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Research Article

JOURNAL OF CANCER SCIENCE AND CLINICAL THERAPEUTICS

ISSN: 2637-5079

Headway of miR200 Family as a Novel Biomarker in Head and Neck Cancers

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Abstract

Head and neck squamous cell carcinoma (HNSCC) a varied disease, comprising variety of tumors that grow on the mucosa of the aerodigestive tract and arise in the regions of hypopharynx, oropharynx, salivary gland, oral cavity, nasopharynx, or larynx. About 650,000 new cases of HNSCC are diagnosed annually all over the world, with a ratio comprising of 3:1 between men and women. The role of microRNAs (miRNAs) in cancer development was known to be as oncogene or tumor suppressor. One of the miRNA family, miR-200 was mainly characterized as a tumor suppressor in head and neck cancers, it is composed of five highly conserved miRNAs, including miR-141, miR-200a/200b/200c, and miR-429. Alterations observed in miR200 family genes concerning HNSCC can be well explained by epigenetic modifications like miRNA methylation and expression, In-silico analysis to facilitate the development of targeted therapies, leading to improved patient outcomes.

Keywords: Cancer Hallmarks; Epigenetics; Head and Neck Cancer; Micro RNAs; miR200 Family

Introduction

Overview of Head and Neck Cancers

Head and neck cancer usually begins at mucosal surfaces of the aero digestive tract (hypo pharynx, oropharynx, salivary gland, oral cavity, nasopharynx, or larynx)by forming the tumors, and these tumors are popularly known as malignant tumors between "dura matter and pleura" [1,2]. Head and neck cancer is also referred to as Head and Neck Squamous cell carcinoma (HNSCC) and is the sixth most common malignancy of humans and belongs to the most aggressive form of cancer [2,3]. The maximum number (90%) of HNSCCs are squamous cell carcinomas, in which 60-70% are oral cavity, and Laryngeal squamous cell carcinoma (LSCC) and other malignancy include nasal cavity, pharynx, middle ear, thyroid gland, salivary glands [3]. The highest frequency of LSCC is seen in persons of advancing age and occurs to a large extent in males. The incidence ratio of LSCC in males and females is 5:1 [4], Global epidemiology of LSCC is reported as 210,606 cases (2.76 new cases per100,000 inhabitants), and the mortality rate is 126,471 deaths (1.66 per 100,000 inhabitants), while the prevalence of LSCC in India is 3-6% and 0.2-1% in male and females respectively, the age-adjusted incidence rate of LSCC in western, central India is between 3.5 and 5 per 100,000 inhabitants [5]. The progression of LSCC is seen in four different stages. The early-stage cancers are seen in stage I and II (vocal cords become unstable) (3.8 months), advanced stage (extra nodal extension, metastasis) is seen in stages III and IV (4.7 months) and spreading of the tumor to thyroid cartilage, prevertebral

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Citation: Shivani Kadarla, Rajesh Kumar Galimudi, Surekha Rani Hanumanth, Srimanth Kumar Barigela, Durga NeeharikaRani, Madhavi Jangala, Pardha P Reddy, Raja Meghanadh Koralla. Headway of miR200 Family as a Novel Biomarker in Head and Neck Cancers. Journal of Cancer Science and Clinical Therapeutics 6 (2022): 392-410.

Received: September 23, 2022
Accepted: October 11, 2022
Published: November 18, 2022

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DOI:10.26502/jcsct.5079179

space, carotid artery, and lungs is seen the final stage. Major symptoms of LSCC are associated with a higher tendency of lymph node metastasis [4].

Therapeutic Strategies of HNSCC: Head and neck squamous cell carcinomas (HNSCC) start to arise in the mucosal lining of the upper-aero digestive tract. HNSCC is mostly diagnosed at advanced stages in about 70% of affected individuals. Inspite of many intensive multimodal treatment etiquettes, an overall survival rate for patients with advanced stage of cancer in the past 5 years is 50–60% and seems to have reached a plateau [6]. Wong et.al. (2016), Moscow et.al. (2018) has revealed that during the last two decades, the therapeutic strategies in treating cancer have been expeditiously changing, and treatment for various types of malignancies is progressively based on tumor genetics to decrease the toxicity and to improve the efficacy of therapeutics [7,8]. Regardless of various efforts in the treatment strategies, surgery and radiotherapy are the mainstays in treating the HNSCC based on tumor site, stage, imaging and post-operative histological findings [6]. Of all the carcinomas, approximately 30% of tumors are diagnosed in the early stages [9,10,6] and the patients with early-stage tumors are treated with radiotherapy or surgical resection in the specific site of tumor growth. DeSantis et.al.,2014 have demonstrated that a complete cure is obtained only after the treatment process, and around 90% of 5- years survival rate is seen in HNSCC patients [11]. However, more than half of the patients (70%) are in the advanced stages with regional or distant lymph node metastasis [9,10] and Concomitant chemo radiotherapy, surgical salvage and post-operative chemo radiotherapy are the treatment measures used to treat these types of advance staged cancers [12,13]. A molecular view of head and neck cancers has been interpreted in great detail; identification of druggable targets can be achieved in the absence of oncogenic mutations to improve the therapeutical outcome of HNSCC. At present, functional genomic approaches are being prospected to discover potential therapeutic targets that consider the diagnosis and targeted therapy of oral premalignant (pre-HNSCC) changes, and that may further prevent the development of the tumors. Earlier it was revealed that the DNA damage response and cell cycle regulation pathways had been significantly altered in HNSCC, resulting in replication stress, which is an approach in further exploitation as an HNSCC susceptibility for treatment. Our aim is to review the current literature on micro RNA studies in HNSCC, which may further act as potential biomarkers in the early diagnosis of disease [6].

Micro RNAs (miRs)

Micro RNAs (miRs/ miRNA) are endogenous non-coding single-stranded RNAs, interspersed between the introns and exons of protein-coding genes with the length of 18–25 nucleotides and a minor set of miRs were mapped to long interspersed nuclear elements (LINEs). Besides, miRs have also been found in many other areas (fragile sites, regions of amplification, and LOH regions) of the genome [14,15]. Lee et al., (1993) and Wightman et al., (1993) were the first to discover the Micro RNA (miR) *lin-4* gene in Caenorhabditis elegans in 1993 [16,17]. These small non-coding miRs developed during the post-transcriptional regulation by messenger ribonucleic acid (mRNA) cleavage, which hangs on the complementarity of miR-mRNA. The cleavage of mRNA occurs only when there is a perfect match, while the flawed combination results in gene repression [18]. Many studies have identified the importance of miRs in the progression of various cancers and were found to be linked with proliferation, differentiation, apoptosis, metabolism, invasion, metastasis, and drug resistance. The pathological origin of cancer is directly related to the dysregulation of miRs. Furthermore, miRs are tissue-specific. Each tumor has its own miR expression profiles [19,20].

