. The mechanism of the synergistic action of *H19* and dopamine agonists in prolactinomas was investigated in a recent study by Wu *et al.* (71). It was revealed that *H19* promotes the effects of dopamine agonists by inhibiting miRNA-93a and stimulating ATG7 expression, and this is another example of *H19* action by sponging mi-RNA. *H19*/miRNA-93a/ATG7 axis was elucidated as a potential target of therapy, especially in drug-resistant prolactinomas.

Opposite results regarding the influence of *H19* on drug resistance, but also describing *H19* impact on ATG7, were demonstrated by Pan *et al.* (72). In non-small cell lung

cancer cell lines and xenograft models, they observed that *H19* sponges miRNA-615-3p and regulates ATG7 expression, and that this mechanism is probably involved in erlotinib resistance.

Thyroid Cancer

Ambiguous associations between *H19* expression and tumour development have also been illustrated for thyroid cancer. In thyroid cancer samples and cell lines, Liu *et al*. (73) observed over-expression of *H19*. *H19* enhanced tumour growth by inhibiting apoptosis and promoting progression, migration and invasion. Moreover, the researchers found that *H19* affects miR-17-5p and antagonizes its effect on YES1 expression. The association between *H19* and miR-17-5p has also been illustrated in gastric cancer cells (74), whereas a positive correlation between the levels of these two RNA was determined. In that study, *H19* was associated with larger tumour size, more advanced TNM stage and lymph node metastases. Corresponding outcomes, but for thyroid cancer, were exemplified in the study by Liu *et al*. (75). Moreover, higher *H19* expression was related with lower 5-year survival rate.

The mechanism through which *H19* contributes to thyroid cancer development was the subject of the studies of Li *et al*. (76) and Wang *et al*. (77). In the Li *et al*. study (76), *H19* was found to function through the PI3K/AKT signalling pathway, which plays an important role in carcinogenesis. Similarly, the association of *H19* with PI3K/AKT was illustrated in colorectal cancer cell lines (78) and melanoma (79). An additional finding of Li *et al*. was over-expression of *H19* in thyroid cancer tissues compared to adjacent healthy thyroid tissues (76). Moreover, *H19* expression was higher in poorly differentiated thyroid cancer tissues. In an *in vitro* model, knockdown of *H19* resulted in cancer cell viability inhibition and induction of apoptosis (76).

In contrary, Wang *et al*. (77) showed that *H19* overexpression inhibits viability, migration and invasion and induces tumour cells apoptosis and these effects might be mediated *via* down-regulating the expression of IRS-I (insulin receptor substrate I). Moreover, IRS-I expression might be induced also by PI3/AKT signalling pathway. The results of Wang *et al*. suggest that *H19* could be potentially used in thyroid cancer treatment.

The *H19* effect on the development of specific types of thyroid cancer was the subject of several studies presented below. For papillary thyroid cancer (PTC), higher tissue expression of *H19* was observed in the studies of Liang *et al*. (80) and Li *et al*. (81). Different mechanisms were proposed for expounding *H19* involvement in PTC development. In the first study, higher expression was positively correlated with mesenchymal phenotype biomarkers (vimentin, ZEB2, Twist, Snail2), which indicates that *H19* RNA induces epithelial–mesenchymal transition (EMT) process. EMT has been described to play a critical role in cancer invasiveness and metastasis (82). A similar effect of *H19* on EMT was depicted for ovarian (65), oesophageal (41) cancers and cholangiocarcinoma (58). Moreover, in the ovarian cell line, *H19* was shown to promote EMT-related activity and contribute to cisplatin resistance (83). Li *et al*. (81) proposed a mechanism that was related to ERβ (oestrogen receptor beta). Oestradiol enhanced *H19* expression by ERβ whereas high expression of *H19* promoted expression of ERβ (as a positive feedback). Additionally, *H19* acted through miR-3126-5p and this is another example of sponging mi-RNA by *H19*.

