**MicroRNAs as Master Regulators in Cervical Cancer Offering New Avenues for Diagnosis Prognosis and Targeted Therapy**

**ABSTRACT**

Cervical cancer is a significant global health concern and remains one of the most common malignancies affecting women, particularly in low- and middle-income countries. The primary etiological factor is the persistent infection with high-risk strains of human papillomavirus (HPV), notably types 16 and 18. While current screening techniques, such as the Pap smear and HPV DNA testing, have contributed to early detection and reduced mortality, their limitations in sensitivity and specificity underline the urgent need for more accurate biomarkers. In recent years, microRNAs (miRNAs)small, non-coding RNA molecules that regulate gene expression post-transcriptionallyhave emerged as pivotal players in cancer biology. They are known to modulate critical cellular functions such as proliferation, apoptosis, invasion, immune response, and metastasis. Aberrant expression of specific miRNAs has been identified in cervical cancer and is increasingly associated with the initiation, progression, and clinical outcomes of the disease. Some miRNAs function as oncogenes (oncomiRs), promoting tumor growth, while others act as tumor suppressors. This dual role presents opportunities for their use not only as diagnostic and prognostic biomarkers but also as therapeutic targets. Moreover, the stability of circulating miRNAs in body fluids like blood and cervical mucus enhances their potential as non-invasive biomarkers. This review provides an overview of miRNA biogenesis and regulatory mechanisms, outlines the most significantly upregulated and downregulated miRNAs in cervical cancer, and discusses recent advances in miRNA-based therapeutic strategies. Understanding the molecular interplay between HPV infection and miRNA dysregulation may pave the way for the development of precision medicine tools, improving early detection, risk assessment, and personalized treatment in cervical cancer care.

***Keywords:*** Cervical Cancer, MicroRNAs, Human Papillomavirus (HPV), Gene Regulation, Biomarkers, Diagnosis, Prognosis, Targeted Therapy, miRNA Biogenesis, Cancer Therapeutics

1. **INTRODUCTION**

Cancer is marked by unchecked cell division and expansion, which leads to the formation of lesions that have the potential to invade nearby tissues and spread to other areas of the body. Leukemia, lymphomas, sarcomas, and cancers are its four primary classifications [1]. Among females, cervical cancer is a prevalent illness with a high global incidence and death rate.[2]. Cervical cancer is the 4th most prevalent cancer worldwide affecting women.[3] [4]. The primary cause of the associated risk factors is human papillomavirus (HPV) infection. Covering more than 99.7% of all cases.[5]. Further considerations reported to elevate the risk of cervical cancer include poor, immunosuppression, smoking sexual health, and failure to attend regular screenings [6]. Every time cervix cancer arises, the cervical cells go through a process called dysplasia, which causes aberrant cells to form inside the cervical tissue. These aberrant cells have the potential to develop into malignant cells over time, spreading to deeper cervix layers and surrounding tissues. In children, cervical cancer is rather uncommon [7]. Although HPV can't trigger cervical cancer on its own, it is a significant contributing factor to the disease's progression. done [8]. HPV (Human Immunodeficiency Virus) strains can be classified as either low-risk or high-risk. High-risk strains can result in cancer, although low-risk strains might cause anogenital warts or stay asymptomatic. High-risk HPV infection is the cause of more than 99 percent of cervical dysplasia and cervical carcinoma precancerous lesions.[9]. Forty of the approximately 200 HPV strains that are known to exist impact the anogenital area. High-risk genotypes have been assigned to 1518 HPV strains in total. Most cervical neoplasia and cancers are caused by high-risk HPV genotypes, with types 16 and 18 accounting for over 70% of all cervical cancer occurrences. About 20% of cervical adenocarcinomas are type 18, whereas 50% of squamous cell carcinomas and 55% to 60% of all cervical malignancies are type 16.Types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 are additional carcinogenic HPV strains that together account for 25% of cervical carcinomas.

