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THE MIRNAS: A POTENTIAL BIOMARKER FOR CERVICAL CANCER

Oncology

Praveen Kumar Ph.D. Scholar
Dr. Nisha Singh Professor
Dr. Suchi Agrawal Additional Professor
Dr. Preeti Agrawal Additional Professor
Surbhi Gupta Ph.D. Scholar
Neha Rawat Ph.D. Scholar
Kirti Upadhaya Ph.D. Scholar
Ankit Singh Negi M.Tech Biotechnology
Dr. Nitu Nigam* Additional Professor *Corresponding Author

ABSTRACT

MicroRNAs (miRNAs) are small, non-coding RNA molecules consisting of 21-25 nucleotides. They play a crucial role in post-transcriptional gene regulation, influencing several signaling pathways, including Notch, Wnt/beta-catenin, PI3K-Akt, and the epithelial-mesenchymal transition (EMT) pathway. The EMT pathway is linked to various malignant behaviors such as proliferation, invasion, and metastasis. The miRNAs are known to play a crucial role in controlling the EMT phenotype. Understanding the relationship between EMT-associated miRNAs and cancer chemoresistance is essential for both basic and clinical research, particularly in cervical cancer (CC) where miRNAs have been associated with chemoresistance. Utilizing miRNA-based treatments could be a potential method to overcome chemoresistance. One notable advantage of miRNAs is, their stability in body fluids like blood, urine, and tissue, making them effective biomarkers for human cancers. However, the translation of miRNA-based biomarkers from the laboratory to practical applications remains a challenge, despite their potential as biomarkers for pre-cancer diagnosis in humans. This review include the biogenesis of miRNAs development of cervical cancer, their pathways, various types of miRNAs involved in cancer are also elaborated in later part of review.

KEYWORDS

miRNAs, EMT, metastasis, chemoresistance, cell proliferation, cervical cancer.

1. INTRODUCTION

In the twenty-first century, cancer is usually cited as a major cause of mortality. As a major global health problem, cancer death and incidence rates are higher than ever before. It is believed that there are nearly 200 different types of cancer i.e., cervical cancer, lungs cancer, prostate cancer, and oral cancer, etc. [1] Despite various therapeutic advances in recent years, the rate of treatment resistance and tumor recurrence among these individuals remains very high [2]. One of the most prevalent cancers in the world is the cervical cancer was reported with a high mortality rate in women .[3] The mortality rate is dependent on the diagnosis of the cancer, if diagnosed at early stages then cervical cancer is curable with various treatment options. The development and spread of cervical cancer is the result of many complex circumstances. In developing nations, cervical cancer is the second most prevalent malignancy and the fourth most common gynecologic cancer globally. [4] Cervical cancer is primarily caused by human papillomavirus, it is thought to be the etiologic cause of cervicogenic squamous intraepithelial lesions that can proceed to high-grade dysplasia [5], as well as some other risk factors such as cigarette smoking.

Non-coding, single-stranded RNA molecules, known as miRNAs, consisting of 21-25 nucleotides, regulate the expression of genes after transcription and provides instructions for a number of biological processes. They exhibit excellent stability in body fluids such as blood, urine, and tissue, making them an effective biomarker for human cancers. [6, 7, 8] Since then, more than 2500 miRNAs have been discovered, and the human genome is thought to contain more than 1700 miRNAs. MiRNAs play post-transcriptional roles in embryonic development and stem cell self-renewal. They may also act as tumour suppressors and oncogenes. MiRNAs are characterised by their selectivity (they can recognise tumours more accurately than mRNA) and their persistence in a cell-free environment. They are not easily destroyed by extreme pH and temperature variations.[9] The expression of signature miRNAs is a much-discussed and much-noted topic among cancer researchers because it is differentially expressed in a variety of cancers .[10] Numerous cancers, including hematologic malignancies, have been associated with specific miRNA biomarkers in extensive studies .[11] MicroRNAs have been found to influence gene expression post-transcriptionally by blocking translation or beginning degradation at partly complementary locations in the 3'-untranslated region (UTR) of certain mRNA targets .[12] MiRNAs are involved in a variety of biological activities such as cell division, proliferation, and apoptosis .[13, 14] This review incudes the biogenesis of miRNA and development of cervical cancer, their pathways. Various types of miRNAs involved in cervical cancer are also elaborated in later part of the review.

