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Review Article

Epigenetic modulation of long noncoding RNA H19 in oral squamous cell carcinoma-A narrative review

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ABSTRACT

Oral squamous cell carcinoma (OSCC) showed a seemingly increasing incidence in the last decade. In India, despite the use of tobacco decreased rapidly, in the past five years, the incidence pattern of OSCC over gender and age showed a drastic shift. About 51 % of the head and neck cancers are not associated with habits. Studies exploring various contributing factors in the incidence of this malignancy have documented. Recently, the epigenetic factors associated with the induction and progression of OSCC were explored. More than 90 % of the human genome is made up of non-coding transcriptome, which believed to be noises. However, these non-coding RNAs were identified to be the major epigenetic modulators, which raises concern over incidence of carcinoma in non-habit patients. H19 is a long non coding RNA which proved to be an effective biomarker in various carcinoma. Its role in oral squamous cell cancer was not investigated in depth. This review discusses in detail the various epigenetic role of H19 in inducing oral carcinogenesis.

1. Introduction

Oral cancer is the sixth most common cancer in the world [1]. Oral squamous cell carcinoma (OSCC) is the most common sub-type of malignancy occurring in oral cavity. Studies have stated that OSCC constitutes about 90 % of all oral cancers [2]. They may occur commonly in tongue, buccal mucosa, gingiva and/or floor of the mouth [3]. Most of the malignant lesions of the oral cavity are due to usage of tobacco. Although diagnostic and therapeutic field have shown immense development, survival rates for OSCC are still not satisfactory [4]. Oral cavity is the most accessible region of the body, hence the potentially malignant changes can be easily appreciated at the initial stages. Early diagnosis of the pre-malignancies such as oral sub-mucous fibrosis, leucoplakia, erythroplakia and proliferative verrucous leukoplakia will help in decrease of mortality rates. Global survey shows that about 350, 000 new cases recorded every year [5]. Moreover, the incident rate increased slowly in accordance to the demographic and clinical data. Heavy smoker's, and males above 60 years of age are more susceptible for OSCC development, there is a paradigm shift in incidence of the disease and its pattern resulting in incidence of the disease among individuals of middle age and without habit [6]. Genetic and environmental factors play a major role in OSCC incidence and development.

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Apart from genetics, role of epigenetics in the initiation and progression of oral cancer was found to be massive [7].

Human genome consists of about 98 % of non-coding transcriptome. These non-coding regions between the exons or antisense regions gives rise to various types of RNAs [8]. Based on their origin, function and size of those non-coding RNAs named as microRNA, PIWI-interacting RNAs (P-element Induced WImpy testis in Drosophila), small nucleolar RNAs, long non coding RNA, ribosomal RNA, transfer RNA and transcribed ultraconserved regions [9]. The long non-coding RNAs (lncRNA) are the transcriptome with >200 nucleotides, which have a revolutionary role in development, diagnosis and prognosis of oral cancer [10]. They act as a promoter, insulator, enhancer and silencer in various genomic activity. These lncRNAs are very much time and tissue specific [11]. Various types of long non-coding RNA in association with OSCC were discovered. TUG 1 (taurine-upregulated gene 1), HOTTIP (HOXA transcript at the distal tip) and H-19 lncRNAs are associated with epithelial mesenchymal transition [12]. UCA-1 (urothelial cancer associated 1), NEAT-1 (nuclear enriched abundant transcript 1), LINC RNA ROR (Long intergenic non-protein coding RNA, regulator of reprogramming), MALAT 1 (Metastasis-Associated Lung Adenocarcinoma Transcript 1) showed to be associated with apoptosis [13]. H-19 is a competing endogenous RNA (ceRNA) that modulates biological processes such as epithelial-mesenchymal transition and apoptosis [14]. Thus, the role of H-19 as an epigenetic regulator in oral cancer reviewed in this article.

2. Classification

LncRNA is been classified based upon criteria's such as molecular weight, location, regulation, stability, biological processes the. As discussed, earlier lncRNAs are transcripts of <200 nt (nucleotide). Very long intergenic non-coding RNAs (vlincRNAs) are those of length 50 KB to 1 MB. Unspliced sense PINs-partially intronic RNAs which emerged from transcriptional forests. Totally intronic RNAs-TINs make about 70 % of total non-coding nuclear-encoded RNA and 40-50 % of cellular RNAs. Few transcripts, which regulate the parent gene expression, is referred to as circular intronic ncRNAs (ciRNAs) and those circular RNA from exons are referred to as exonic circular RNAs (ecircRNAs). Sense ncRNA, natural antisense ncRNA, mirror antisense, standalone ncRNAs made from 3′UTRs and transcription start site-associated RNAs are other lncRNAs that are classified based on association with protein coding genes. Based upon function, non-coding RNAs named as enhancer, upstream antisense, PROMoter uPstream Transcript, Telomeric repeat-containing RNA and promoter lncRNA. These ncRNAs involve in transcriptional regulation, chromatin signalling plasticity and dynamics of nuclear architecture. Based on their resemblance to mRNA, they referred to as long intervening ncRNAs (lincRNAs) and mRNA like noncoding RNAs mincRNAs [15–23] (Table 1).