HPV infections can lead to cancer in the anus, vulva, vagina, penis, and oropharynx [10]. HPV infection is linked to several cervical cancer risk factors. It could take up to 20 years for aggressive cancer to grow from a precursor lesion caused by sexually transmitted HPV. Sexually transmitted diseases are a risk factor for cervical cancer. Ameta-analysis found that the highest prevalence of HPV occurs between the ages of 25 and 35, which may be related to changes in sexual behavior, HIV is the virus that causes HIV. Women with HIV are more susceptible to infection from high-risk HPV strains [11]. high parity, and long-term Cigarette smoking use of oral contraceptives are among the behavioral and environmental risk factors that are important co-factors in the persistence of disease. Hereditary host variables may also influence HPV persistence and disease progression. Cervical cancer may run in families, according to earlier studies. According to research on the family clustering of cervical cancer, women who have an afflicted first-degree cousin are up to two times more likely to develop invasive cervical cancer or cervical intraepithelial neoplasia grade 2/3 [12]. Early detection and treatment may result from efficient screening. A pap smear test can detect early cervical epithelial alteration and is the primary screening tool for precancerous cervical intraepithelial neoplasia and the early stages of invasive cervical cancer.[13]. Short, non-coding RNA molecules known as microRNAs (miRNAs) control gene expression and other biological functions.[14] [15]. miRNA synthesis involves transcription from DNA sequences, followed by processing into precursor and mature forms. Typically, miRNAs interact with the 3’ untranslated region (UTR) of target mRNAs, triggering, degrading, or translational repression, however, interactions with other areas have been described. Extracellular miRNAs can be released and transferred to target cells, allowing for cell-cell communication [15]. The therapeutic potential of miRNAs is being intensively investigated, with some candidates entering the preclinical and clinical trials [14]. Recently, miRNAs have been proposed as promising biomarkers with high sensitivity and specificity for the non-invasive detection of cervical cancer. Non-coding RNAs with 19–24 nucleotides are called miRNAs. It was found that miRNAs are frequently uncontrolled in cancer.[16].

***Figure 1 :* Absolute number, Incidence, Females, in 2022 World**

**2. MiRNA :**

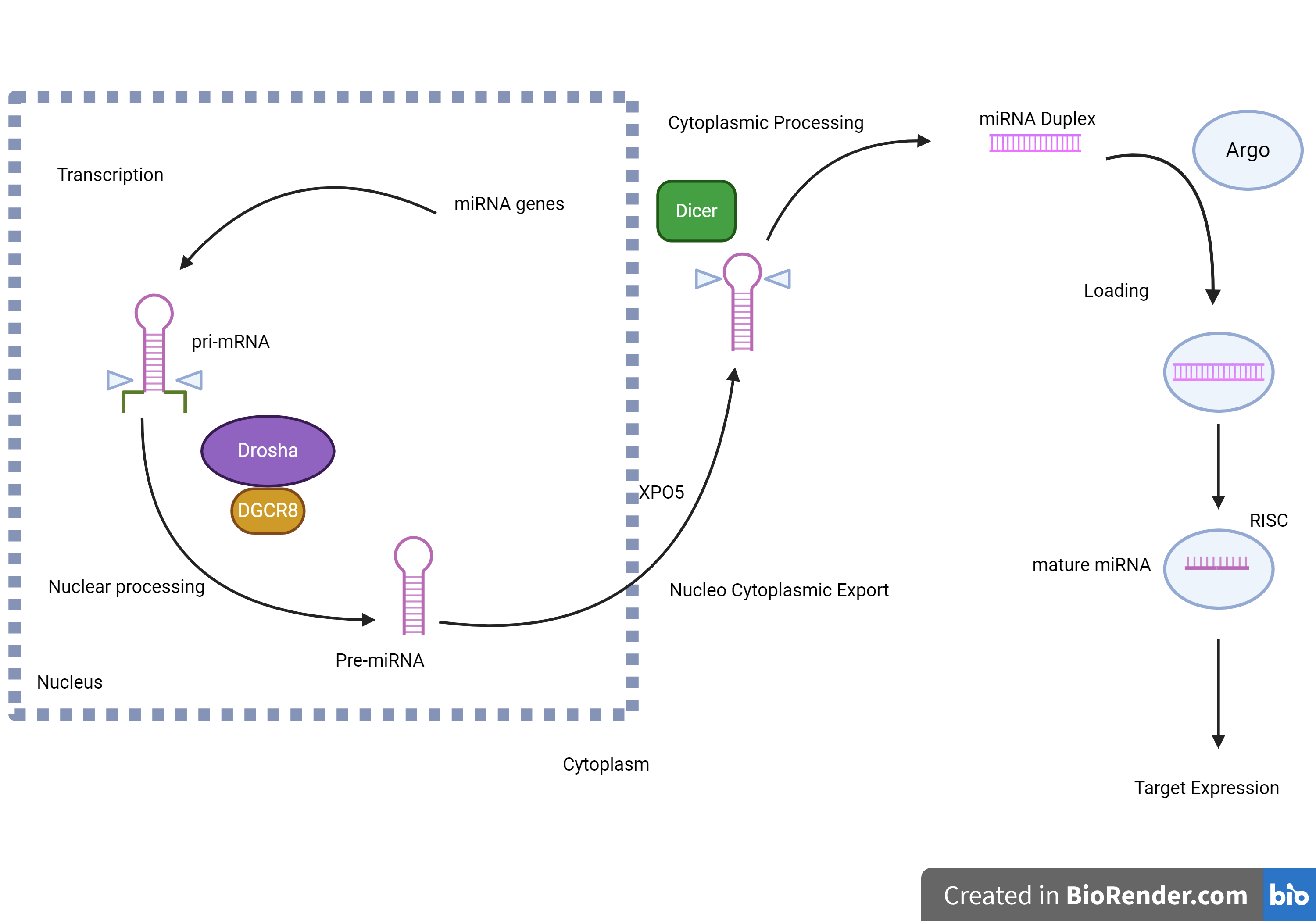
In 1993, miRNAs were discovered. They are a kind of short non-coding RNA that ranges in length from 19 to 24 nucleotides and are essential for controlling post-transcriptional levels of gene expression miRNAs work by either inhibiting the translation of mRNAs or by breaking down their RNA targets. Much research conducted over the past 20 years has demonstrated the critical role that miRNAs play in controlling vital cellular functions such as metabolism, stress response, apoptosis, migration, differentiation, and proliferation. It has been shown that miRNAs have a crucial role in the pathophysiology of illness, including cancer [17]. Even though just 3% of human genes code for proteins, miRNAs can control about 30% of these genes. After it was discovered that the first miRNAs to be identified, let-7 and lin-4, were involved in cell cycle regulation in C elegans, miRNA studies started to focus on the functional roles of miRNAs. Since a miRNA may have several targets, it can regulate a wide range of significant human pathways. that can regulate a number of biological functions, including metabolism, growth, development, and immunity. It is not unexpected that they can regulate the pathophysiology of numerous diseases, including cancer, given their wide range of targets [18].