2. Biogenesis of miRNAs related to cervical cancer

The initial stage of miRNA synthesis involves post- or co-transcriptional modification of RNA polymerase II/III transcripts. [15] Although miRNA precursors can be identified in both exons and introns, they are more commonly found in intergenic sequences and introns of genes encoding proteins. [16] The conversion of precursors into mature microRNAs involves a series of events. Ribonucleases Drosha and Dicer cleave human miRNA in the cytoplasm and nucleus. The primary miRNA (pri-miRNA), which is formed by translation of the miRNA gene, is followed by the precursor miRNA (pre-miRNA). The many types of division processes and the association of various enzymes lead to the occurrence of other biogenesis processes. Depending on the site of origin, microRNA sequence, and thermodynamic stability, microRNA precursors are apparently sorted by a number of different pathways. The RNA-induced silencing complex (RISC) is responsible for microRNA regulation. The target of the microRNA that creates the RISC complex is messenger RNA (mRNA), which identifies the microRNA.[17] miRNA biogenesis routes are classified into two types: canonical and non-canonical.

3. The miRNA canonical pathway

DGCR8 and DROSHA have been shown to regulate the biogenesis process from primary-miRNA to pri-miRNA. DGCR8 recognizes N6-methyladenylated GGAC and other patterns in pri-miRNA transcribed from their genes. DROSHA cleaves the pri-miRNA duplex at the base of the pri-miRNA's distinctive hairpin structure, resulting in a 2nt long 3' overhang. [18] RNase III endonuclease then exports the resultant pre-miRNA to the cytoplasm. The exportin 5 (XPO5)/RanGTP

complex is broken down by Dicer into a miRNA duplex. [19] The mature miRNA duplex has two strands, 5p and 3p, which come from the 5' and 3' ends of a pre-miRNA hairpin, respectively. It is customary to use the strand with the least amount of 5' stability—the 5' uracil—as the guide strand and insert it first. Depending on how complimentary it is to the guide strand, there are numerous techniques to separate the uncharged strand, also known as the passenger strand. When miRNA passenger strands are shortened and removed from the cellular machinery without AGO2 mismatch, significant strand distortions occur. Alternatively, miRNAs that lack AGO2 loading or nuclear mismatches are pulled apart and passively removed. [20, 21]

4. Noncanonical miRNA biogenesis pathways

The two primary pathways responsible for non-canonical miRNA synthesis have been identified as Drosha/DGCR8-independent and Dicer-independent processes. Pre-miRNAs that mimic Dicer substrates are produced by a process unrelated to Drosha/DGCR8. In the absence of Drosha cleavage, exportin 1 rapidly transports these newly produced RNAs to the cytoplasm. Drosha converts endogenous short hairpin RNA (shRNA) transcripts into Dicer-independent miRNAs. Pre-miRNAs are formed in the cytoplasm with the assistance of AGO2. [22] As a result, AGO2 loads all pre-miRNA, and truncation of the 3p strand is dependent on AGO2. The formation of the 5p strand is completed by truncation at the 3' and 5' ends [23].

5. The role of EMT –related miRNAs in the metastasis of cervical cancer

It is believed that the role of miRNAs in CC metastasis EMT is to enhance N-cadherin, vimentin, and other proteins while lowering E-cadherin, allowing cancer to spread and invade. Details of the EMT diagnosis. [24] The zinc finger E-box connecting homeobox 1 (ZEB1), ZEB2, Snail1 and Snail2 has been linked to EMT.[25] TGF, Wnt, Hedgehog (Hh), Notch, integrin-linked kinase (ILK), and urokinase-type plasminogen activator receptor (uPAR) signalling pathways all have significant roles in either promoting or repressing EMT .[26] Moreover, miRNAs like miR-34a and miR-200b have been identified.[27] They impact metastasis by regulating EMT via particular signalling pathways. As discussed above, we have entered a new exciting era and have further explored the present research about the role of EMT-related miRNAs in the metastasis of CC.