H19 is a conserved gene cluster located at 11p15.5, whose expression is monoallelic. It is an imprinted gene expressed from maternal allele, that plays a vital role in early stage of embryogenesis as well in growth and development. They also regulate other genes from imprinted gene network like Insulin like growth factor 2(*Igf2)*, paternally expressed gene 1(*Peg1), Slc38a4(solute carrier family 38 member 4)*. Other factors such as C/EBP, CTCF insulation, imprinted control region and matrix attachment regions regulate H19 expression [24]. The primary transcript of H19 gene is processed in a similar way as a mRNA, H19 gene produces, a 2.4 kb mature transcript. LncRNA H19 transcribed in nucleus and transported to cytoplasm [25]. They remain untranslated. They are not identified with any open reading frames; therefore, no protein coding function was identified physiologically. H19 and *Igf2* are co-expressed during embryogenesis in mesoderm and endoderm derived tissues. *Myo H* or H19 expression is associated with skeletal and cardiac muscle differentiation [26]. Studies showed that H19 could be an oncogene/tumour suppressor gene. Recent study has hypothesized that H19 could have a role in cell cycle, as p53 modulates the expression of H19. It sponges miR138, miR200. Studies have shown that on silencing H19, increased expression of miR-138 was observed thereby progression and invasion of OSCC was inhibited [27].

Table 1
Classification of long noncoding RNA based upon various parameters.

Types	About	Example	Reference
Transcript length			
Long non-coding RNA	lncRNA >200 nt	ANRIL,H19, HOTAIR, HOTTIP, lincRNA-p21, XIST	15
Very long intergenic non-coding RNAs	50 kb to 1 MB	Vlinc 21, vlinc_185	15
Annotated protein-coding genes			
Intronic ncRNA	TIN,PIN	ANRASSF1	18
Circular ncRNAs	ciRNA	ci-ankrd52, ci-sirt7	19
Sense ncRNA	Sense strand having exons of protein coding genes.	senZfp536	16
Antisense ncRNA	asRNA,NAT	SOX21-AS1	16
Functional association with DNA			
Enhancer	eRNA	LEENE	17
Promoter	PALR		17
Upstream antisense RNA	uaRNA		17
PROMoter uPstream Transcript	PROMPT		17
Telomeric repeat-containing RNA	TERRA		17
Genomic Location and context			
Intergenic lncRNAs	lincRNA		20
Intronic lncRNAs	Formed from introns of the protein coding genes.		20
Sense and antisense lncRNAs	NAT, asRNA	aHIF	20
Resemblance to mRNA			
mRNA-like noncoding RNAs	mlncRNA	HOTAIR	21
Long intergenic non-coding RNA	lincRNA	ANRIL,H19, HOTAIR, HOTTIP	21
Target mechanism of action			
Signal	Cell specific expression	Xist	22
Decoy	Binds and evaluate target protein	PANDA	22
Guide	Localization of RNP complex	HOTAIR	22
Scaffold	Helps in localizing multiple proteins to configure RNP complex	HOTAIR,7SL	22
Mechanism of Function			
Transcriptional Regulation	Gene transcription via transcriptional interference	H19,MEG3, HOTAIR, ANRIL	23
Post-transcriptional regulation	Splicing Regulation, Translational control	H19, PTENP1b, MIAT, MALAT1	23
Other function	Protein localization, telomere replication, RNA interference	meiRNA, *TERC*	23

3. Biogenesis and degradation

LncRNAs have their biogenesis similar to mRNA. These are conserved, less evolutionary and contained fewer exons in comparison to mRNA. They are expressed less abundantly possibly due to the repressed histone modification in their gene promoters. Their 5′ end has m^7G caps and the 3′ end has polyadenylated tails. Many studies stated that formation, processing and degradation of lncRNAs are linked to their fate and function [28]. Most of the lncRNAs are inefficiently processed by phosphorylation dysregulated polymerase II (Pol II) and held back in nucleus rest are spliced and transported to cytoplasm by nuclear RNA export factor 1(NXF1). Those poorly transcribed RNAs in nucleus are degraded by exosomes (nuclear). LncRNA with U1snRNA (U1 small

nuclear RNA) binding motif recruit consecutive nucleoprotein (U1RNP) and establish association with polymerase resulting in number of non-coding RNA formation [29]. Factors in cis and trans such as U1 small nuclear ribonucleoprotein (U1snRNP) and heterogenous nuclear ribonucleoprotein K (hnRNPK) also enhance nuclear localization. Due to shorter PPT (polypyrimidine tract) few lncRNAs undergo inefficient splicing. Other RNPs such as PPIE (peptidylprolyl isomerase E) down-regulates the splicing process and contribute in nuclear localization. Increased accumulation of lncRNA occurs in chromatin when SPT6, a pol II associated elongation factor is altered functionally [30]. Loss of SPT6 will eventually result in active transcription of lncRNA genes instead of protein coding genes, subsequently causes increased lncRNA accumulation to result in DNA damage associated R-loops. LncRNA in cytoplasm showed to interact diversely with many RNA binding proteins (RBP) and some with ribosomes. Pseudo 5' untranslated regions help in association of lncRNA with ribosomes [31]. Those lncRNA showed to have half reduced half-life period. Many lncRNAs mobilised into mitochondria, without known function. Exosomes also identified with few lncRNAs, RNA array studies reveal that 29 % of lncRNA were unstable with half-life period of 2h or even less. Cytoplasmic lncRNAs are more stable than lncRNAs of nucleus. LncRNAs structurally mimic mRNAs and might degrade in the same way as mRNAs by processes such as deadenylation, decapping and exo/endonucleolytic degradation [32]. Studies hypothesized, that lncRNA decay by nonsense-mediated mRNA decay (NMD), STAU1-mediated mRNA decay (SMD), no-go mRNA decay (NGD) and non-stop mRNA decay (NSD). Decay machineries recruited by miRNAs and RNA binding proteins (RBPs) are also thought to be involved in lncRNA decay. Evidences suggested that H19 sequences are targeted by let-7. Overexpression of let-7a was reported to reduce H19 levels. However, the exact mechanism of degradation of lncRNA yet to be explored [33].