**2.1. *miRNA Biogenesis :***

Human microRNA (miRNA) biogenesis is a multi-step process involving a number of important enzymes and regulatory elements.[20], [21], [22]

RNA polymerase II transcribes miRNAs as longer primary transcripts with a stem-loop structure, known as prior-miRNAs.[22]. The prior-miRNA is then cleaved by the Microprocessor complex, which is made up of the RNase III enzyme Drosha and the double-stranded RNA-binding protein DGCR8, to produce a precursor miRNA. The pre-miRNA is exported from the nucleus to the cytoplasm by the Exportin-5 protein. The pre-miRNA in the cytoplasm is further broken down by another RNase III enzyme called Dicer, which cleaves it and creates a miRNA duplex. The miRNA duplex is then loaded onto an Argonaut (AGO) protein, which is a part of the RNA-Induced Silencing Complex (RISC).   
A number of important enzymes and regulatory variables are involved in the multi-step process of human miRNA synthesis.20] [21][22] RNA polymerase II transcribes miRNAs as longer primary transcripts (rip-miRNAs) with a stem-loop structure [22]. The microprocessor complex, which is composed of the double-stranded RNA-binding protein DGCR8 and the RNA ace III enzyme Dicer, cleaves the cytoplasm to produce a miRNA duplex. An Argonaut (AGO) protein, a component of the RNA-induced Silencing Complex, is then loaded with the miRNA duplex.   
The guide strand of the miRNA duplex is kept intact within the RISC, whereas the passenger strand is frequently broken down. Translational suppression of the mRNAs' destruction takes place when the mature miRNA points the RISC toward the target mRNAs.[21]. Interestingly, the spliceosome removes the hairpin precursor from the host gene intron in a Drosha-independent manner for a subgroup of miRNAs known as mirtrons.

Splicing factors like SRSF1 and SRSF2 can control the processing and levels of mirton-derived miRNAs in cancer cells, hence regulating their expression [20]. Several human cancers have been linked to the onset and spread of dysregulation of the miRNA biogenesis pathway, which includes changes in the expression of the Drosha, Dicer, DGCR8, and Aeronaut proteins [22]. In conclusion, human disorders, including cancer, can arise as a result of disturbances in the miRNA biogenesis pathway, which consists of a sequence of processing steps regulated by important enzymes and regulatory factors. [20-23]

***Figure 2 :* miRNA biogenesis pathway.**

1. **Biomarkers :**

The biomarkers consortium and a working committee of the US National Institutes of Health (NIH) define a biomarker as a characteristic that can be objectively assessed as an indication of typical infection processes or a pharmacological response to a therapeutic intervention.[25]. Better ways to forecast a person's risk of developing cancer and detecting tumors early when they can be treated more successfully are the main objectives of biomarker development, in addition to improved treatments.[24]. Blood tissues and other bodily fluids typically contain biomarkers that show whether a process or disease is normal a pathological. A biomarker can be identified via genetics, Proteomics, or cellular or molecular components that are present in higher-than-normal concentrations in a cancer patient's bodily fluids (blood, urine) [26]. None of the biomarkers that are currently on the market meet the ideal sensitivity and specificity of 100% [27].