6. miRNAs in the context of oncogenic EMT and CC metastasis

Frist, we discuss the promoting role of EMT-related miRNAs in the metastasis of CC. TGF- is well known for its complicated and contradictory role in cancer formation, operating as a tumour suppressor in early cancer stages and a tumour promoter in late cancer stages. The "TGF paradox" refers to the alteration of TGF function, the signs and symptoms of which are related to the onset of EMT [28]. For example, miRNA-17-5p increases cervical cancer cell metastasis by blocking the transforming growth factor receptor 2 (TGF-R2) [29] component of the TGF pathway. miRNA-519d, which relies on the same signalling mechanism as Smad7 [30], promotes CC metastasis by suppressing it. Through the TGF/Smads signalling system, one of the Smads family members has been demonstrated to play a crucial part in the spread of cancer. [31] By increasing N-cadherin and vimentin while decreasing E-cadherin, overexpression of miR-20b promotes metastasis and EMT. [32] CircRNA 000284 regulates miRNA-506 in the opposite direction, resulting in a 265% reduction in metastasis. The oncogene Snail2, which is associated with EMT, was suppressed. [33] Increased miRNA-92a expression was shown to reverse the inhibiting effect of Dickkopf-related protein 3 (DKK3) on metastasis CC. [34] Through interaction with the Wnt signalling pathway associated with EMT and its involvement in a number of biological processes, DDK3 suppresses tumour growth. [35] Up-regulation of miRNA-200b via its known target FoxG1 is thought to inhibit cancer metastasis. [36] As a potential carcinogen, FoxG1 is considered to negatively regulate the TGF signalling pathway. These signalling pathways are shown in **Figure 1** in conjunction with the aforementioned miRNAs.

7. CC metastasis and oncosuppressor EMT-related miRNAs

MiRNA-142-3p plays a role in cancer growth by inhibiting Frizzled 7 (FZD7), vimentin and Snail receptors and upregulating E-cadherin, with the inhibitor being involved in EMT and CC cell invasion. [37] It is known that both canonical and non-canonical Wnt signalling pathways must be active for the Wnt receptor FZD7 to function. MiRNA-212 prevents CC metastasis by reducing the expression of transcription factor 7-like 2 (TCF7 L2). The TCF7 L2 gene was located. It induces EMT in cancer cells as a new transcription factor and crucial element of the Wnt signalling pathway. In developing CC, MiRNA-638 acts as a tumour suppressor and regulates the Wnt/catenin signalling pathway. [38]

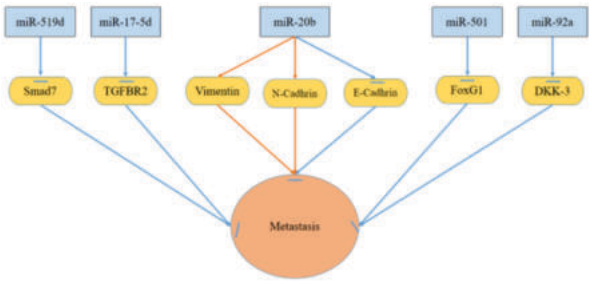

Figure 1: EMT-related miRNAs target TGF-β R2, Smad7, E-cadherin, N-cadherin, vimentin, Snail2, and FoxG1, and advance CC migration, invasion, and metastasis

The pituitary tumour-transforming gene 1 (Pttg1)/miR-3666/ZEB1 pathway or miRNA-211/ZEB1 pathway dramatically decreased CC metastasis. [39] Moreover, miRNA-377 inhibits CC cell invasion by negatively regulating ZEB2 expression. MiRNA-195, whose expression is downregulated in cervical cancer and which has a poor interaction with Smad3, appears to inhibit cell invasion and motility of CC. [40] member of the Smad family of TGF signalling proteins is Smad3. TGF/Smad3 has been shown to promote EMT, CC cell invasion and motility.