Genomic Organization of miRs: Currently, 46,554 miRs are registered in the miR database for eukaryotes.2300 true human mature miRs are known, of which 1115 were annotated according to bioinformatic data obtained from miRbase V22. Micro RNAs (miRs) are named as miRs- plus number, with few notable exceptions, while the miRs with a similar sequence is differentiated by an additional letter (such as a, b, c) followed by the miR number (e.g., miRs-200a). Identical mature miR sequences may find at several genomic loci with distinct precursor sequences. In such cases, the miR genes are represented by miRs-200a-1. Roughly one-third of the miRs of humans are arranged in clusters. Usually, the given cluster is found to be a single transcriptional unit, associated with the regulation of suggested miRs in the cluster. In silico analysis identified that most miRs of the same cluster were found to have a similar sequence [21]. However, it is scarce to find a duplicate sequence of the same miRs in a given cluster. It has been confirmed that the synchronized expression of similar miRs may possibly lead to combinable diversity and synergy in the biological ramification [22].

miRs Action and Mechanisms: miRs suppress the targeted mRNA expression through interaction with the 3'untranslated region (3' UTR). However, the mechanism for miRs on their target sites is still controversial. Most miRs targeted sites had bulges because of mismatches while the siRNA and mRNA show perfect complementarity sequence. Previous studies have suggested that the siRNA destabilizes mRNA, whereas the miR inhibits the mRNA translation without affecting the mRNA level [22]. Even though the translational repression mechanism still holds true for many miRs, studies from yesteryears have demonstrated that the miRs were associated with decreased levels of a targeted mRNA despite of imperfect complementarity sequence between the miRs and the mRNA target [23,24]. Degradation of mRNA by miRs is distinguished from Small interfering

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DOI:10.26502/jcsct.5079179

RNA (siRNA)-mediated mRNA cleavage, which is further explained by RNA processing bodies and location for RNA decay. Usually, miRs inhibit targeted mRNAs' translation, which was then sequestered to P-bodies and subjected to degradation [25]. While in few cases mRNA level remains similar in spite of miRs inhibition, and each individual miR& mRNAs have their unique interactions.

miR Expression Mechanisms: Transcription of miR genes is mediated by RNA polymerase II to form primary miR (Pri-miRs) with an altered nucleotide at the 5′ end and a polyadenylated tail at the 3′end.The Microprocessor Complex, formed by Di George Syndrome Critical Region 8 and Drosha ribonuclease, convert primRNAs Molecules into pre-miR. Exportin-5 then transports this pre-miR into the cytoplasm, where Dicer cleaves it to form a miR duplex. In order to form the complex that exhibits gene silencing, the duplex needs to be separated into the functional strand and loaded along with argonaute proteins into the RNA-induced silencing complex (RISC). This final complex mediates gene expression by binding target mRNAs and inducing mRNA degradation [26] (as depicted in Figure 1).

miR expression can be measured by techniques like RNase protection assay or primer extension assay. Initially, the petite size of these micro RNAs hampered the PCR-based expression assays. Later on, due to their high sensitivity, qRT-PCR-based techniques have become widely used in miR expression profiling. Further Microarray techniques have become popular as they completely assay the entire miRNAome (global miR expression profile) in tissues or cell lines. If global gene expression profiles are compared between cancers and normal tissues, many miRs are found to be deregulated. Hence, it is very likely that tumorigenesis or progression of cancer may result from alterations in the entire miRNAome rather than from modifying a single miR that regulates an oncogenic or tumour-suppressive gene [27]. Deregulation of miRs in head and neck cancers indicating its role in tumorigenesis has accumulating evidence from studies comparing miR expression profiles in tumors and corresponding normal tissues. Alterations in miR expression in the context of head & neck cancers can be attained by abnormalities in chromosomes, transcription binding factors and other epigenetic alterations. Such epigenetic repression of tumor suppressor miRs can be potentially reversed as a strategy for future epigenetic therapies. However, the lack of efficient techniques is a significant hurdle in the effective use of this strategy [28].

miRs as Key Regulators in Human Cancers

To understand the framework of neoplastic disease Hanahan and Weinberg, 2000 have proposed six hallmarks of cancers (sustaining proliferative signaling, evading growth suppressors, activating invasion and metastasis, enabling replicative immortality, inducing angiogenesis, resisting cell death), and they also discussed how normal cells get evolved to form neoplastic state [29]. During this evolution, the hallmarks' capabilities undergo multi-step processes to develop the traits that enable them to form malignant tumors. In addition to the above conventional hallmarks Negrini et al., (2010), Luo et al. (2009) and Colotta et al. (2009) have

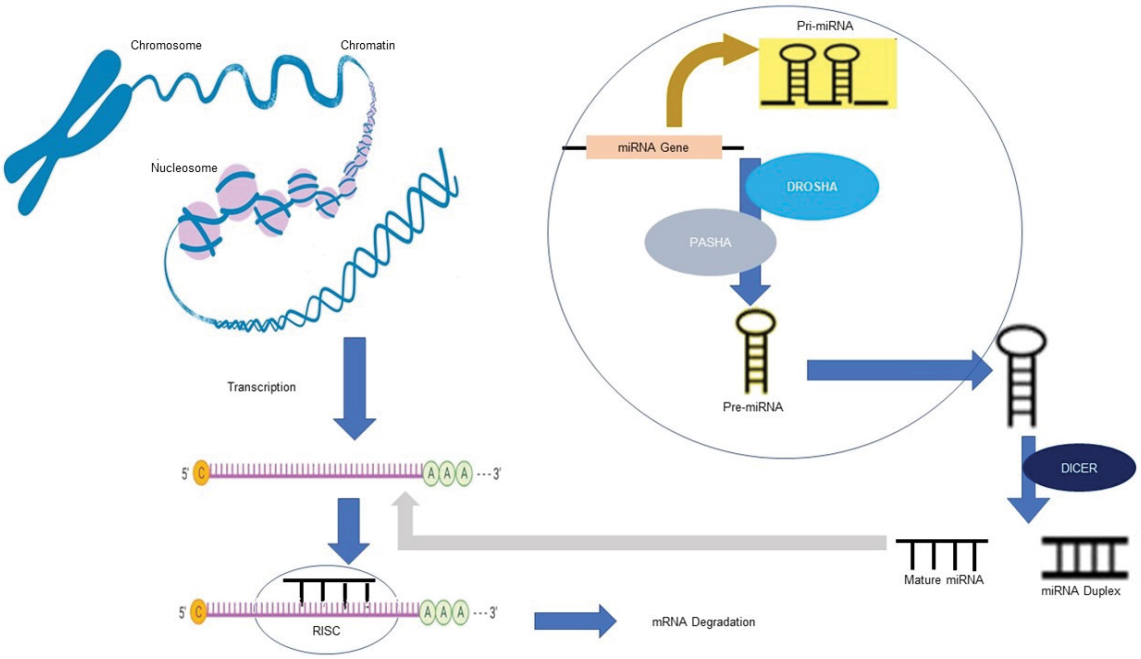

Figure 1: Involvement of miR in mRNA degradation. Formation of mature miR occurs by the Involvement of enzymes such as DROSHA (Ribonuclease), DICER (cleavage enzyme), and PASHA (a cofactor). The so formed mature miR associates with the RISC complex and binds to mature mRNA leading to mRNA degradation.

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DOI:10.26502/jcsct.5079179

proposed reprogramming of energy metabolism and evading immune destruction hallmarks which also play a significant role in tumorigenesis [30-32]. Invasion and metastasis are clinically the most important hallmarks of cancers. Though the above mechanisms are studied extensively, their findings were very limited in cancer management [33]. Micro RNAs are considered vital points in the development of cancers. They are found to be linked with cancer stem biology, angiogenesis, epithelial-mesenchymal transition (EMT), metastasis and drug resistance, etc [34].