**3.1. *Biomarkers' significance in cervical cancer* :**

Despite its intra-observational subjectivity, microscopic examination of biopsied materials has long been the cornerstone of screening and diagnostic procedures. As a result, even while significant technological advancements have been made to detect cancer in its early stages, many malignancies are discovered at the microscopic level too late for therapeutic intervention. [28]. Cervical cancer typically does not exhibit acute symptoms as burning, itching, or vaginal discharge, in contrast to many genitourinary illnesses.[29]. Although they are not cancerous, a few of cells in the cervical cavity may exhibit early change. The epithelium layer of cells experiences dysplasia or squamous intraepithelial lesion (SIL) as a result of these precancerous cells.

**3.2 *miRNA as biomarkers in cervical cancer* :**

Small non-coding RNAs known as miRNAs control the expression of genes and have become promising biomarkers for several illnesses, most notably cancer [30]. Accessibility, high specificity, and sensitivity are traits of excellent biomarkers that these compounds display [31]. In addition to regulating apoptosis, cell cycle progression, proliferation, and differentiation, miRNAs are associated with the genesis, development, metastasis, and prognosis of cancer. [32] miRNAs have emerged as promising markers for cervical cancer staging, diagnosis, and prognosis. Studies have shown that a number of miRNAs may be important for cervical cancer diagnosis and prognosis. Urine samples that included a combination of miR-145-5p, miR-218-5p, and miR-34a-5p, for instance, shown great sensitivity and specificity in analysis when separating precancer and cancer patients from healthy controls, as well as good association with serum and tumor tissue samples. Interestingly, miRNA profiling in urine samples has shown potential as a non-invasive method for early detection and prognosis of cervical cancer.[33]. miRNAs, or small non-coding RNAs, regulate gene expression and have emerged as prospective biomarkers for a number of diseases, most notably cancer [30]. These compounds have excellent biomarker qualities, such as high accessibility, sensitivity, and specificity. [31]. In addition to regulating apoptosis, cell cycle progression, proliferation, and differentiation, miRNAs are associated with the genesis, development, metastasis, and prognosis of cancer [32]. non-invasive sample techniques like urine-based diagnostics.[33-36] In conclusion, miRNAs have demonstrated significant potential as biomarkers for the early detection, diagnosis, and prognosis of cervical cancer and play a significant role in its development. Combining miRNA analysis with other molecular markers and developing non-invasive sampling techniques, such as urine-based diagnostics, may enhance future cervical cancer screening and therapy methods.[34-36]

1. **The relationship between HPV and miRNA influences cellular and cancer progression :**

Particularly in connection with Human papillomavirus (HPV) infection, miRNAs are important in the initiation and spread of cervical cancer. With its oncogenic proteins E5, E6 and E7 playing important roles in carcinogenesis, HPV is the main cause of cervical cancer [37]. A significant risk factor for the development of cervical cancer is infection with the human papillomavirus (HPV), especially high-risk 16 and 18[38].

Numerous investigations of cervical pre-cancerous tissues have repeatedly revealed the dysregulation of several miRNAs, including miRNA 34a, miRNA-9, miRNA-21, miRNA-145, and miRNA-375. These miRNAs may play a role in the early transformation processes brought on by HPV’s E6 and E7 oncoproteins. miRNAs may be used as biomarkers for early diagnosis and prognosis because their expression profiles in HPV-infected cervical cancer tissues differ considerably from those in normal tissues [39].

It is currently unclear exactly how miRNAs contribute to HPV-related cervical cancer development, but their potential as targeted biomarkers for diagnosis, prognosis, and maybe treatment is promising. Additional studies in the field could yield important information about how miRNAs can be used to enhance cervical cancer treatment plans [40]. By altering DROSHA levels, HPV interferes with normal miRNA processing, impairing gene control and encouraging the growth of cervical cancer [41].

1. **Types of miRNAs in cervical cancer :**

Different types of microRNAs (miRNAs) present in serum/plasma, urine, and cervical mucus show distinct expression patterns in cervical cancer. These miRNAs, including miR-21-5p, miR-199a-5p, and miR-145, offer high diagnostic accuracy and are promising non-invasive biomarkers for early detection, prognosis, and monitoring of cervical cancer progression and treatment response.