MiRNA-124, which was discovered to preferentially target the downregulated astrocyte elevated gene-1 (AEG-1) in cancer cells, is probably an anti-miRNA that inhibits EMT and metastasis. Both AEG-1 (metadherin) and the lysine-rich CEACAM1 co-isolate protein (LYRIC) are crucial for the growth of tumours and cancer. AEG-1 alteration lowered miR-1297's inhibitory effect on CC and EMT metastasis. [41] MiR-145 may be downregulated, and SMAD-interacting protein 1 (SIP1, also known as ZEB2) expression may rise, leading to EMT and CC metastasis. [42]

SIP1, a known E-cadherin suppressor, has been shown to repress multiple genes, promoting invasion and metastasis. By decreasing MUC4 and SPARC (serine-rich acidic protein), limiting the invasion of CC cells, and reversing EMT characteristics, MiRNA-211 appears to act as an anti-miRNA. [43] CC EMT may be affected by SPARC, a secreted matricellular protein that interacts with the cell matrix and influences cell growth. MiRNA-218 suppresses EMT, migration, and invasion in cancer cells by preferentially targeting the 3'UTRs of Scm-like with four MBT domains 1 (SFMFBT1) and DCUN1D1 (deficient in cullin neddylation 1 domain containing 1). [44] By lowering the expression of Notch signalling, Notch-1, and Jagged1, increased miR-34a expression prevents CC cells from invading. [45] Gene known as miRNA-204 has been demonstrated to be connected to metastasis. Through its regulation of transcription factor 12, an E-cadherin transcriptional repressor, miRNA-204 can encourage CC metastasis. Also repressed by miRNA-204 is the ephrin type B receptor 2 (EphB2), a tumour suppressor involved in the development of CC. EphB2 can hasten the progression of cancer by triggering EMT and regulating the vital PI3K/AKT signalling pathway that lies downstream from it. [46] Overexpression of miRNA-200b inhibits cell migration and EMT in CC cells by raising E-cadherin levels while lowering vimentin and MMP-9 levels. [47]

The synthesis of miRNA-29b and miRNA-12 has been demonstrated to decrease metastasis and EMT in CC cells by targeting the Signal Transducer and Activator of Transcription 3 (STAT3) pathway, a crucial cellular signalling mechanism. Forkhead Box M1 (FOXM1) overexpression can prevent CC metastases from being inhibited by miRNA-214, miRNA-342-3p, and miR-320. [48] FOXM1 overexpression has been linked to EMT and cancer metastasis. MiRNA-374c-5p CC inhibits cell invasion, migration, and EMT by targeting FOXC1, a member of the FOX transcription factor superfamily involved in EMT and cancer metastasis. [49] MiRNA-376c CC encourages metastasis by specifically targeting the B cell-specific moloney murine leukaemia virus insertion site 1 (BMI1), which has a major impact on EMT. MiRNA-340 has been demonstrated to prevent cancer metastasis via the ephrin receptor A3

(EphA3). [50] During the EMT process, overexpression of miRNA-340 lowers vimentin and -SMA levels while increasing E-cadherin expression. By upregulating the expression of the epithelial indicators E-cadherin and -cadherin and downregulating the expression of the mesenchymal marker vimentin, miRNA-223 reduces CC metastases [51]. By upregulating the expression of Bax and E-cadherin while downregulating the expression of NF-B and Bcl-2, overexpression of miRNA-218 inhibits cell migration. **Figure 2** shows the signalling networks controlling the above miRNAs.

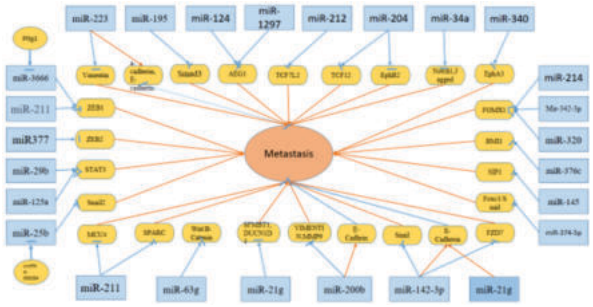

Figure 2: EMT-related miRNAs inhibit CC migration, invasion, and metastasis by targetting ZEB1/2, Smad3, AEG-1, TCF7 L2, MUC4, SPARC, Wnt/β-catenin, SIP1, SFMBT, Bcl-2, Bax, NF-κB, E-cadherin, α-cadherin, Notch1, Jagged1, TCF-12, EphB2, Vimentin, MMP-9, STAT3, FZD7, Snail, FOMX1, BMI1, and EphA3.