Evading Growth Suppressors and Sustained Proliferative Signaling: Cell proliferation is one of the most critical cancer hallmarks, and its generated abnormalities are associated with tumorigenesis. Usually, the cell cycle progression is controlled by an intra-extra cellular program signaling molecule to attain the balance between promoting cell proliferation and suppression [35]. It has been evident that some of the micro RNAs functionally incorporate into various critical cell proliferation pathways, and the dysregulation of such micro RNAs are associated with evading growth suppressors and sustaining proliferative signaling. The progression of the cell cycle depends on a variety of cyclins, cyclin-dependent kinases (CDKs) and their inhibitors which are highly regulated by miRs. Hatfield et.al. (2005) have provided the first evidence that germline stem cells of drosophila with dicer-1 knockout were blocked in the G1/S transition, suggesting that microRNAs act as crucial requirements for germline stem cells to pass the normal G1/S checkpoint [36]. It is also evident that dicer deficient germline stem cells are associated with increased expression of DACAPO (P21/P27 family of CDK inhibitors), suggesting that this protein is negatively controlled by microRNAs to promote the progression of the cell cycle. Yi et.al., (2012) demonstrated that miR-663 is upregulated in nasopharyngeal cancer, promoting the cellular transition of cells in invivo and in vitro by targeting $p21^{CIP1}$ [37]. Peng et.al., (2013) have demonstrated that miR-486 is substantially downregulated in non-small-cell lung cancer, promoting cell migration and proliferation through P13K signaling pathways and insulin growth receptor (IGF) targeting IGF1, IGF1R and P85α [38].

Resisting Cell Death: The evasion of apoptosis is another important hallmark of cancer that is regulated by microRNAs [39,40]. Cancer cells emit a variety of scenarios in controlling apoptosis. A variety of signaling genes are involved in the apoptosis pathway where, the function of P53 is widely studied as an example in this process. The loss of P53 function against the tumor suppressor activity leads to the generation of the apoptotic pathway. Up regulation of anti-apoptotic regulators, suppression of pro-apoptotic factors and inhibition of death pathway induced by extrinsic ligands are the various regulatory pathways that play a significant role in controlling the function of apoptosis [35]. MicroRNAs regulated by P53 were found to have actively participated in P53 functions. Pichiorri et.al. (2010) described the functions of miR192, miR194, miR215 in multiple myeloma, which P53 transcriptionally activates to suppress MDM2 expression via binding to its mRNA [41]. Thereby, degradation of P53 is controlled, which ultimately restricts the development of multiple myeloma. The other novel target for P53 mediated transcriptional repression under hypoxia is the cluster of miR17-92, where the downregulation of microRNAs sensitizes the cells to undergo apoptosis, while the overexpression inhibits apoptosis. Hence, tumor cells with increased expression of miR17-92 may skip hypoxia-induced apoptosis [42].

Activating Invasion and Metastasis: Metastasis is a highly complex dynamic biological event. Epithelial-mesenchymal transition (EMT) is considered as a key step in the cascade of metastatic events, where it losses the cell adhesion through repression of E- Cadherin and activation of genes linked with motility and invasion. A variety of signaling pathways (Transforming growth factor-beta (TGF-β), Zinc finger E-Box (ZEB), Zinc finger protein SNAI1 (SNAIL), Twist- related protein (TWIST)) were regulated by the EMT pathway [43]. Growing shreds of evidence revealed that microRNAs are part of epithelial-mesenchymal transition and cancer metastasis. microRNAs regulated by TGF-β was associated with TGF-β signaling to induce EMT and promote metastasis in advanced malignancy. miR 155 is one among them involved in the regulation process [44].

Inducing Angiogenesis: Angiogenesis is an immensely interconnected process to grow new blood vessels from pre-existing ones to gratify the requirements for oxygen and food in tumor growth and metastasis [45]. As tumor tissues have considerably minimal oxygen concentration than the nearby normal tissues, hypoxia has an essential role in the tumor microenvironment by enabling the improvement and maintenance of cancer cells. Hypoxia-inducible factor (HIF) is a significant transcription factor regarding hypoxia, which impacts the expression of several genes, including miRs. Therefore, miRs that target HIF or VEGF signaling pathways probably hold a considerable impact on angiogenesis. It is now well explained that the process of angiogenesis is intricately regulated by miRs [46].

MicroRNA in the Regulation of Head and Neck Cancer

During sustained cell proliferation, altered microRNAs enhances cell proliferation by targeting the regulators of the cell cycle. miR- 137, miR- 193a participates in downregulating the expression of CDK6 and E2F6 transcription factors, respectively and results in reduced cell growth of oral squamous cell carcinoma [47]. In addition to that, miR- 125b, miR-100 also plays an essential role in suppressing the oral squamous cell region tumours. Another importantly studied hallmark of HNSCC is the evasion of apoptosis, wherein tongue squamous cell carcinoma (TSCC)

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inhibition of apoptosis is attributed to the overexpression of miR21 [48]. The study by Zhang et.al., (2012) suggested that microRNAs could have an association with reactive oxygen species (ROS), one such microRNA named as microRNA-21 is linked with ROS by suppressing the antioxidants (Superoxide dismutase family) activity which limits the production of TNFα and ultimately participates in tumorigenesis [49]. The upregulated miR- 24 in OSCC targets RNA binding protein dead end-1 (DND1), which directly contributes to the apoptosis resistance and proliferation by downregulating the cyclin-dependent Kinase inhibitor 1B (CDKN1B) [34,50]. Human telomerase reverse transcriptase (hTERT) is expressed in the early step of oral carcinogenesis, which maintains the length of telomerase and provides an escape from replicative senescence. Studies have found that miR-31 gets activated in hypoxia conditions and targets FIH (factor inhibiting HIF) gene. Therefore, during the state of hypoxia, telomerase gets activated by the transcriptional function of the hTERT enzyme, which is further regulated by a transcription factor called HIF-1α [51]. In vitro studies by Hung et.al. (2014) have demonstrated that the introduction of miR-31 along with hTERT causes the immortalization of oral keratinocytes [52]. In OSCC, it was reported that miR 124 inhibits metastasis by regulating the expression of ITGB1, which indicates a possible interrelation between miR 124 and hTERT. Another tumor suppressor miR called miR-512-5p suppresses tumor growth in HNSCC by targeting hTERT. Hypoxia-inducible factor (HIF) regulates a number of genes associated with tumor angiogenesis and metastasis [53]. C.-J. Liu et.al., (2010) Xiao et.al., (2012) and Hung et.al. (2014) demonstrated that the oncogenic miR31 along with its passenger strand (miR-31*) have been found to be upregulated in OSCC and oral leukoplakia (OLP) [52,54,55]. Differentially overexpressed miR 31 directly represses the expression of HIF in HNSCC. At the same time, it activates the HIF pathway in normal growth conditions. While the elevated expression of miR 31 is linked with vascular endothelial growth factor up regulation and downregulation of E- cadherin in oral premalignant disease [54]. In HNSCC patients, the spread of neoplastic cells to loco-regional lymph nodes is found to be very high. Routine clinical check-up has not provided the details regarding the advancement of tumor stages. Therefore, miRs are considered as a novel potential prognostic marker in classifying the various stages of tumor. One such miR called miR 205 is regarded as a marker to identify lymph node metastasis [56]. The elevated levels of miR -10b, reduced levels of miR- 138 and miR-222 were found to be associated with metastasis of tongue squamous cell carcinoma (TSCC) [57]. Similarly, miR-29a is downregulated in OSCC tissues and inhibits the expression of MMP2 by its direct binding to the 3′-UTR regions. Active studies unveiled that transfection with miR-29a mimics increased apoptosis rate, attenuated invasive potential and increased chemosensitivity towards cis-platinum (CDDP) in OSCC cell lines [58]. Metabolic reprogramming of tumor cells is an essential step for tumorigenesis and metastasis, which is finely regulated by miRs [59]. Xu et.al., (2016) reported that decreased expression of miR 340 in OSCC is induced by the metabolic switch. The downregulated miR 340 was associated with increased glucose transporter -1 (GLUT-1) expression, which subsequently increases the lactate secretion and rate of glucose uptake [60]. Therefore, altered metabolism induced by miR 340 results in the rapid proliferation of oral cancer cells by regulating the glycolysis period. Further up regulation of miR 23a controls expression of SMAD- 4. Hence, the translocation of GLUT-4 indirectly regulates the glucose transport period [61]. Though sufficient oxygen is present malignant tumors acquire a high glycolytic effect (Warburg effect). To attain this, cancer cell dysregulates the inevitable glucose metabolism steps. Peschiaroli et.al., (2013) demonstrated that the expression of miR143 is inversely correlated with hexokinase-2 and the upregulated HK-2 promotes the metabolic shift to attain aerobic glycolysis in OSCC [62].