* 1. ***Serum/plasma miRNAMicroRNAs (miRNAs)* :** in serum and plasma have become promising indicators for the prognosis and diagnosis of cervical cancer. By comparing cervical cancer patients to healthy controls, multiple investigations have found dysregulated miRNAs. High cervical cancer detection accuracy was demonstrated by a panel of four plasma miRNAs (miR-146a-5p, miR-151a-3p, miR-21-5p and,miR-2110) (Ma et al., 2019). According to (Jiang et al., 2017), Reduced expression of miR-101 was a substantial adverse risk factor for patient prognosis, and it was discovered that miR-101 was down-regulated in cervical cancer tissues relative to normal cervical tissues. Cervical cancer patients had lower plasma miR-145 levels than those with cervical intraepithelial neoplasia (CIN) and healthy controls, and low levels were linked to advanced FIGO stage, HPV, poor cancer differentiation, and lymph node metastases (Wei et al., 2017).
  2. ***Urinary miRNAs :*** 60% of pre-cancer urine samples and 80% of cancer urine samples were positive for HPV, indicating a high incidence of HPV infection, namely HPV16, in pre-cancer and cancer cases, according to PCR-based urine analysis. These results imply that urine is not only a practical, noninvasive diagnostic tool but also has potential for identifying miRNA biomarkers, which are essential for comprehending the molecular processes underlying the development of cervical cancer and for creating focused diagnostic and treatment plans.The strongest diagnostic efficacy is demonstrated by urine miRNAs, specifically miR-21-5p and miR-199a-5p, which have high sensitivity, specificity, and AUC values. These miRNAs hold great promise for noninvasive cervical cancer detection (Aftab et al., 2021).Urinary miRNAs are perfect for biomarker analysis because they are concentrated in the centrifuged pellet and remain stable in the face of several nucleases. The study confirms that qRT-PCR is a trustworthy technique for precisely measuring urine miRNAs for clinical diagnostic purposes (Mall et al., 2013).
  3. ***Mucus miRNAs Mucus miRNA :*** A cervical mucus miRNA panel may be able to distinguish between patients with cervical intraepithelial neoplasia (CIN) 3 and healthy people, according to Wittenborn et al. (2020). Cervical mucus contains a number of microRNAs (miRNAs), including miR-20b-5p, miR-451a, miR-126-3p, and miR-144-3p. Cervical cancer and its precursor disorders have significantly higher levels of these miRNAs. According to Kawaki et al. (2018), these miRNAs have a high degree of accuracy in detecting cervical cancer and high-grade cervical intraepithelial neoplasia (CIN). Additionally, the five miRNAs(miR-126-3p, miR-451a, miR-144-3p,, miR-55-5pand miR-20b-5p) present in cervical mucus, HPV genotype, and age can be used to generate a nomogram that reliably predicts the risk of cervical cancer and its precursor lesions. For cancer and CIN 3+, the nomogram's accuracy is 0.983 and 0.966, respectively.

1. **Upregulated and Downregulated miRNAs in cervical Cancer :**

Numerous microRNAs' (miRNAs') expression profiles are markedly changed in cervical cancer, which aids in the growth and spread of the tumor. MiR-21, miR-155, and miR-196a are examples of frequently elevated miRNAs that are linked to increased cell invasion, proliferation, and apoptosis resistance. On the other hand, downregulation of miR-143, miR-145, and miR-218 often results in the loss of tumor-suppressive properties. Gaining knowledge of these miRNA dysregulations can help with targeted therapy, diagnosis, prognosis, and cervical carcinogenesis.

**6.1. *OncomiRs :***

One way to characterize oncogenes is as miRNAs that are significantly overexpressed in cancers. They all appear to act as oncogenes, albeit some have been described in detail. Known as oncomirs, these oncogene miRNAs usually promote tumor growth by negatively inhibiting genes that control cell differentiation or death as well as tumor suppressor genes.[42]. Depending on the stage of cervical cancer development, oncomiR expression patterns can change. Certain dysregulated miRNAs have been linked to particular phases of cervical cancer development, indicating that they may be used as biomarkers for cancer monitoring and categorization. Additionally, via controlling several cellular pathways, oncomiRs contribute to medication and radiation resistance in cervical cancer [43].

Numerous cancer forms have been found to have miRNA-21 as an oncogene. Research has demonstrated that in these malignancies, miRNA-21 inhibits apoptosis while promoting cell invasion, proliferation, and survival [44]. The suppression of tumor suppressor genes, particularly phosphatase and tensin homolog (PTEN) and programmed cell death 4, is the main way that miR-21 induces cancer. It has been shown that when miRNA-21 is blocked or PTEN and PDCD4 are overexpressed, cancer cells undergo apoptosis and tumor growth suppression.[40].