8. The function of EMT-associated miRNAs in chemoresistance CC

Recent research has revealed a link between miRNA production and cancer therapies targeting genes involved in chemoresistance or chemosensitivity. MiRNA antagonists are used to stop the activity of cancer-causing miRNAs, whereas miRNA mimetics are used to restore the function of tumour suppressor miRNAs. [52] In this section focuses on miRNA-mediated signalling pathways responsible for susceptibility or resistance to cervical cancer.

MiRNA-20a

In cervical cancer, MiRNA-20a has been linked to epithelial-mesenchymal transition (EMT), cell proliferation, invasion, metastasis, cancer stem cells, chemoresistance, radioresistance, and a poor prognosis. [53] miRNA-20a controls of the B-cell translocation gene 3 (BTG3) and the F-box and leucine-rich repeat protein 5 (FBXL5). It has been demonstrated that FBXL5 inhibits EMT, lowers metastasis, and lowers cisplatin resistance. [54] BTG3 inhibits both invasion and proliferation. [55] The tumour suppressor genes FBXL5 and BTG3 are downregulated in cervical cancer. Suppression of miR-20a may be a possible therapeutic approach for cervical cancer in order to boost the expression of FBXL5 and BTG3 and enhance sensitivity to cisplatin. In first-line chemotherapy, the well-known anticancer drug cisplatin is used to treat a variety of cancers. Advanced or recurrent cervical cancer is also treated with this platinum complex. [56]

MiRNA-195

MiRNA-195, a tumour suppressor miRNA, prevents cyclin D1a expression, which reduces cancer cell motility, invasion, and proliferation. [57] Epigenetic modulations, such as promoter hyper methylation, decrease miRNA-195 expression in hepatocellular cancer [58]. The plasmacytoma variant translocation 1 (PVT1) gene affects chemosensitivity in cervical cancer. Chemoresistance is caused by overexpression of PVT1 in a number of malignancies. [59] By triggering EMT, PVT1 and miRNA-195 can make cervical cancer cells more responsive to paclitaxel. According to Shen et al., PVT1 can reduce the production of miRNA-195 by raising histone H3K27me3 in the miRNA-195 promoter. The PVT1/miRNA-195 axis may increase paclitaxel sensitivity in cancer cells by influencing EMT. [60] The therapeutic efficacy of paclitaxel ranges from 29 to 63%, although it is considered an effective treatment for cervical cancer. [61] Up-regulation of P-glycoprotein or other drug efflux pumps [62], alterations in microtubules involved in drug binding [63], changes in cell cycle and cell survival pathways and treatment-induced autophagy [64] are some of the mechanisms behind paclitaxel resistance.

MiRNA-25-3p

MiR-25-3p has been shown to influence carcinogenesis in numerous cancers, including cholangiocarcinoma and cervical cancer. [65] MiRNA-25-3p has also been associated with chemoresistance. [66] In cervical cancer cells, decreased miRNA-25-3p expression and enhanced invasion, migration, and EMT abilities were observed. MiRNA-25-3p levels were found to be high in tumours, promoting E-cadherin expression and suppressing Sema4C expression. The induced overexpression of miRNA-25-3p makes cervical cancer cells more sensitive to cisplatin by targeting Sema4C and reversing EMT. Overall, overexpression of miRNA-25-3p may provide a therapeutic alternative for cervical cancer that has developed resistance to chemotherapy. [67]

MiRNA-124

The study found that miRNA-124 specifically targets iASPP, lowers its expression, and thus inhibits cervical cancer cell proliferation and invasiveness. Cervical cancer, among other malignancies, has downregulated levels of the tumour suppressor miRNA-124. MiRNA-124 is downregulated in association with low 5-year survival and overexpression of iASPP mRNA. As a result, miRNA-124 restoration reduces iASPP expression and results in p53-dependent tumour suppression. These findings point to miRNA-124 as a potential therapeutic target for iASPP-related cervical cancer. [68]