3.1. Biogenesis and degradation of H19

H19 is transcribed from the H19 gene, which is maternally imprinted and paternally expressed. It is transcribed by RNA polymerase II. The expression of H19 and its reciprocally imprinted gene, insulin-like growth factor 2 (IGF2), is regulated by an imprinting control region. Methylation status at this region affects the expression of both genes. Post-transcriptional modifications and processing, like 5′ capping, 3′ polyadenylation, and splicing, prepare the nascent H19 RNA for export from the nucleus to the cytoplasm [28].

The stability of H19 RNA is regulated by various factors, including RNA-binding proteins, microRNAs (miRNAs), and other regulatory molecules that influence its half-life. H19 can act as a molecular sponge for miRNAs, regulating their availability to target mRNAs. Some miRNAs can target H19 for degradation, affecting its stability. Endonucleases and exonucleases can degrade RNA molecules, including lncRNAs like H19. Enzymes like RNase P and RNase R are involved in RNA degradation pathways. Various cellular signals and stress conditions can influence the degradation rates of RNAs, including H19, by altering the activity of degradation machinery or affecting RNA-protein interactions. The intricate regulation of H19's biogenesis and degradation contribute to its diverse functions in cellular processes. Understanding these processes is crucial for unravelling the roles of H19 in development, diseases, and potential therapeutic interventions [34].

4. Expression and function of H19

In situ hybridisation technique evaluation of extraembryonic tissue of mouse shows that expression of H19 was evident by E5.5 and in embryo soon after implantation by E6.5- biallelical [35]. Expression of H19 identified throughout the foetal development in comparable levels of β-actin expression. *Igf*2 expressed in a similar pattern of H19. Their expression reduced in all tissues except skeletal muscles after birth [36].

In-vivo study of mouse models helps in identification of regulatory elements of the expression pattern of imprinted genes. Imprinting control region (ICR), differentially methylated domain (DMD), differentially methylated region (DMR) identified in H19 transcription start site between −4 and −2 kb. Enhancers and promoters also controlled the H19 gene by Ref. [37].

The expression pattern of the long non-coding RNA H19 is dynamic and tissue-specific, playing essential roles during development and in various physiological processes. Few key aspects of its expression pattern are.

4.1. Developmental expression

H19 is highly expressed in the placenta and during embryonic development, particularly in various embryonic tissues, including muscle, liver, and placenta. Its expression pattern is drastically reduced after birth and altered during chronic diseases [35]. H19 is subject to parental imprinting, meaning that its expression is allele-specific and depends on whether it is inherited from the mother or the father. In most tissues, the maternally inherited H19 allele is active, while the paternally inherited allele is silenced due to DNA methylation at the imprinting control region (ICR) [37].

4.2. Tissue-specific expression

H19 is highly expressed in the placenta during development, where it plays a role in regulating placental growth and function. H19 involves in muscle development and differentiation, particularly in regulating myogenesis. H19 found to be expressed in the liver, where it may contribute to liver development and function [38].

4.3. Disease and pathological conditions

Altered expression levels of H19 was observed in various cancers such as breast cancer, hepatocellular cancer. In some cancers, H19 is overexpressed and contributes to oncogenesis by acting as an oncogene, regulating cell proliferation, migration, invasion, and apoptosis. While in retinoblastoma it acts as a tumour suppressor gene with low expression pattern. H19 implicated in diabetes-related complications and metabolic disorders affecting insulin signalling and pancreatic beta-cell function [39].

4.4. Regulation

H19 expression is regulated by epigenetic mechanisms, including DNA methylation at the Imprinting Control Region-ICR, histone modifications, and chromatin remodelling. Various transcription factors and signalling pathways can modulate the expression of H19 in response to developmental cues or environmental stimuli. The tissue-specific and developmentally regulated expression pattern of H19 underscores its diverse roles in normal physiology and disease. Its aberrant expression in certain pathological conditions highlights its potential as a biomarker or therapeutic target in various diseases, including cancer and metabolic disorders [40].

H19 helps in limiting cell proliferation and body weight. H19 was found to be involved in number of cancers such as hepatocellular carcinoma, bladder carcinoma, choriocarcinomas, breast cancer, oral cancer and in association with syndrome such as Beckwith wideman syndrome [41]. They showed to have upstream effect in hormonal regulation and downstream effect in metabolism, tissue invasion, migration and angiogenesis. H19 levels were down regulated in type 2 diabetes [42]. H19 via TGF-β pathway induces osteoarthritis, and rheumatic arthritis. H19 was also observed to be a mediator in stress induced inflammation. Increased expression of H19 was observed in hypertrophied cardiomyocytes of mouse and in cardiac ischemia. Conversely, in ischemic stroke. H19 modulates Notch1 and inhibit the transcriptional activity of p53, hence increasing the susceptibility of the

disease [43]. Many animal model experimental studies conclude that deletion of a 13-kb and 3-kb region resulted in overgrowth. H19 Δ 13 mutants cause deletion of DMR thereby expression of Igf2 allele is enhanced. H19 expression was hyper-pronounced during development. Although no viable data has been collected on its role in embryogenesis/development. Studies done so far conclude that H19 could play a major role in development. H19 also functions as competing endogenous RNA (ceRNA), encoding proteins necessary for myotube formation [44].