In the study by Liang *et al*., *H19* expression was positively correlated with tumour size and grade, as well as with lymph node metastases (80). The opposite results were obtained by Lan *et al*. (84). Jiao *et al*. (85) observed down-regulation of *H19* in papillary thyroid cancer tissues compared to paracancerous or benign nodes. Additionally lower expression of *H19* coincided with the presence of lymph node metastasis (84, 85), as well as with other features of poorer prognosis, such as higher tumour size, more aggressive histological type and poorer diseases-free survival (85).

For minimally invasive follicular thyroid cancer, Dai *et al*. examined whether *H19* could be a marker of distant metastasis and patients' prognosis (86). The study revealed low expression of *H19* in cancer tissues and *H19* levels were negatively correlated with tumour size, vascular invasion, distant metastasis and poorer overall survival.

Zhang *et al*. demonstrated that *H19* RNA is over-expressed in anaplastic thyroid carcinoma tissues and cell lines (87). Moreover, they showed that reduction of *H19* expression can be a potential target of molecular therapy – it decreased cell proliferation, migration and invasion *in vitro* as well as inhibited tumorigenesis and metastasis *in vivo*.

Alike divergences of *H19* expression levels in different types of thyroid cancer samples were observed by Wächter *et al*. (88). In anaplastic carcinoma, it was upregulated in six cases, down-regulated in two and was similar to healthy thyroid tissue in four. In follicular thyroid cancer, it was down-regulated in five samples and was the same in three cases. In papillary thyroid cancer it was overexpressed in five samples, down-regulated in two and stable in four. Thus, no association was observed between *H19* levels and type of thyroid cancer. In summary, in thyroid cancer, *H19* was found to act both as an oncogene as well as a suppressor.

Adrenals

During embryonic and foetal life adrenal expression of *H19* is very high (89, 90). In adulthood it remains highly expressed – it shows approximately 50% of the foetal

expression (91). Gao *et al*. (92) and Liu *et al*. (91) showed that in benign adrenal adenomas and hyperplastic adrenals, *H19* is expressed at about the same level as in healthy glands. However, similarly to Glover *et al*. they showed that in adrenocortical carcinomas the expression was reduced and it was significantly lower than in normal adrenals (91-93), whereas in pheochromocytomas the expression was variable, but generally decreased (91). Upon further investigation, Liu *et al*. showed that *H19* expression was also decreased in virilizing adrenal adenomas (94). The proposed mechanism causing the low *H19* expression in adrenocortical carcinomas was methylation of the promoter area (92). The degree of methylation of the promoter CpG regions in patients with adrenocortical cancers and adenomas was the subject of the study of Barreau *et al*. (95). The characterized cancers had a higher degree of methylation compared to adenomas that corresponded to patients' poorer prognosis. *H19* was found to be one of the genes with a hypermethylated promoter region leading to its down-regulation. Moreover, it showed the strongest observed inverse correlation between methylation levels and gene expression in this study, leading to a conclusion that *H19* plays a role as a suppressor. A comparable effect of methylation of the *H19* promoter on carcinogenesis was shown for bladder cancer (25) and Wilms' tumour (30). Additionally, Creemers *et al*. (96) proposed that the methylation status of *IGF2* and *H19* regulatory regions as useful markers in distinguishing malignant adrenocortical carcinomas from benign adenomas. Thus, we could conclude that *H19* expression levels and the methylation pattern of its regulatory regions could be promising tools in the diagnosis of adrenal tumours.

In addition, the various degrees of *H19* promoter methylation in benign ovarian teratomas (97) as well as in different types of germ cell tumours (GCTs) (98, 99), illustrated the diversity in origin and processes involved in the development of these neoplasms. Hence, reduced methylation in adrenocortical carcinomas may reflect their primordial features, however, further investigations are needed to evaluate this hypothesis.