Role of miR200 Family in Cancers

miR200A, 200B, 200c, 141, 429 are 20- to 22-nucleotide noncoding RNAs which belongs to the miR200 family, which can be divided into 2 subfamilies based on a 1-nucleotide difference in seed sequences. miR200A and miR141have a seed sequence of AACACUG, whereas miR200B, miR200C and miR429 have a seed sequence of AAUACUG. Cytogenetic location of miR200A, miR200B, and miR429 are mapped to 1p36.33 which are clustered on chromosome 1 with the genomic sequences as 1:1,167,862-1,167,951; 1:1,167,103-1,167,197 and 1:1,169,004-1,169,086 respectively, whereas Cytogenetic location of miR200C and miR141 are mapped to 12p13.31 which are clustered on chromosome 12 with the genomic sequences as 12:6,963,698-6,963,765 and 12:6,964,096-6,964,190 respectively. These micro RNAs inhibit gene expression at the post transcriptional level by binding to complementary sequences in the 3-prime UTRs of target mRNAs**.** Expression of these miRs showed a positive correlation with expression of E-cadherin, an epithelial cell marker and a negative correlation with expression of vimentin, a mesenchymal cell marker. Aggressiveness in human cell lines is reduced due to the induction of mesenchymal-to-epithelial transition (MET) by increasing the levels of miR200A and miR200C.Conversely, induction of epithelial-to-mesenchymal transition (EMT) is observed by the reduction in the levels of miR200 [63] (as depicted in Figure 2).

Microarray analysis revealed a negative Correlation between miR200A expression and genes involved in MET, while it is shown a positive Correlation with oxidative stress genes.miR200c is one of the five members of the microRNA-200 family that regulates the epithelial-

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DOI:10.26502/jcsct.5079179

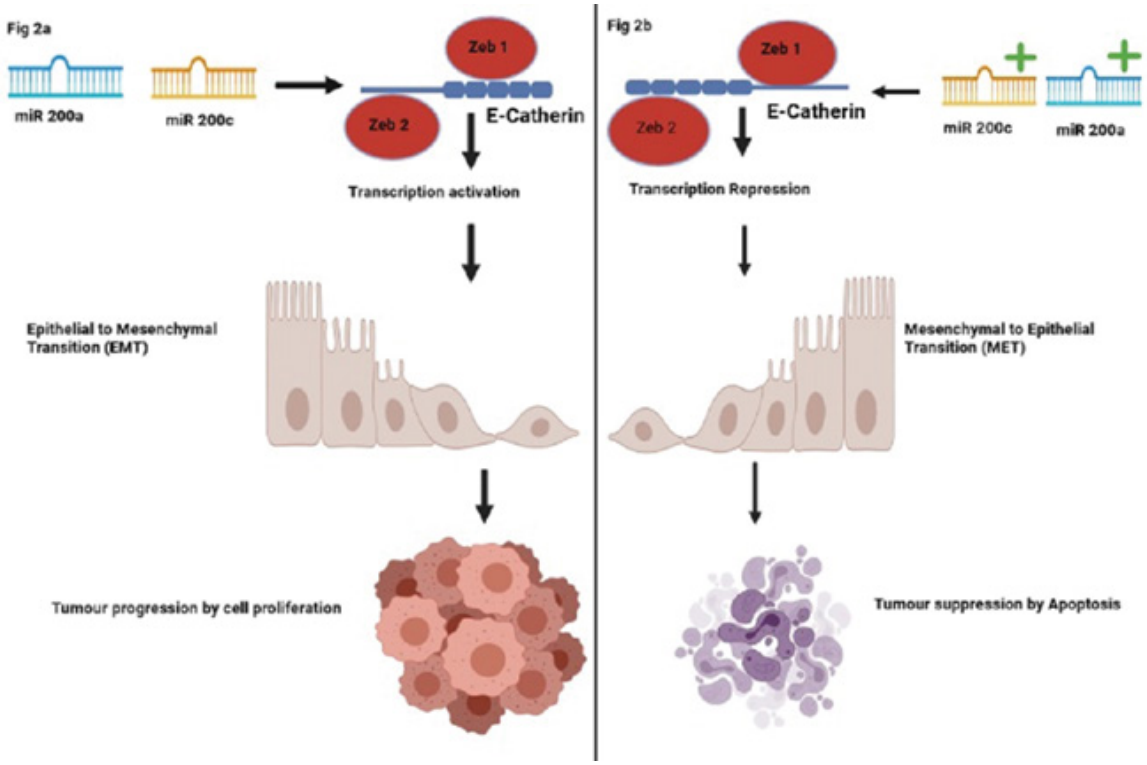

Figure 2: Correlation of miR200 family with EMT/MET pathways. Figure 2a depicts the positive Correlation of miR expression with E-cadherin (epithelial cell marker); low levels of these miR200 family genes induce epithelial to mesenchymal transition (EMT). Figure 2b depicts the Correlation of miR200 family genes with E- cadherin expression; high levels of miR200A and miR200C induces mesenchymal-to-epithelial transition (MET) in human cancer cell lines, reducing their aggressiveness.

mesenchymal transition (EMT) by targeting EMT-related gene expression exhibiting tumour-suppressive properties [63]. miR200B and miR429 have their role in various physiological mechanisms like mediating myometrial transition to a contractile phenotype. miR200b and miR429 target the ZEB1 gene in the regulation of mammalian reproduction. Thus, the hypothalamus-pituitary-ovarian axis requires miR200b and miR429 to support ovulation.

MicroRNA200 Family in the Regulation of Head and Neck Cancer

Predominantly, miRs play a significant role in the normal and pathological processes, including cancer; they could stimulate the genes post-transcriptionally, which further participates in the development of tumor [64]. In various tumors, the levels of miR-141 expression are predominantly lesser than the healthy tissue, and its enhanced expression can prevent tumor progression. For instance, miR-141 has been shown to inhibit the growth of colorectal, liver, gastric and prostate cancers by restraining cell proliferation, metastasis and promoting cell apoptosis [65–67]. Liet.al., (2018) demonstrated that the levels of miR 141 are predominantly lesser in healthy tissue, and its enhanced expression can prevent tumor progression in HNSCC patients by increasing their survival rates [68].