Deletion mutation in H19 results in overgrowth phenotype, this could be due to modification of chromatin structure as a result of deletion. In addition, this results in change in accessibility of Igf2 promoter, it could be also due to interference of H19 RNA in loss of Igf2 imprinting. H19 functions as both in cis and in trans [45]. Trans function of H19, it was evident in H19 Δ 13 and H19Δ 3 mutants, change in amount of methylation of Igf2 DMRs was evident in opposite allele thus suggesting of trans effect. H19 also modulate polysomes thereby affecting the translation of Igf2. Many *in-vitro* experiments were done to show the trans effect of H19. Study by Hansen et al. showed that H19 could interfere with Igf2 regulation and translation [46].

5. H19 and epigenetics

The expression of H19 depends upon the DNA methylation, addition of CH3-methyl group to the cytosine in a CpG dinucleotide of the residual DNA. CpGs occurs in islands and enzyme DNA methyl transferases process DNA methylation. Methyl transferases can create new methylation patterns [47]. Conventionally, genes with methylated promoter cannot be expressed. Other epigenetic modifications apart from methylation are demethylation, acetylation and deacetylation of specific amino acid residues [48]. Paternal chromosome has methylated H19 promoter thence no transcription takes place. Enhancers are short DNA sequences, which helps in transcription of genes [49]. Animal studies on deletion of enhancers showed decrease in H19 expression especially in endoderm derived tissues. Chromosome 11p15 has two imprint control regions *ICR1, ICR2. ICR1* corresponds to differentially methylated region-H19 DMD which has abundant CpG residues. H19 *ICR1* plays a vital role in transcription of H19 as well as preventing enhancers from accessing Igf2 promoters in maternal chromosome. Studies done on immune-precipitated cells suggested that paternal H19 allele was hypoacetylated in comparison to maternal allele which could affect H19 imprint [50]. Mir-let-7 seem to be in association with H19 in the process of inhibition of insulin receptor and lipoprotein lipase [51]. H19 encodes mir-675 that might affect the expression of TGF-β. H19 also downregulates hypertrophy factor via mir-675 in cardiomyocyte hypertrophy [52]. They also inhibit autophagy of cardiomyocyte by promoting phosphorylation of mammalian target of rapamycin. H19 showed to regulate mir-200, mir-138 in association with epithelial mesenchymal transition in hepatocellular/colorectal cancers [53] (Fig. 1)

6. H19 and other systemic diseases

H19 has been associated with many systemic diseases. H19 expression was strongly correlated with many aging processes, inflammation, diabetes, pre-eclampsia, osteoarthritis, Rheumatoid arthritis, Alzheimer's, cardiovascular diseases, obesity, auto immune diseases, liver diseases, and chronic kidney disease. They also modulate telomere length, heterochromatin formation, senescence, proteostasis, cell cycle regulation, stem cell differentiation and intracellular communication [54–56].

The diverse involvement of H19 in these diseases and biological processes highlights its multifaceted roles in health and disease, making it a promising target for understanding disease mechanisms and potential therapeutic interventions.

6.1. Disease associations

H19's expression is linked to cellular senescence and aging-related mechanisms. It plays roles in modulating telomere length, which is associated with cellular aging, and it contributes to regulating senescence pathways [57]. Inflammatory processes often involve dysregulation of H19 expression, contributing to the regulation of inflammatory responses and cytokine production. Dysregulation of H19 expression has been observed in pre-eclampsia, a pregnancy complication characterized by high blood pressure and signs of damage to other organ systems. H19 plays roles in joint health and inflammation, contributing to the pathogenesis of arthritis conditions [58]. Studies have suggested associations between H19 dysregulation and Alzheimer's disease progression, though the exact mechanisms are still being explored [59]. Long non-coding RNAs (lncRNAs) play a pivotal role in governing cellular biological processes via diverse molecular mechanisms. Their prevalence within the cardiovascular system emphasizes their substantial role in cardiovascular functions and diseases. One such lncRNA, H19, exhibits high evolutionary conservation and is notably abundant in cardiac and vascular tissues. This abundance underscores its crucial

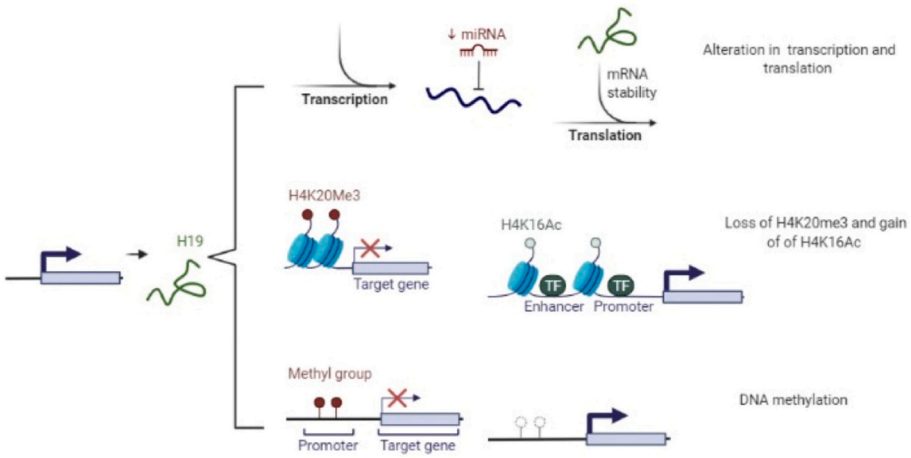

Fig. 1. Various epigenetic modulation of H19 in influencing the initiation and progression of tumorigenesis in oral squamous cell carcinoma. Image created using biorender.com (accessed on 18 May 2023). H19, H4K20Me3 (histone H4 lysine 20 tri-methylation), and H4K16Ac (histone H4 lysine 16 acetylation) are all related to epigenetics and chromatin regulation, but they play distinct roles in gene expression and chromatin structure. H19, H4K20Me3, and H4K16Ac, they all contribute to the complex regulatory mechanisms that control gene expression and chromatin structure in cells.

contribution to preserving the balance and proper functioning of the cardiovascular system [60]. H19 expression is linked to adipogenesis and adipocyte function, influencing obesity-related pathways. Its involvement in modulating immune responses can contribute to autoimmune disease pathogenesis. H19 dysregulation showed to be associated with liver diseases such as hepatocellular carcinoma and fibrosis, as well as chronic kidney disease progression [55].