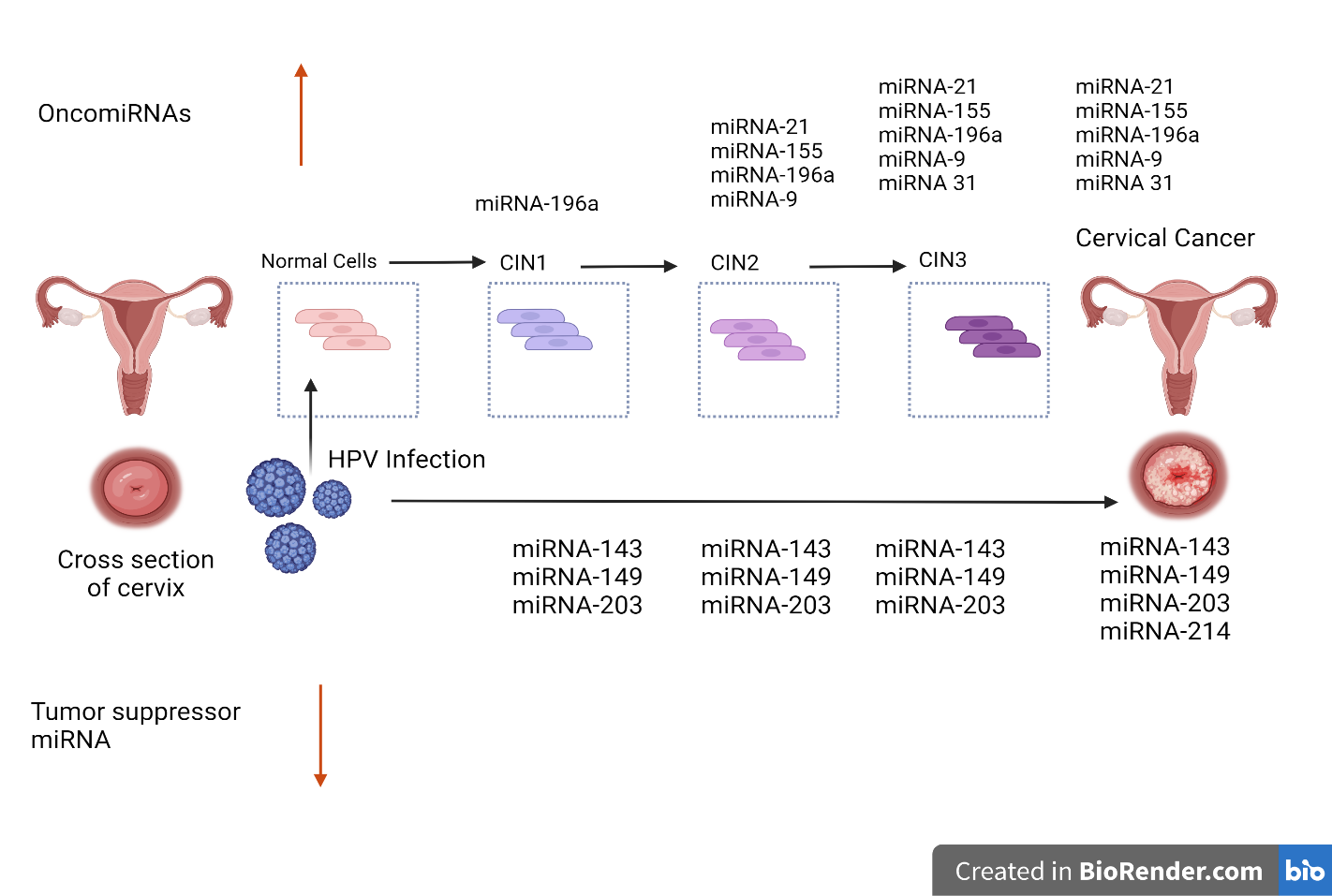
Cervical cancer development is strongly impacted by miRNA-155. Studies have shown that the levels of miRNA-155 were higher in cervical cancer tissues than in non-cancerous tissues that were close by. Overexpression of miRNA-155 promotes cervical cancer cell invasion, migration, and proliferation, whereas downregulation inhibits these processes. LKB1 and other tumor suppressor genes are selectively targeted by miRNA-155, which also suppresses their expression.[47] [48]. At different phases of the development of cervical cancer, there is a marked increase in the expression levels of miRNA-155. In particular, its expression rises in stages two and three of cervical intraepithelial neoplasia (CIN) and even more in invasive cancer [49]. miRNA-196a has an important role in the regulation of many cancers. Studies have shown that miRNA-96a is upregulated in oral squamous cell carcinoma (OSCC), lung cancer, cervical cancer, and hepatocellular carcinoma (HCC). Overexpression of miRNA-196a in several cancer types promotes cell invasion, migration, and proliferation while suppressing apoptosis. MiRNA-196a's carcinogenic effects are mediated by its direct targeting of tumor suppressors such FOXO1 and p27.[50] [51]. There are notable increases in miRNAs 196a expression levels at various stages of cervical cancer progression. Its expression specifically increases in cervical intraepithelial neoplasia (CIN) stages 1, 2, and 3, as well as in invasive cancer. [52]