EGFR plays a crucial role in the migration, angiogenesis, proliferation and apoptosis of cancer cells. Zhao et.al., (2019) illustrated that EGFR is greatly expressed in HNSCC tissues and miR-141 targets and bounds to EGFR. Therefore, higher expression of miR-141 could inhibit the expression of EGFR at both mRNA and protein levels [69]. Zhao et.al., (2019) reported that overexpression of miR-141 inhibits proliferation of HNSCC cells by inhibiting the expression of CDK4 and facilitates the apoptosis of HNSCC cells by inhibiting bcl-2. In addition, miR-141 inhibits the migration and invasion of HNSCC cells by inhibiting the expression of MMP2 [69]. Zhao et.al., (2019) has demonstrated that the tumor suppressor property of miR 141 suppresses tumor growth and metastasis by EGFR signaling. By this way, miR 141 appears to be a potentially beneficial therapeutic target for the treatment of HNSCC [69]. In this review, we have focused on the expression of miR141 and miR 200c in the regulation of tumorigenesis. miR-200c exhibits important roles in radio chemoresistance, regulating self-renewal and metastatic properties of HNSCC cancer stem cells, including the progression and metastasis of HNSCC. Higher expression of miR200c vitiates tumorigenic and metastatic oppression effects in HNSCC partially during the inhibition of ZEB1, ZEB2, BMI1 and EMT properties. Hence, miR200c could illustrate a new therapeutic attitude in treating advanced HNSCC [70]. miR expression profiling based on recent

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studies in the context of HNSCC are summarized in Table 1. The vast majority of studies included a sparse number of cases, and information's are not conclusive yet. miR200 family genes (miR200a, 200b, 200c, 141, 429) are selected because of their important role in tumorigenesis/ apoptosis and on the basis of previously found associations with cancer and has also been frequently observed in Head and Neck Squamous Cell Carcinoma as reported in Table 1. http://mircancer.ecu.edu/. In this review, we have outlined few microRNA genes and their role in different types of head and neck cancers, as shown in Table 1 and the number of miRs regulating various cancer hallmarks are depicted in Figure 3 based on the data referred from table 1. The databases and resources searched for articles included in Table I are PubMed Central. The inclusion criteria for articles search: (a) Published between 2010 and 2020(b) Published only in the English language. Keywords included in the literature search are epigenetic gene names, cancer, epigenetics, tumorigenesis, Head and neck cancer, microRNA. The literature search retrieved articles that met the set criteria. Head and Neck cancers were majorly studied in different ethnicities, but the data is not complete due to the vulnerability of the disease. The microRNA genes included in the Table 1 mainly was found to up regulate or downregulate the RNA expression of tumor suppressor or oncogenic genes. miRs play significant roles in the physiological and pathological processes of Head and neck cancer through regulating tumor cell proliferation, metastasis, invasion, and apoptosis. The expression of multiple mRNAs can be regulated by a single miR, and different miRs can modulate an individual mRNA. It is considered that miRs can regulate approximately 60% of genes in the human genome. One of the miR family, miR-200, was mainly characterized as a tumor suppressor in head and neck cancers, composed of five highly conserved miRs, including miR-141, miR-200a/200b/200c, and miR-429. They are located in two clusters of chromosomal locations: the miR-200ba/429 cluster on chromosome 1p36 and the miR-200c/141 cluster on chromosome 12p13 [149,150] as shown in Figure 4A& Figure 4B.

According to previous studies, abnormal miR expression is involved in many human diseases, especially cancers, and may act as potential prognostic biomarkers. Also, miRs play a significant role in the pathogenesis of cancers, acting as oncogenes, tumor suppressors, or modulators of cancer stem cells. miRs may act as oncogenes by inhibiting tumor suppressor genes and act as tumor suppressor genes by downregulating oncogenes [35].

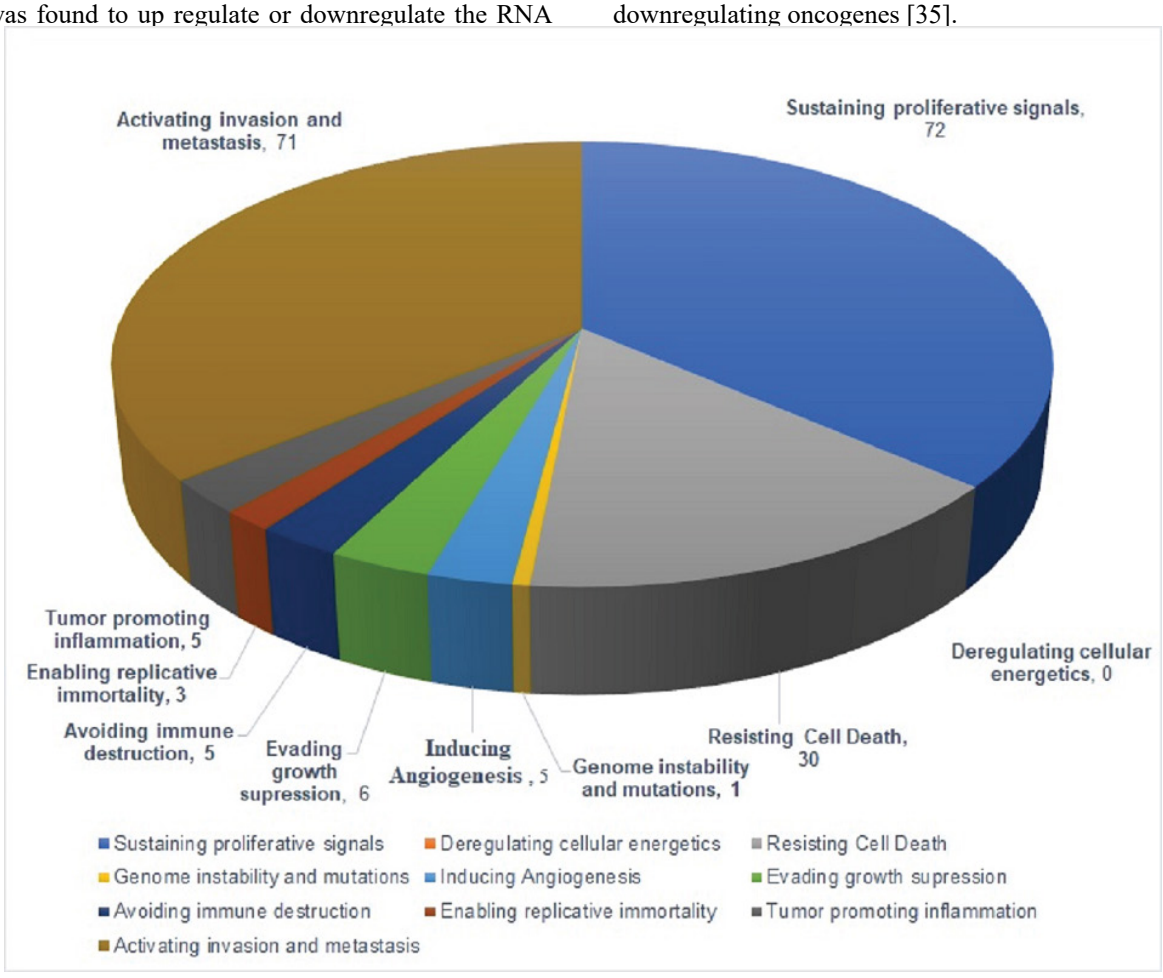

Figure 3: Pie chart showing the number of miRs regulating different hallmarks of HNSCC as reported in Table 1.

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DOI:10.26502/jcsct.5079179

Table 1: MicroRNAs epigenetically regulated in Head & Neck Cancer are reported.