6.2. Biological processes

The role of H19 in modulating telomere length and senescence pathways links it to cellular aging and longevity. H19 influences proteostasis mechanisms, contributing to protein homeostasis and cellular function. H19 participates in cell cycle regulation, impacting cell proliferation and differentiation processes. It has been implicated in regulating stem cell differentiation in various tissues. H19's regulatory functions extend to modulating intracellular communication pathways, affecting cellular signalling and responses [57].

7. Role of H19 in cancer

H19 is a lncRNA that has been studied extensively in various contexts, including cancer. Here are some potential reasons, why H19 might be of interest in comparison to other ncRNAs in OSCC [61].

Imprinted Gene Regulation: The imprinted nature of H19 adds another layer of complexity to its role in cancer. As an imprinted gene, H19 exhibits mono-allelic expression, meaning only one copy inherited from either the mother or father is actively expressed, while the other copy is silenced. This exclusive expression pattern is critical in normal development and growth regulation. However, in cancer, disruptions in this imprinting can occur, leading to abnormal expression levels or loss of imprinting. Such alterations can contribute to dysregulated cellular behaviours, including uncontrolled proliferation, evasion of growth suppressors, and resistance to cell death—fundamental traits of cancer cells. H19's involvement in these imprinting abnormalities positions it as a compelling candidate for understanding the underlying mechanisms driving cancer initiation and progression. Its disrupted imprinting might serve as an early indicator or contribute to the cellular changes that lead to malignancy. Moreover, investigating the regulatory mechanisms behind H19 imprinting alterations could provide valuable insights into potential therapeutic targets or strategies aimed at restoring normal imprinting patterns, potentially impacting cancer progression and treatment outcomes [62].

Epigenetic Regulation: The link between H19 and epigenetic modifications, particularly in chromatin remodelling, is a crucial aspect of its involvement in cancer biology (Fig. 1). Epigenetic alterations, which include modifications like DNA methylation, histone modifications, and chromatin remodelling, are pivotal in regulating gene expression patterns without changing the underlying DNA sequence. H19's association with epigenetic modifications, such as DNA methylation changes in its regulatory regions or its influence on chromatin structure, highlights its role in modulating the expression of various genes involved in cancer-related pathways. Understanding how H19 contributes to these epigenetic alterations can provide significant insights into cancer development and progression. For instance, aberrant methylation patterns around the H19 locus or its interaction with chromatin-modifying enzymes might influence the expression of tumor-suppressor genes or oncogenes, impacting cancer cell behaviour. Furthermore, therapies targeting epigenetic modifications have gained attention in cancer treatment. Investigating the relationship between H19 and these modifications could unveil potential avenues for therapeutic intervention. By elucidating the mechanisms by which H19 influences epigenetic changes, researchers may identify new targets for precision medicine approaches aimed at restoring normal epigenetic regulation in cancer cells [63].

Interactions with microRNAs: H19's role as a molecular sponge or a competing endogenous RNA (ceRNA) is a fascinating aspect of its function in regulating gene expression networks. MicroRNAs (miRNAs) are small non-coding RNAs that typically bind to the 3′ untranslated regions (UTRs) of target mRNAs, leading to their degradation or inhibition of translation. H19, as a long non-coding RNA, contains miRNA binding sites, allowing it to competitively bind to miRNAs, essentially acting as a sponge that sequesters these miRNAs. By doing so, H19 can modulate the availability and activity of miRNAs, preventing them from binding to and regulating their target mRNAs. This competitive binding mechanism could have significant downstream effects on gene expression networks. If H19 sponges certain miRNAs, it leads to an increase in the levels of miRNA targets that would have otherwise suppress by these miRNAs. Consequently, this can affect various cellular processes by altering the expression of genes involved in pathways related to proliferation, apoptosis, differentiation, and other critical functions. In the context of cancer, dysregulation of this ceRNA network involving H19 and miRNAs can contribute to the aberrant expression of genes associated with oncogenesis or tumour suppression. Understanding these interactions provides insights into the intricate regulatory mechanisms governing cancer development and progression, offering potential therapeutic targets for manipulating these networks to modulate cancer cell behaviour [64] (Fig. 2).

Metastasis and Invasion: H19's precise role in cancer is complex and multifaceted, several studies have suggested its involvement in promoting cancer metastasis and invasion. The mechanisms underlying this promotion of metastasis and invasion by H19 are diverse. The ability of H19 to influence various cellular processes, including proliferation, migration, and epithelial-mesenchymal transition (EMT), contributes to its impact on cancer progression. By regulating downstream target genes through its interactions with miRNAs or other molecular pathways, H19 can affect the expression of genes involved in metastasis and invasion. It might modulate factors that control cell adhesion, motility, and the ability of cancer cells to invade surrounding tissues and migrate to distant sites. Additionally, H19's involvement in signalling pathways associated with metastasis, such as those involving TGF-beta or Wnt signalling, further supports its role in promoting these aggressive cancer phenotypes [61].