The development and metastasis of cervical carcinoma are significantly influenced by miRNA-9. It is excessively expressed in Cervical Cancer tissues and cells and may be p53-independently triggered by the human papillomavirus (HPV) [53]. MiRNA-9 stimulates the invasion and migration of cervical cancer cells selectively targeting and blocking FOXO1 [54]. Apoptosis is inhibited and cell division is stimulated by regulating FOXO3 and its downstream proteins Bax, Bcl-2, and p-Akt [55]. At various stages of cervical cancer progression, there is a noticeable rise in miRNA-9 expression levels. Its expression specifically increases in cervical intraepithelial neoplasia (CIN) stages two and three, and it increases even further in invasive carcinoma.[49].

MiRNA-31 is an oncogenic factor in head and neck squamous cell carcinoma (HNSCC) and cervical cancer. MiRNA-31 is increased in Cervical cancer and targets BAP1 to induce the epithelial-mesenchymal transition, accelerating tumor development and metastasis [56]. Likewise, miRNA-31 increases oncogenicity and stemness in HNSCC by targeting ARIDIA. Several miRNAs, including miRNA-31, have been identified as dysregulated in Cervical Cancer and may serve as biomarkers for prognosis, early identification, and therapy response tracking [58]. There is a marked increase in miRNA-31 expression levels at different phases of cervical cancer progression. In particular, its expression elevates in invasive cancer and cervical intraepithelial neoplasia (CIN) 3 [59].

**6.2. Tumor suppressor miRNA :**

Certain miRNAs are downregulated in malignant cells during oncogenesis. Tumor suppressor gene includes these kinds of miRNAs. By adversely affecting oncogenes and genes that regulate cell differentiation or death, tumor suppressor miRNAs typically stop tumor growth [60]. In many cancer types, these miRNAs are frequently downregulated, which increases the expression of their target genes and speeds up the growth of tumors. For example, miRNA-152 targets gene involved in cell invasion, migration, and proliferation and is a tumor suppressor in a number of malignancies [61].miRNA-143 has an important role in cervical cancer progression. In cervical cancer cell lines and tissues, it is significantly downregulated in comparison to normal controls. Mi143 inhibits tumors by promoting apoptosis and inhibiting cell invasion, migration, and proliferation [62]. According to research, over-expression of miRNA-143 dramatically decreased the proliferation and boosted apoptosis of cervical cancer cells by indirectly targeting B-cell lymphoma-2 (Bcl-2) [63]. There is a noticeable rise in miRNA-31 expression levels at various stages of cervical cancer growth. Its expression is especially elevated in cervical intraepithelial neoplasia (CIN) and invasive carcinoma 123 [64].

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***Figure 3 :* Dysregulated miRNAs in the Cervical Cancer Progression**

Both cervical cancer tissues and cell lines exhibit down regulated levels of the tumor suppressor miRNA 149. In vitro, miRNA-149 expression restoration promotes cell death and suppresses invasion, migration, and proliferation. Furthermore, miRNA -149 overexpression inhibits Cervical Cancer cell proliferation in vivo. The G-protein coupled receptor (GPCR) kinase interacting protein-1 (GIT1) plays a crucial role in controlling lamellipodia generation, cell migration, and focal adhesion. It has been determined that miRNA-149 directly targets and negatively regulates GIT1. MiRNA-149 adversely regulates the PI3K/AKT/ mTOR pathway, which is involved in the process [65]. At different phases of the advancement of cervical cancer, there is considerable increase in the expression levels of miRNA-149. Its expression specifically rises in invasive cancer and cervical intraepithelial neoplasia (CIN) 123.

In cervical carcinoma, miRNA-214 has been found to be tumor suppressor. Its low expression is linked to poor tumor differentiation and advanced tumor stage, and it is downregulated in cervical cancer tissues, overexpression of miRNA-214 suppresses cervical cancer cell proliferation by EZH2 and ARL2 [66] [67]. At different phases of the development of cervical cancer, miRNA214 is markedly increased. Its expression specifically rises in invasive cancer and CIN123 [49].