S.No.	miRNAs of HNSCC	Regulation of miRs	References
	miR139-3p	Down	[71]
	miR363	Down	[72]
	miR874	Down	[73]
	miR93	Up	[48,74]
	miR451	Down	[75]
	miR205	Up	[76]
	miR141	Down	[69]
	miR204	Down	[77]
	miR876-5p	Down	[78]
	miR34a	Down	[79]
	miR372	Up	[80]
	miR375	Down	[81]
	miR203	Down	[82]
	miR422a	Down	[83]
	miR206	Down	[84]
	miR1	Down	[84]
	miR96-5p	Up	[85]
	miR9	Down	[86]
	miR125a-5p	Up	[87]
	miR218	Down	[87]
	miR25	Up	[48]
	miR27a	Down	[88]
	miR29a	Down	[89]
	miR29c	Down	[89]
	miR300	Down	[90]
	miR30a-5p	Up	[91]
	miR31	Up	[92]
	miR184	Up	[92]
	miR196a	Up	[93]
	miR200c	Down	[70]
	miR106b	Up	[48]
	miR107	Down	[94,95]
	miR128	Down	[96]
	miR133a	Down	[97]
	miR134	Up	[98]
	miR138	Down	[99,100]
	miR149	Down	[101]
	miR16	Up	[91]
	miR150-5p, miR150-3p	Down	[102]
	miR182	Up	[103]
	miR675	Up	[104]
	miR223-3p	Up	[105]
	miR192	Up	[106]
	miR451a	Down	[106]
	miR203	Up	[107]
	miR504	Down	[108,109]
	miR217	Down	[110]
	miR632	Up	[111]
	miR23a	Up	[112]
	miR181a	Down	[113]
	miR885-5p	Down	[14]
	miR21-3p	Up	[14]
	miR525-5p	Up	[14]
	miR125a	Down	[114]
	miR27a	Up	[115]
	miR503	Down	[116]
	miR26b	Up	[117]
	miR423-3p	Up	[118]
	miR379	Down	[119]
	miR101	Down	[120]
	miR129-5p	Down	[121]
	miR221	Up	[122]
	miR195	Down	[123]
	miR365a-3p	Up	[124]
	miR155	Up	[125]
	miR301a-3p	Up	[126]
	miR19a	Up	[127]
	miR153	Down	[128,129]
	miR148a	Up	[130]
	miR375	Up	[130]
	miR4497	Down	[131]
	miR7	Up	[132]
	miR144	Down	[133]
	miR194	Down	[134]
	miR101	Down	[135]
	miR145	Down	[136,137]
	miR125b-5p	Down	[138]
	miR625	Down	[139]
	miR145-5p	Down	[140]
	miR143-3p	Down	[141]
	miR218	Down	[142]
	miR26a	Down	[143]
	miR613	Down	[144]
	miR21-5p	Up	[145]
	miR181a	Down	[146]
	miR155	Up	[147]
	miR370	Down	[148]

Citation: Shivani Kadarla, Rajesh Kumar Galimudi, Surekha Rani Hanumanth, Srimanth Kumar Barigela, Durga NeeharikaRani, Madhavi Jangala, Pardha P Reddy, Raja Meghanadh Koralla. Headway of miR200 Family as a Novel Biomarker in Head and Neck Cancers. Journal of Cancer Science and Clinical Therapeutics 6 (2022): 392-410.

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DOI:10.26502/jcsct.5079179

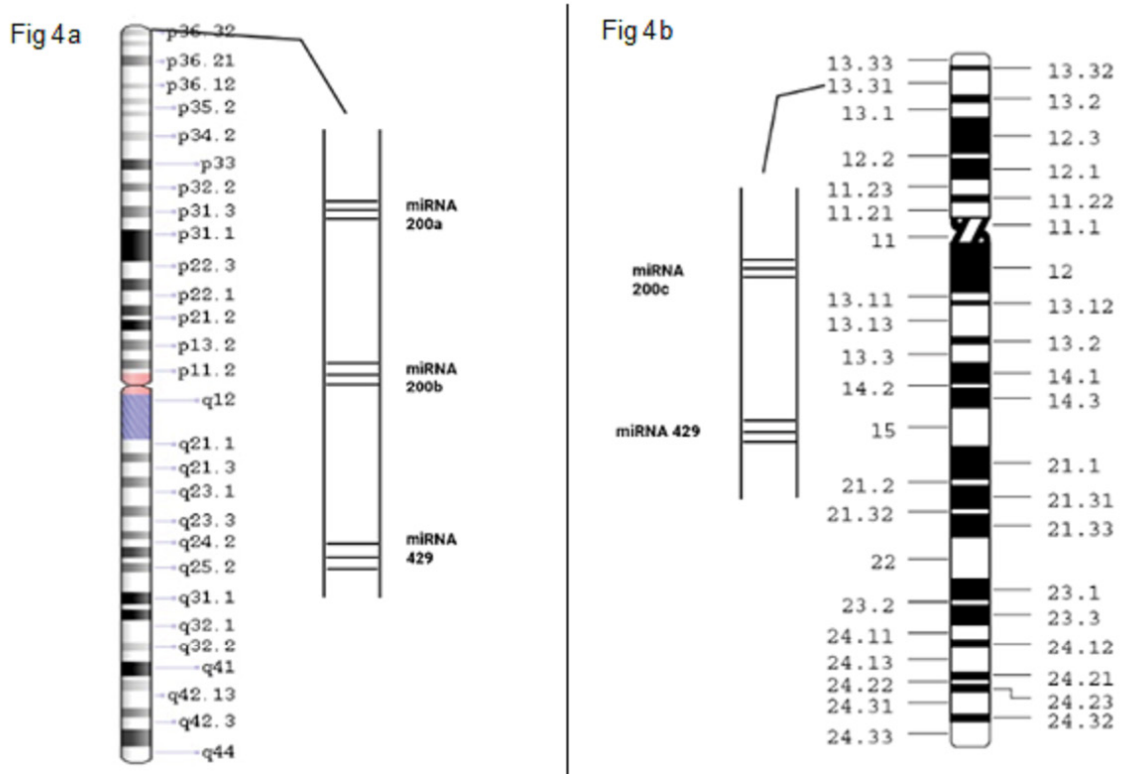

Figure 4: Figure 4a: depicts the cytogenic locations of miR200a, miR200b, mir429 mapped on chromosome 1(1p36.33). Figure 4b: depicts the cytogenic locations of miR200c, miR141 mapped on chromosome12 (12p13.31).

Prediction and Identification of miRs

Each miRs exerts its function by regulating the targeted mRNAs; hence it is imperative to identify the miRs targets. The first eight nucleotides (seed sequence) of miRs play a vital role in the specificity of miRs-mRNA interaction [151]. Several computational algorithms studies have predicted the targeted mRNAs, but they were found to be very far from perfect. The gold standard experiment demonstrated that the luciferase reporter fused with 3′UTR of the predicted target was found to be repressed by the overexpression of the miRs, and the repression is revoked by the point mutation in the target sequence(s) at 3′UTR [152] (Yong et.al.,2009).

Role of Epigenetics in Cancer

Epigenetic mechanisms are necessary for the normal maintenance of tissue-specific gene expression patterns in humans. The precise epigenomic landscape present in normal cells undergoes extensive distortion in cancer. These epimutations, along with widespread genetic alterations, play a vital role in cancer initiation and progression. Advancements in the field of cancer epigenetics have shown rigorous reprogramming of every component of the epigenetic machinery in cancer, including DNA methylation, histone modifications and non-coding RNAs (microRNA expression). In addition to inactivating tumor suppressors, epimutations can also promote tumorigenesis by activating oncogenes. The events that lead to the initiation of these epigenetic abnormalities are still not fully understood [153].

Epigenetics and HNSCC: Epigenetic research aims to unearth how psychosocial factors, nutrition and environment may affect an individual's phenotypical expression of genetic information. In eukaryotes, different phenotypes may be expressed from a single genotype because of the targeting ability of inheritable epigenetic markers that appear during development. From previous research, it is already evident that the division and differentiation of single-cell during embryogenesis is strongly associated with epigenetic attributes. Hence, even though monozygotic twins have the same genetic information, they may differ in their epigenetic profiles, leading to potential differences in their health and disease phenotypes. Theoretically, Epigenetics plays a crucial role in cell division and differentiation. Therefore, it can answer variable phenotypes and their effects on different chronic diseases [154]. Increasing evidence suggests that epigenetic alterations play a critical part in the development of head and neck carcinoma. Compared with squamous cell carcinoma of other head and neck regions, studies on the epigenetic dysregulation of laryngeal cancers are relatively few. Most studies focused only on few epigenetic changes. With the recent advancement in technologies such as next-generation sequencing and microarray (e.g., methylation array and microRNA array), one could foresee those epigenetic

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studies on LSCC may shift from candidate gene approach to global high-throughput profiling. This contributes to further exploration of the disease from novel perspectives. Therefore, understanding the disease could identify suitable epigenetic markers [20,155].