Understanding the precise mechanisms through which H19 contributes to metastasis and invasion is crucial for developing targeted therapies aimed at disrupting these processes. H19 being a part of complex regulatory networks involving other molecules known to be important in OSCC, that might be chosen for study due to its potential to provide a comprehensive view of these networks.

The process of carcinogenesis is highly regulated by inflammation, many factors such as tumour necrosis factor-α and interleukin 6 (IL-6) play a remarkable role in carcinogenesis. H19 is considered to be an oncofetal lncRNA, as the end product of this gene is RNA, they are abundantly expressed prenatally as well decreased expression was observed post-nataly [61]. They are hyper expressed in cancer cells, post-nataly. H19 was first reported to be upregulated in bladder cancer and was identified to be the predictive marker in early diagnosis of recurrence [65]. In esophageal cancer and colorectal cancer, the H19 levels were upregulated, while in breast and lung cancer it is down regulated. It has been found to be associated with cholangiocarcinoma, H19 sponges mir-let-7 and induce IL-6 to initiate carcinogenesis [66]. In breast cancer H19 sponges with mir-152 and promotes proliferation in cancer cells. H19 modulates the expression of p53 thereby affecting cell repair as well apoptosis. H19 associated with epithelial mesenchymal transition (EMT), as well mesenchymal epithelial transition [67]. H19 acts as a microRNA sponge and results in EMT in colorectal cancer [68]. H19 has been shown to inhibit E-cadherin subsequently promoting EMT. Role of H19 in number of pathways that promotes tumorigenesis was identified, such as p38/MAPK, NF-κB, PI3-AKT/mTOR. cMyc, an oncogene was identified to regulate H19. Many studies performed to relate H19 in every stage of cancer progression. Thereby, it seems to be a potent marker in diagnosis and prognosis [69–71].

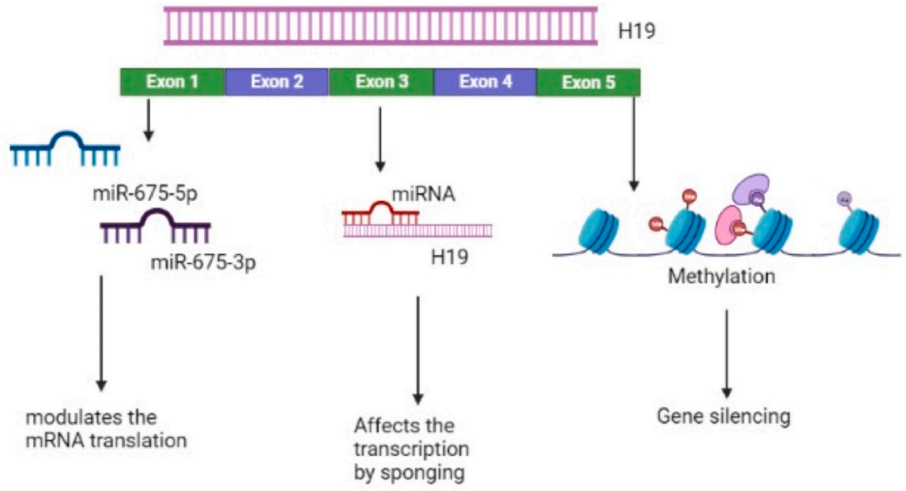

Fig. 2. H19 influencing miR675-5p; miR675-3p; miR21; miR200; miR-200 for regulating transcription, translation and Gene silencing thereby causing various epigenetic triggers in initiation and promotion of oral cancer along with the genetic factors. Image created using biorender.com (accessed on 18 May 2023).

Oncogenic and Tumor Suppressor Activities: The dual nature of H19 as both an oncogene and a tumor suppressor gene in different types of cancer adds complexity to its role in cancer biology. Its diverse functions are context-dependent, varying based on the cellular environment, specific cancer type, and the intricate signalling pathways involved. For example, H19 exhibits oncogenic properties by promoting cancer cell proliferation, invasion, and metastasis through various mechanisms like acting as a ceRNA, modulating gene expression, or influencing critical signalling pathways. On the other hand, in certain contexts or cancer types, H19 demonstrated tumor-suppressive effects by inhibiting cell proliferation, inducing apoptosis, or regulating pathways associated with suppressing tumor growth and progression. This context-dependent behaviour of H19 emphasizes the importance of considering its multifaceted roles in different cancers. Factors such as the microenvironment, genetic background, and interactions with other molecules within the cellular network can influence whether H19 acts as an oncogene or a tumor suppressor [61,62].

Understanding the specific conditions under which H19 exerts its oncogenic or tumor-suppressive functions is crucial for targeted therapeutic interventions. It highlights the need for personalized approaches in cancer treatment, taking into account the specific molecular characteristics of the tumor and its microenvironment. The intricate nature of H19's roles in cancer underscores its potential as a diagnostic biomarker and therapeutic target. Further research aimed at elucidating these context-specific roles will be essential for harnessing the full potential of H19 in cancer management [72,73].