MiRNA-195 plays a crucial role in stopping cervical cancer from spreading. Studies have shown that miRNA-195 is significantly downregulated in cervical cancer cell lines and tissues. Low levels of miRNA-195 are associated with advanced cancer stage, nodal metastases, and deep stromal invasion. In terms of function, miRNA-195 stops cervical cancer cells from invading, migrating, and proliferating. Several direct targets of miRNA-195 have been discovered, including Smad3.[68]. At different phases of the development of cervical cancer, miRNA 195 is markedly increased. Its expression increases in cervical intraepithelial neoplasia 123 and even more in invasive cancer [69].

The progression of cervical cancer is significantly influenced by miRNA-203. According to studies, promotor methylation frequently causes miRNA-203 to be downregulated in cervical cancer tissues and cell lines [70]. By specifically targeting VEGFA and survivin, miR-203 suppresses tumor development, angiogenesis, and cell proliferation [7]. At different phases of cervical cancer's development, miRNA-203 is markedly increased. Its expression increases in cervical intraepithelial neoplasia 123 and even more in invasive cancer [64].

***Table: 1* miRNA's function in controlling apoptosis and cell division in cervical cancer and the target genes linked to it.**

|  |  |  |  |
| --- | --- | --- | --- |
| Target genes for upregulated miRNAs are found at various stages of cervical cancer. | | | |
| All Stages | **miRNA 196a (Foxo1/ p27 kip1)** | | |
| Stage 2,3, and 4 | **MiRNA21 (PDCD4/PTEN)** | **miRNA 155 (LKB1)** | **miRNA 9 (FOXO3/PDCD4)** |
| Stage 3 and 4 | **miRNA 31(ARID1A)** | | |

***Table: 2* The function of miRNA in controlling cervical cancer's cell division and death as well as the target genes linked to it.**

|  |  |  |  |
| --- | --- | --- | --- |
| Downregulated miRNAs present at different stages of cervical cancer with their target genes | | | |
| All Stages | MiRNA-143  (Bcl-2/HIF-1α) | MiRNA-149  (GIT1) | miRNA -203 (VEGFA/Survivin**)** |
| Stage 2,3,4 | SMAD-3 | | |
| Invasive Carcinoma | EZH2/ARL2 | | |

**Conclusion:**

This review emphasizes the critical role that miRNAs play in HPV infection-related cervical cancer initiation and progression. HPV mostly causes cervical cancer, particularly high-risk strains 16 and 18, whose oncoproteins E5, E6, and E7 have a major impact on miRNA expression and synthesis. HPV promotes carcinogenesis by interfering with normal gene regulation and modifying cellular miRNA processing machinery, including DROSHA. For the prognosis and diagnosis of cervical cancer, serum/plasma, urine, and mucus miRNAs are reliable, non-invasive biomarkers. High sensitivity and specificity are displayed by dysregulated miRNAs, such as miR-21-5p, miR-199a-5p, miR-145, and others, which offer information on the course of the disease and the effectiveness of treatment. Through sophisticated predictive models, cervical mucus miRNAs improve diagnostic accuracy when paired with HPV genotype and age. These findings highlight the importance of miRNAs in comprehending the pathophysiology of cervical cancer and creating focused diagnostic and treatment strategies. Among the examined miRNAs, miRNA-196a was a significant oncogenic miRNA consistently raised at all stages of cervical intraepithelial neoplasia (CIN1, 2, 3 and invasive carcinoma). Its extensive overexpression emphasizes how important it is for HPV-driven transformation and tumor growth. However, only at CIN-4 stages was the tumor suppressor miRNA-214 shown to be downregulated, highlighting its potential role in the later stages of the disease. The prior studies showed that miRNAs are actively controlled at different phases of cervical cancer, and that specific miRNAs, such as miRNA-196a and miRNA-214, function as reliable predictors of the disease’s growth. Their potential for diagnosis and treatment is highlighted by the distinct expression patterns of OncomiRNAs and tumor suppressor miRNAs across the stages of CIN. Despite these promising findings, challenges remain in translating miRNA-based research into therapeutic applications. To validate miRNA biomarkers in bigger cohorts, comprehend the molecular interactions of miRNA biomarkers with HPV oncoproteins, and create effective miRNA-targeting treatment approaches, more research is required. To sum up, miRNAs present a revolutionary approach to enhancing the management of cervical cancer. Their potential as therapeutic targets and biomarkers for early diagnosis makes precision medicine development and improved clinical outcomes for patients with cervical cancer viable.

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