MiRNA-181a

MiRNA-181a acts as an oncogene in cervical cancer and promotes cisplatin. Numerous malignancies, including lung, cervical, ovarian, and prostate cancers, share chemosensitivity with the protein kinase C (PKC) pathway. In nude mice, miR-125a enhanced the expression of miRNA-181a, which increased PRKCD suppression and decreased apoptosis inhibition. [69]

MiRNA-125

The miRNA-125 family, which includes miRNA-125a, miRNA-125b-1, and miRNA-125b-2, has been linked to cancer. [70] An anti-oncogene called miRNA-125a inhibits cancer growth in several ways. [71] Cisplatin- and paclitaxel-resistant cervical cancer cells have been found to have downregulated levels of this miRNA. In cervical cancer, miRNA-125a has been shown to affect resistance to paclitaxel and cisplatin by decreasing transcription 3 (STAT3) and increasing apoptosis. STAT3 promotes the synthesis of BCL2 and BCL-XL, leading to chemoresistance and carcinogenesis. In addition, paclitaxel-resistant cervical cancer cells were found to overexpress STAT3, BCL2, and BCL-Xl. [72] Chen and coworkers. In nasopharyngeal carcinoma cells and colon cancer cells, overexpression of miRna-125a was observed to increase sensitivity to paclitaxel and cisplatin. [73] According to these studies, increasing miRna-125a expression in conjunction with paclitaxel and cisplatin treatment may be beneficial in the treatment of chemoresistant cervical cancer by decreasing STAT3 expression.

MiRNA-375

In the cervical area, miRNA-375 expression is very low. [74] Overexpression of miR-375 dramatically decreased proliferation by preventing the G1-S cell cycle transition, highlighting the role of miRNA in tumour suppression. It has been found that it can hasten the development of cancer. Shen et al. discovered a connection between miRNA-375 expression and the use of the medication paclitaxel in their examination of cervical cancer cell lines and clinical data. Paclitaxel-using cervical cancer patients run the risk of acquiring medication resistance. Their findings demonstrated that paclitaxel-induced chemoresistance enhanced miRNA-375 expression. In cervical carcinoma, induced overexpression of miRNA-375 decreased sensitivity to paclitaxel. In cervical cancer, miRNA-375 may be a possible target for paclitaxel resistance. [75]

MiRNA-130a

Cancer cells become more internalised and sensitive to cisplatin when copper transporter protein 1 (CTR1) expression is increased. CTR1 has been linked to cell proliferation in cervical cancer patients receiving cisplatin therapy. By concentrating on PTEN, MiRNA-130a can affect CTR1 and encourage the growth of cervical cancer cells. [76] Research on miRNA-130a's role in cisplatin resistance has revealed that it can bind to CTR1. By functioning as both an oncogene and a tumour suppressor, the transcription factor SOX9 can boost cisplatin resistance in cervical cancer. [77] Therefore, the SOX9/miR-130a/CTR1 axis may impact cisplatin resistance and open up new therapy options for cervical cancer. [78]

MiRNA-214

The previous studies demonstrated to be downregulated in cervical cancer tissues. In cervical cancer, miRNA-214 expression suppresses cellular migration, invasion, and proliferation. Cells become more susceptible to cisplatin when this miRNA promotes apoptosis by decreasing the anti-apoptotic protein BCL2. [79]

MiRNA-126

The previous literature supports upregulation of the anti-apoptotic protein c-FLIP associated with an increase in TRAIL resistance in cervical cancer. Due to dying of cancer cells by these drugs by activating caspase-8 leads to increase c-FLIP expression [80]. TRAIL-induced apoptosis was significantly boosted by lowering chemosensitivity in cervical cancer, although miRNA-126 overexpression has been linked to the disease. [81] C-FLIP, a cellular caspase-8 antagonist, was identified as a miRNA-126 target and has been shown to inhibit caspase-8. MiRNA-126 enhances the cytotoxicity of caspase-8 inducers such as TNF- and FasL, whilst lowering c-FLIP synthesis makes cervical cancer cells more susceptible to TRAIL. [82]