Diagnostic and Prognostic Biomarker Potential: H19 is an intriguing biomarker with diagnostic and prognostic potential in certain cancers. As a long non-coding RNA, it plays an important role in various cellular processes, including cancer development and progression. Studies have shown its aberrant expression in cancers like bladder, breast, colorectal, and gastric cancer, among others. For diagnostics, detecting elevated levels of H19 in bodily fluids or tissues might indicate cancer presence. It could serve as a non-invasive screening tool, aiding in early detection when treatment outcomes are generally more favourable. Regarding prognosis, the expression levels of H19 might correlate with cancer aggressiveness, metastasis, and patient survival rates. Higher H19 expression could indicate a poorer prognosis or treatment response, helping clinicians tailor therapies or anticipate disease progression [74,75].

However, further research is crucial to validate H19's efficacy, specificity, and sensitivity across various cancer types and stages. While promising, its clinical application as a reliable biomarker requires extensive validation and standardization to ensure accuracy in diagnosis and prognosis.

8. H19 and oral cancer

H19 has a vital role in regulating the proteins involved in carcinogenesis. It sponges number of miRNAs and regulate them. Their tissue specific expression suggest that they could act as an early prognostic/diagnostic marker [76]. Study by Yu et al. reported the role of H19 in aberrant activation of fibroblast thereby playing a crucial role in fibrogenesis- oral sub mucous fibrosis (OSMF) [77]. Overexpression of H19 in OSMF is associated with disease progression by sponging miR-29b. Study done by Guan et al. showed that the upregulation of H19 was in correlation with poor overall survival rate and disease-free survival [78]. Kou et al. studied the role of H19 as competing endogenous RNA by sponging miRNA let- 7a in tongue squamous cell carcinoma (TSCC) [79]. Their findings concluded that H19 plays an important role in regulation of TSCC migration and invasion. Ghapanchi et al. [80] studied H19 gene polymorphism in oral squamous cell carcinoma (OSCC) tissues and analysed H19 rs217727T allele mutation. They concluded significant association between the OSCC susceptibility and H19 polymorphism. Guo et al. also analysed the association between OSCC and H19 gene polymorphism sites such as rs217727, rs2735971, rs2839698 and rs3024270 [81]. Their research indicated that rs217727 polymorphism was statistically correlated with OSCC incidence. These results were in support of Ghapanchi et al. Zhang et al. analysed clinico-pathological characteristics and expression pattern of H19 and enhancer of zest homolog 2 (EZH2) in TSCC [82]. They concluded that H19 promotes the progression of TSCC via EZH2. Zhao et al. investigated the effect of H19 on migration and invasion in oral cancer cell line [83]. The regulation of H19, mir-107and cyclin dependent kinases 6 were analysed. It was concluded that inhibition of H19 decreased migration and invasion. Vishwakarma et al. studied the expression of various lncRNA by real time PCR in OSCC tissues and determined that H19 was downregulated in OSCC tissues [84]. The expression of H19 was associated with smoking status. Lee et al. studied transcription and methylation status of H19 by PCR in OSCC cell line and patient tissue [85]. They observed hypomethylation of H19 in OSCC tissue in comparison to normal mucosa and inferred that it could act as a prognostic biomarker.

Zhou et al. revealed, the major role of H19 depletion has a in growth and invasion of malignant cells in oral cancer [86]. Thereby they could act as a potential target as they bind with ZEB1 protein which aids in epithelial mesenchymal transition. Yang et al., examined the profiles of H19 in normal fibroblast and cancer associated fibroblast of OSCC

tissues [87]. Knockdown of H19 suppressed MAPK pathway and miR-675-5p which h involved in glycolysis pathway and concluded that it could act a biomarker in diagnosis. El-Naggar et al. assessed the imprinting status of H19 and IGF2 in head and neck cancer by real time PCR and suggested their role in tumorigenesis of head and neck malignancy [88]. Hong et al. analysed the aberrantly expressed lncRNAs in OSCC [89]. They also quantitatively analysed the expression levels of H19 and correlated with their clinical characteristics and prognosis. Downregulation of H19 inhibited proliferation, invasion, migration and epithelial mesenchymal transition in OSCC cells *in-vitro*. They also detected correlation between miR-138 and H19. H19 by competing with miR-138 they regulated the expression of (EZH2) enhancer of zeste homolog 2. Wang et al. studied the expression of lncRNA H19 in tongue squamous cell carcinoma and he inferred that overexpression of H19 causes reduced proliferation of tumour cells [90]. They explained the role of H19 through miR-675-5p/GPR55 axis. Esteves et al. correlated loss of allele specific expression of IGF2 and H19 with differentially methylated region in head and neck squamous cell carcinoma [91]. They detected H19 expression levels were in relation with recurrence indicating that it could act as a potent prognostic marker (Table 2).

9. H19 and cancer associated fibroblast

The important component of tumor micro environment, cancer associated fibroblast (CAF) play an important role in promoting tumorigenesis. Cross talk between the CAF and tumor cells are believed to cause tumor progression [92]. The role of H19 in promoting glycolysis was identified. H19 showed to modulate the enzymes, biomolecules and oncogenes and regulate the pathways associated with glucose metabolism [93]. Inhibitors of enzymes that play a role in glycolysis. The functional role of H19 in modulating glycolysis in oral CAFs were analysed and it was observed that knockdown of H19 impairs glucose uptake and as well hinders lactate secretion. Studies have also shown that H19 mediates glycolysis via miR-675-5p in oral CAFs. CAFs attain their stemness of cancer cells via wnt/βcatenin signalling pathway, studies showed that exosomal H19 play an important role in transferring the cancer stem cell property by acting as a ceRNA through miR-141 [94].