DNA Methylation Aberrations: A cancer epigenome is marked by genome-wide hypomethylation and site-specific CpG island promoter hypermethylation. Even though the underlying mechanisms initiating these global changes are still under investigation, recent studies suggested that few of these alteration mechanisms may contribute to cancer initiation [156]. Hypomethylation of DNA promotes abnormal activation of genes and non-coding regions through various mechanisms that contribute to cancer development and progression. In contrast to hypomethylation, which increases genomic instability and activates proto-oncogenes, site-specific hypermethylation contributes to tumorigenesis by silencing tumor suppressor genes. DNA hypermethylation indirectly silences the gene expression by silencing transcription factors and DNA repair genes. In addition to this, it also directly inactivates the expression of tumor suppressor genes [156,157]. Studies in the context of HNSCC documented that in normal mammalian cells, promoter genes, LINEs & SINEs generally exhibit high methylation status, while during carcinogenesis, and they are hypomethylated, which contributes to activating transcription of sequences through genome destabilization. In normal cells, CpG islands of transcriptionally active genes are poorly methylated. Whereas hypermethylation in gene promoters is a characteristic for epigenomes of cancerous cells that may lead to transcriptional silencing of tumor suppressor genes, thus promoting malignant transformation [156]. Previous studies have shown that the group of proteins with methyl DNA binding activity, including Methyl-CpG binding domain protein 1 (MBD1), methyl CpG binding protein 2 (MeCP2), and Kaiso [also known as ZBTB 33 (Zinc finger and BTB domain-containing protein 33)] mediates the link between DNA methylation and histone modifications. These group of proteins localize to DNA methylated promoters and recruit a protein complex that contains histone deacetylases (HDACs) and histone methyltransferases [158-160]. Studies by Okitsu and Hsieh et.al., (2007), Weber et.al., (2007) suggest that chromatin structural changes are induced by DNA methylation with alteration of histone modifications [161,162]. It is known that DNA methylation inhibits H3K4me, which also acts as evidence that DNA methylation affects histone modifications. Despite that, earlier studies in fungi (Neurospora Crassa) demonstrated that mutations of histone H3K9 methyltransferase lowered DNA methylation, signifying a simple linear model. Where H3K9 methylation acts as an upstream epigenetic mark that signals to DNA methylation [163,164].

Histone Modifications: Histone protein modifications play a regulatory role in modifying chromatin structure and transcriptional activity of DNA. DNA tightly wrapped around the Histone octamer (two copies of H2A, H2B, H3, and H4) comprises the primary unit of chromatin known as a nucleosome. These are basic group proteins that consist of a C-terminal domain (globular form) and an N-terminal domain (tail form) [165]. The N-terminal domains of histone proteins undergo different post-translational modifications like acetylation, methylation, phosphorylation, ubiquitination, and ADP-ribosylation modulating the interactions between DNA and histone octamer. These post-translational histone modifications are mediated by enzymes that add or remove the chemical group on the amino-acids serine or lysine and arginine [165]. Histone acetyltransferases (HATs) and histone deacetylases (HDACs) catalyze the process of acetylation and deacetylation, respectively. Acetylation of lysine results in chromatin structure relaxation, thus, facilitates gene transcription. Whereas deacetylation leads to gene silencing and decreased accessibility of DNA to the activity of transcription factors [165]. Methylation of lysine, histidine and arginine in histones results in changes in the structure of chromatin and gene activity without any alterations in the charge of histones. The methyl group is added to amino acid residues by histone methylases (HMT), while histone demethylases (HDMTs) reverse this process. The epigenetic effects of methylation depend on the location where the methyl group is added. Phosphorylation occurs by adding a phosphate group from ATP that modifies primarily threonine, serine and tyrosine located in the N-terminal histone tails and is regulated by phosphates and kinases (Figure 5). As a result, the histones will have a lower positive charge that may influence chromatin organization [165]. Recent advances in high-throughput sequencing have enabled genome-wide mapping of chromatin changes that occur during tumorigenesis. Studies have revealed that loss of histone acetylation mediated by HDACs results in gene repression. In addition to changes in histone acetylation, cancer cells also display widespread changes in histone methylation patterns that are associated with aberrant tumor suppressor gene silencing in various cancer forms. DNA methylation and histone modifications work independently and also in concert to alter gene expression during tumorigenesis. Therefore, deregulation of these histone protein alterations may regulate the transcription of various genes and, consequently, may lead to malignant transformations in various cancers like HNSCC [165].

miR Methylation: DNA methylation and histone modification at promoter regions and microRNA regulation at 3 prime UTRs are considered major epigenetic regulator mechanisms in eukaryotes. They predominantly regulate gene expression. Genes with low DNA methylation in the promoter regions are tend to be targeted by miRs. Epigenetic mechanism regulates the miRs; thereby, the expression of

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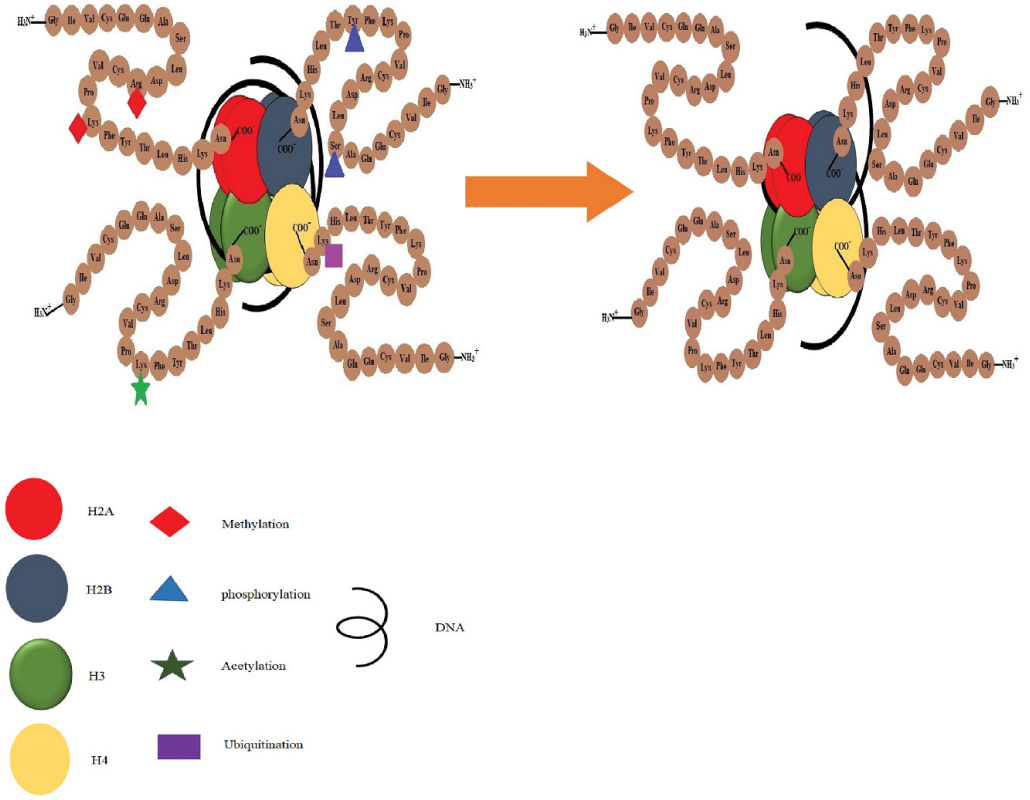