MiRNA-21

In several cancers, including cervical carcinoma, overexpression of miRNA-21 encourages cell proliferation, migration, invasion, and survival. As a result, blocking miRNA-21 in cancers can prevent cell growth and invasion while inducing death. In cervical tumours that are resistant to cisplatin, MiRNA-21 can reduce PTEN expression by attaching to the 3'-UTR of PTEN. [83] PTEN is a suppressive regulator in a number of malignancies, such as chemosensitivity and cervical cancer. Reduced CASC2 (LncRNA cancer susceptibility candidate 2) expression is linked to a poor outcome in cervical cancer. CACS2 downregulation has been linked to cisplatin resistance in cervical cancer tissues. CASC2 increases PTEN expression while suppressing miRNA-21 in cisplatin-sensitive cells. [84]

MiRNA-106a/b

It has been shown that miRNA-106a/b expression makes cervical cancer cells more susceptible to the chemotherapeutic drug cisplatin [85], indicating that it is a potential target for lowering cervical cancer chemoresistance. When miRNA-106a/b expression is altered, which improves tumour growth, metastasis, and cisplatin chemosensitivity, EXres and EXsen are resistant to cervical cancer cells. How miRNAs influence cell chemosensitivity to the chemotherapeutic drug cisplatin was investigated using the modification of the miRNA-106a/b target SIRT1, which promotes carcinogenesis by reducing p53's capacity to inhibit apoptosis. Chemosensitivity may be modulated by MiR-106a/b's SIRT1-dependent pathway. [86]

9. The role of EMT related miRNAs in the cell proliferation of CC

Numerous signaling pathways and chemicals are thought to have a role in the metastasis of CC, according to studies. When it comes to CC migration, invasion, and cell proliferation, the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling system has been identified as one of the key regulators of carcinogenesis. [87] MiRNA-1246 increases cell proliferation and targets thrombospondin-2 (THBS2). Reduction of cancer cell growth has also been associated with regulation of PDCD4 by MiRNA-150. [88] Expression of the CAM family member and putative tumour suppressor CHL1 is negatively associated with CC invasion and migration. MiRNA-501 may promote CC cell invasion and migration by upregulating NF-B/p65 and downregulating CYLD expression. [89] MiRNA-92a increases the proliferation and dissemination of cancer cells by targeting the gene FBXW7, which contains an F-box and WD repeat. [90] Cullin-5 (CUL5), also known as vasopressin-activated calcium mobilisation receptor (VACM-1), which encourages cell proliferation, has been shown to be positively and negatively regulated by miRNA-19a/b. [91] Overexpression of miRNA-206 reduced cell proliferation by lowering the expression of B-cell lymphoma-2-associated athanogen 3 (BAG3), a gene implicated in cell growth and metastasis [92].

The miRNA-218/survivin or miRNA-34a/E2F3/survivin axis is crucial for controlling cell proliferation. Stimulation of miRNA-214 by the mTOR pathway undoubtedly reduces cell growth from CC. The cell cycle, differentiation, and synthesis of the protein survivin are all influenced by the transcription factor E2F3. Pyruvate kinase muscle isoenzyme M2 is inhibited by MiR-let-7a, which prevents invasion and migration of CC cells. [93] At CC, miRNA-26a can decrease cell proliferation, although PRL-1 expression, which inversely correlates with miRNA-26a expression, can compensate. [94] CCND2 controls the G1/S transition in the cell cycle through interactions with CDKs. A biological homolog of v-myb called MYB functions as a transforming oncogene in some cancers. By focusing on the cyclooxygenase-2 gene related to carcinogenesis and metastasis (COX -2), MiR-101 inhibits the proliferation of CC cells. [95] MiRNA-379 can function as a tumour suppressor in CC by lowering the CT10 oncogene homolog-like (CRKL) of the V-crk avian sarcoma virus. Wang et al. found that miRNA-485 has a negative correlation with colorectal cancer 1 (MACC1) cell proliferation. [96] For example miRNA-17-5p, stimulates colon cancer cell proliferation by suppressing tgf-r2, a part of the tgf signalling pathway. Reduced expression of the EMT-related oncogene snail2, which is controlled by circrna 000284, reduces cell growth. By reversing zeb2 expression, mir-377 reduces cc cell invasion and proliferation. [97]