10. H19 role in inducing stemness

Role of H19 in embryogenesis and normal tissue homeostasis are well established. Studies reported that silencing of H19 in embryonic endothelial precursors results in failure of haematopoietic stem cell formation. Role of H19 in various tumor progression processes such as genomic stability, stemness, migration, invasion and chemoresistance were researched. H19 was also found to induce symmetrical and asymmetrical renewal of cancer stem cells (CSCs) in various cancers. Its role in modulating various miRNAs such as let-7c thereby inducing stemness in cancer cells are studied. Role of H19 in inducing CSCs of oral squamous cell carcinoma is one inadequately explored field [93,95].

11. H19 as a biomarker

Biomarkers are those substances which help in early diagnosis, prognostic indicator and therapeutic target. These substances could be a protein, mRNA, DNA or miRNAs [96]. H19 acts as a potential diagnostic and therapeutic marker in diseases such as breast cancer, gastric cancer, colorectal cancer, cardiovascular diseases, multiple myeloma, bladder cancer [97]. Authors such as Lee et al., Yang et al. and Esteves et al. suggested H19 as a diagnostic and prognostic biomarker in OSCC [85,87,91]. Researches was also done to study the efficacy of H19, as a potent therapeutic target to suppress the invasion and metastasis in oral cancer. More studies associating H19 expression pattern with various stages of oral cancer and dysplasia has to be done to understand the expression pattern of this non coding RNA [98]. Studies suggesting the prognostic and therapeutic value of H19 in oral cancer are devoid as they are associated with the metastatic and recurrence potential of the malignancy. H19 was associated with the miR let-7 and promotes metastasis, by promoting the activity of HRAS gene [99]. Role of H19 in metastasis via the cancer associated fibroblasts studied in colorectal cancer. Their role in metastasis of oral squamous cell carcinoma has not been detailed yet [53]. H19 as a potential biomarker in OSCC has to be studied in more detail, as early diagnosis will help in tailor made treatment plan thereby preventing invasive treatments [100].

Table 2
Detailed tabulation of works done by various authors in the oral potentially malignant disorders and oral squamous cell carcinoma in relation to the long non coding RNA H19.

S. No	Study	Inference	Reference
1	Yu et al., 2021 on myofibroblasts in osmf	Overexpression of H19 in OSMF is associated with disease progression	77
2	Guan et al., 2016 on HNSCC	upregulation of H19 was in correlation with poor overall survival rate and disease-free survival.	78
3	Kou et al., 2019 on TSCC	H19 as competing endogenous RNA. H19 plays an important role in regulation of TSCC migration and invasion.	79
4	Ghapanchi et al., 2020 on OSCC	They concluded significant association between the OSCC susceptibility and H19 polymorphism.	80
5	Guo et al., 2017 on OSCC	Their research indicated that rs217727 polymorphism was statistically correlated with OSCC incidence.	81
6	Zhang et al., 2017 on TSCC	H19 promotes the progression of TSCC via EZH2.	82
7	Zhao et al., 2019 on oral cancer cells	It was concluded that inhibition of H19 decreased migration and invasion.	83
8	Vishwakarma et al., 2020 on OSCC	Determined that H19 was downregulated in OSCC tissues.	84
9	Lee et al., 2021 on OSCC	They observed hypomethylation of H19 in OSCC tissue in comparison to normal mucosa and inferred that it could act as a prognostic biomarker.	85
10	Zhou et al., 2020 on Oral cancer cells	Depletion of H19 has a major role in growth and invasion of malignant cells in oral cancer.	86
11	Yang et al., 2021 on CAF in oral cancer cell	H19 suppressed MAPK pathway and miR-675-5p which has been involved in glycolysis pathway and concluded that it could act a biomarker in diagnosis.	87
12	El-Naggar et al., 1999 on HNSCC	Imprinting status of Igf2 and H19 could enhance tumorigenesis	88
13	Hong et al., 2018 on OSCC	Downregulation of H19 inhibited proliferation, invasion, migration and epithelial mesenchymal transition in OSCC cells *in-vitro*.	89
14	Wang et al., 2021 on TSCC	Overexpression of H19 causes reduced proliferation of tumour cells.	90
15	Esteves et al., 2005 on HNSCC	H19 expression levels were in relation with recurrence indicating that it could act as a potent prognostic marker	91

12. Conclusion

LncRNAs play a vital role in the progression of OSCC. Their role in metastasis has not been explored well. Role of H19 as a competing endogenous RNA in various pathways associated with the tumorigenesis of oral cancer should to be studied in more details. Single nucleotide polymorphism of H19 is associated with many cancers as well oral cancer. H19 is hence regarded as a potent biomarker in diagnosis and

prognosis of Oral cancer. Many studies correlate oral cancer and H19 expression. This review provides an overview for the role of H19 in oral cancer. H19, the potential lncRNA can effectively play a major role in tailoring precision therapeutics in OSCC. Unfortunately, literature support the expression pattern of this non coding RNA is not sufficient with respect to head and neck cancer. More research studies are required to be conducted to establish the axis of relationship between various carcinogenesis signalling pathway and H19. Thus, its potential role as a biomarker and therapeutic target can be established.

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Peramaiyan Rajendran: Writing – review & editing, Conceptualization. **Ramya Sekar:** Writing – review & editing, Conceptualization. **Basem M. Abdallah:** Writing – original draft. **Shazia Fathima JH:** Formal analysis, Data curation. **Enas M. Ali:** Writing – original draft. **Selvaraj Jayaraman:** Formal analysis, Data curation. **Salaheldin Abdelraouf Abdelsalam:** Writing – original draft. **Vishnupriya Veeraraghavan:** Supervision, Formal analysis.

Declaration of competing interest

The authors declare no conflict of interest.

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