Neuroendocrine Tumours

In the Ji *et al*. study, aberrant expression of *H19* was described as an important element in the development of non-functional pancreatic neuroendocrine neoplasms (pNENs) (100). In primary tumours as well as in metastatic tumours, the levels of *H19* expression were variable. However, after evaluation of the association between *H19* and tumour's malignancy, the researchers revealed that non-malignant tumours were characterized by low expression of *H19*, whereas in malignant pNENs as well as in liver metastases its expression was high. Moreover, high expression correlated positively with tumour size, lymph node and liver metastasis, local invasion, TNM stage, tumour-related death, poorer progression free and overall survival. In the cell line models, the authors showed that silencing *H19* led to inhibition of cell proliferation, growth and colony formation and the opposite effects were observed after *H19* over-expression. Additionally, overexpression of *H19* promoted tumour growth and Ki67 expression in xenograft mouse models. The paper illustrates the possible association between high expression of *H19* and VGF (neuropeptide precursor) in neoplasms origin, progression and poorer patient prognosis. Additionally, similarly to Li *et al*. (76), *H19* was shown to be involved in the activation of PI3K/Akt signalling pathway.

Ramnarine *et al*. showed that *H19* was an epigenetic regulator, which contributed to neuroendocrine transdifferentiation (NEtD) – a transformation from prostate cancer to neuroendocrine prostate cancer (101). In addition, high expression of *H19* was presented as a practical tool in distinguishing neuroendocrine prostate cancers from prostate adenocarcinomas.

Conclusion

The aim of this review was to demonstrate the current knowledge about *H19* lncRNA and its impact on tumours of the endocrine system. The collected data shed light on the mechanisms and molecular pathways involved in tumorigenesis. *H19* was determined to be involved in epigenetic regulation and in miRNA expression control. Moreover, *H19* may be a useful factor in differentiating malignancies from benign lesions, as it was demonstrated in aggressive pituitary adenomas (67), adrenocortical carcinomas (91-93) and pNENs (100). Another promising aspect is the down-regulation of *H19* as a purpose of targeted therapy, which was illustrated in cell line models of thyroid cancer (76, 87) and pNENs (100). On the other hand, upregulation of *H19* has also been proposed as a therapeutic tool (69, 70, 77). In addition, *H19* may improve the effects of treatment, like it was illustrated for dopamine agonists in prolactinomas (69, 71). Furthermore, abnormal expression of *H19* RNA in different types of malignancies makes it a potential biomarker for cancer diagnosis, prognosis and monitoring. In some reports correlation between *H19* expression and clinicopathological features was observed, which highlights the prognostic value of this RNA (75, 80, 84-86, 95).

Nevertheless, there are still many questions without unequivocal answers and are subjects for further investigation. First, studies concerning tumours of the endocrine system are limited. Particularly, there is a lack of studies exemplifying a connection between *H19* and parathyroid tumours. Additionally, only few studies concerned the potential association between *H19* and hormonal function of tumours. Second, there are

contradictory reports regarding *H19* expression in most of the described pathologies. Similarly, to outcomes obtained for other neoplasms, opposite effects of *H19* on tumorigenesis in endocrine gland tumours were demonstrated. *H19* was proposed to act as an oncogene as well as a suppressor. Currently, the possibility to use its levels as a simple tumour marker is limited. In addition, most presented results were obtained using cancer cell lines and xenograft mouse models. Further investigations on human tumour tissues and plasma concentrations are needed. Finally, the samples of the groups were small in some studies, sometimes due to the rare occurrence of the specific pathology. Therefore, studies with larger sample size are necessary.

In conclusion, *H19* is a novel and intriguing factor, which may allow elucidation of processes involved in carcinogenesis and tumour progression. Nevertheless, further investigation of its biological role in endocrine system tumours are still needed.

Conflicts of Interest

The Authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' Contributions

MR, AJP and MB contributed to the article's conception and design. MR, AJP and KK collected the literature sources. The first draft of the manuscript was written by MR and corrected by AJP, KK and MB. All Authors contributed to the final version of the manuscript and approved it for publication.

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