Figure 5: Histone Modifications.

the given gene gets upregulated or downregulated in specific pathological conditions (tumor progression (HNSCC, Ovarian, Cervical cancer)) [166,167]. Iorio and Croce, 2012 have found that half of the miR genes tend to undergo DNA methylation by epigenetic regulation of miRs [166]. Malumbres, 2013 also reported that hypermethylation of miR 137 in OSCC ultimately targets the expression of CDK-6, E2F-6, NCoA2 and Lsd-1. miRs are found to have fine-tuned feedback systems where the first one controls the expression of vital epigenetic regulators, namely DNMTs, HDACs, PRC1 and PRC2, which are termed as epi-miRs, the other miR recruits the specific protein complexes directly to the promoter region of genomic DNA. Endogenous miRs directly participate in the induction or repression of specific genes; therefore, the gene regulatory mechanisms have their own function in the gene expression profile of specific cells. Disruption in the above two mechanisms may lead to cause various multifactorial disorders, including cancer [168].

miR200 Methylation in Cancers: In the stem-like phenotype, specifically miR200b, miR200a, miR429 cluster tends to get silenced primarily by histone modification (by poly comb) while the other two (miR 200c, miR 141) get repressed by DNA methylation [169]. Studies by Iliopoulos et al., (2010), Iliopoulos et al., (2009) and Shimono et al., (2009) have demonstrated that the re-expression of the miR 200 family in stem-like HMLE (sl- HMLE) have revealed that the miR200 family represses the stem-like properties. In addition to that, they have also found repression of miR-200 family in BCSCS isolated cells of metastatic breast cancer patients [170–172]. miR-200 family acts as a key regulator of the epithelial-mesenchymal transition (EMT). Studies on the regulation mechanism of miR-200 demonstrated that both the DNA methylation and histone modifications were considerably get altered in the stem-like and non-stem like phenotypes [169]. Especially in the stem-like phenotype, polycomb group-mediated histone modifications primarily silence the cluster of miR-429-200b-200a, whereas the miR-200c-141 cluster was suppressed by DNA methylation. The persistent decrease in miR-200 gene expression in stem-like -HMLE cells suggested that epigenetic changes might be involved in the maintenance and/or initiation of the stem-like sl-HMLE subpopulation [169]. CpG hypermethylation was identified across the promoter in the mesenchymal MDA-MB-231 and Hs578T cell lines that never again express the miR-200 genes. Interestingly, HMLE and sl-HMLE cells show a quite similar expression of CpG methylation profiles of the miR-429 -200b-200a gene; the TSS and promoter region was predominantly unmethylated except for region B, where a slight increase in DNA methylation of sl-HMLE cells is seen [173]. conversely, miR200c-141 gene silencing and primary transcript and CpG promoter methylation were positively correlated in the HMLE and sl-HMLE cell types.

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Methylation of miR 200 in HNSCC: All human cancers, along with OSCC, are polygenic and poly epigenetic by nature [47 suppressor genes is the most common detectable epigenetic alteration [174]. In determining the expression of miRs in cancers, hypermethylation of CpG island plays an essential role in the transcriptional inactivation of miRs, which propagates epigenetic modifications [175]. P53 directly targets the family of miR 34 gene, and their ectopic expression in cancer cells initiates the arrest of the cell cycle followed by apoptosis by targeting MYC [176]. Kozaki et.al., (2008) identified the promoter regions of miR 34b, miR 34c that are found to have hypermethylated in oral and other cancer malignancies. Inactivation of tumor suppressor genes is the most common detectable alteration seen in the mechanism of poly epigenetics [47]. However, DNA hypermethylation epigenetically activates miR-200 in tumors, which is repressed in the absence of hypermethylation, specifically in CD44 high OSCCs. Members of the miR-200 gene family (miR-200a, miR-200b, miR200c, miR141 and miR429) are direct targets of CD44, and their ectopic expression in head and neck cancer cells stimulate apoptosis and cell cycle arrest by targeting BMI1 [34].

miRs as a Biomarker for HNSCC: Due to the miRs unique stability and their availability in body fluids (plasma, serum, sputum, urine, semen and milk), they have grabbed multiple attentions to be used as a biomarker for detecting cancer progression. miRs influence many biological processes such as proliferative signaling, cell death, and metastasis [177]. In carcinogenesis, the expression profile of miRs get altered, and such alterations can be identified very easily by accessible specimens like peripheral blood and saliva (Especially for HNCC) instead of a surgical tumour biopsy, and they have minimal invasiveness [178]. In the last two decades, nearly 20,000 publications have identified that the miRs are a potential biomarker for the prediction of disease progression because of their extreme stability. Studies have been performed to determine the efficacy rate of miRs as a biomarker in various forms of specimens like fresh, frozen, plasma, serum and formalin-fixed paraffin-embedded (FFPE) samples stored for many years, and it has been revealed that the expression of miRs found to be stable and unaffected by storage duration and the conditions. Most of the circulating miRs are not encapsulated in vesicles. Still, they allied with protein complexes containing the Argonaute 2 (Ago2), a vital effector of miRs-mediated silencing [178,179. The potentiality of extracellular miRs is well established in cancer diagnosis, prognosis, and therapy compared to its actual function in cellular signaling [180]. Shreds of evidence have suggested that the altered expression profile contemplate pathogenesis link with tumor initiation, progression, and metastasis [181]. Consequently, the use of miRs as a biomarker in the clinical system may help to predict the patient's survival rate, loco-regional relapse and make up clinical decisions based on the anticipated responsiveness to a specific mode of treatment. Therefore, miRs as a biomarker would be highly useful in head and neck squamous cell carcinomas (HNSCCs) because of their high heterogenic nature [181].

Future prospects and Challenges

The epigenetic revolution that has come about in the field of biology during the last few decades has challenged the conventional view of the genetic code as the key determinant of cellular gene function and its alteration being the major cause of human diseases. Advances in cancer epigenetics have led to understanding genome packaging as potentially important for preserving cellular identity and giving rise to disease states like cancer. Deeper insights into the global patterns of epigenetic modifications and their corresponding changes in cancer may enable designing novel treatment strategies. A combinatorial approach utilizing different epigenetic therapeutics along with standard chemotherapy holds significance for successful treatment of cancer in future. Further understanding of cancer stem cells and the development of more specific epigenetic drugs may hold the key to successfully resetting the abnormal cancer epigenome. Our understanding indicates that various miRs were found to be significantly associated with poor prognosis in HNSCC patients. Even though many miRs are identified to be deregulated in cancers, their pathological consequences are yet to be explored. We envision that in the near future advanced miR-based studies may become a key component of tumor diagnosis. Therefore, our review highlights the emerging potential of miRs as the key players in cancer management as diagnostic or prognostic tools and for monitoring therapeutic responses.

Author Acknowledgements

Not Applicable.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Funding Statement

No funding was received to assist with the preparation of this manuscript.

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Citation: Shivani Kadarla, Rajesh Kumar Galimudi, Surekha Rani Hanumanth, Srimanth Kumar Barigela, Durga NeeharikaRani, Madhavi Jangala, Pardha P Reddy, Raja Meghanadh Koralla. Headway of miR200 Family as a Novel Biomarker in Head and Neck Cancers. Journal of Cancer Science and Clinical Therapeutics 6 (2022): 392-410.