The miRNA-204 is a gene that controls the expression of the transcription repressor transcription factor 12 (TCF12), which may be involved in the spread of cancer. Additionally, miR-204 inhibits CC cell proliferation by changing the critical downstream signalling pathway PI3K/AKT and triggering EMT in the ephrin type B receptor 2 (EphB2). [98] EMT is impacted by MiRNA-376c's targeting of the B cell-specific Moloney murine leukaemia virus insertion site 1 (BMI1). [99] Alteration of CC cell proliferation was found to require specific HPV-E6-p53-miRNA-145 signalling. The oncogenic HPV E6-targeted miR-195 prevents the migration and proliferation of CC cells because the cullin neddylation 1 domain containing 1 (DCUN1D1) gene is much more expressed in CC. [100] All miRNAs associated with proliferation of CC are shown in **Figure 3.**

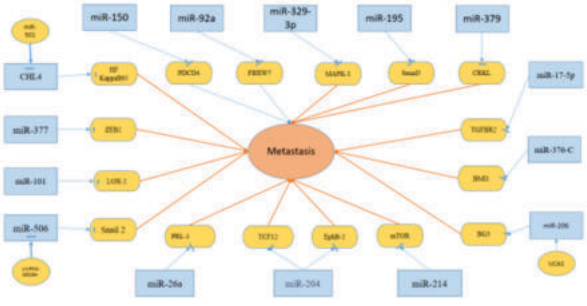

Figure 3: EMT related miRNA s in the cell proliferation of Cervical Cancer Proliferation.

10. CONCLUSION

A wide range of biological functions, including differentiation, proliferation, apoptosis and cell death, metastasis, and invasion, are regulated by miRNAs. Genes involved in cancer development and spread are controlled by miRNA expression. Diagnoses, chemosensitivity, and chemoresistance are affected by the disruption of important genes by miRNAs and their interactions with other signalling networks. MiRNAs play an important role in cancer chemoresistance. According to recent studies, variations in miRNA expression can successfully influence the sensitivity of cancer cells. Compared to other ncRNA-based treatment alternatives, miRNAs are believed to increase the efficacy and safety of cancer therapy in preclinical studies. MiRNA mimics and anti-miRNAs are the most commonly used RNA-based treatments in cancer cell lines and xenograft models, depending on whether they are upregulated or downregulated. However, despite these encouraging results, there are some negative aspects. Although it is a complex structure controlled by numerous miRNAs, current research provides little insight into the role of individual miRNAs. Moreover, little is known about the specific biological mechanisms by which miRNAs contribute to cancer chemoresistance. Cancer therapy based on miRNAs has been proposed as a result of recent research that has highlighted the potential importance of miRNAs for the clinical treatment of human cancer. It has been shown that miRNAs are essential for the spread of cancer. The basic understanding of the inherent properties and biological functions of miRNAs during CC metastasis is shown in conjunction with previous research. It is straightforward to distinguish between miRNAs that interact with oncogenes or tumour suppressor genes and those that regulate cell division, invasion, and metastasis. Each stage of cancer development, including cell invasion, proliferation, migration, and tumour metastasis, depends on miRNAs. Since miRNAs are associated with CC metastasis, a more thorough investigation of their functions is urgently needed to identify new

potential CC therapeutic targets. Recently, thanks to the rapid progress of miRNA profiling microarray technology and high-throughput sequencing, the link between CC and miRNAs has been much better investigated. Based on changes of various miRNA levels in serum, secreted miRNAs can be detected for cancer diagnosis, including early metastasis of CC. Extracellular vesicles (EVs), circRNAs, and lncRNAs are just some of the previously unidentified molecules with which miRNAs can interact thanks to improvements in sequencing depth and cancer metastasis identification. These drugs have been shown to have a synergistic effect on cancer growth when combined with miRNAs.

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