MICRORNA AS MARKERS INVOLVED IN THE PROGRESSION OF CERVICAL CANCER

Abstract

The most communal cancer-related cause of fatality in women in emerging nations is cervical cancer (CC). Persistent infection with hr-HPV primarily 16/18 is acknowledged as major risk factor for cervical carcinogenesis. However, the fact that only a small number of women who have morphologic manifestations of HPV infection develop invasive illness suggests the presence of additional variables in the development of CC. Conserved tiny ncRNAs termed as miRNAs, control the genes expression, comprising those intricate in basic living processes and human cancer. MiRNA Dysregulation has frequently been linked to CC. Evaluating the miRNAs impacted by the infection process of HPV and the miRNAs that support the growth and upkeep of malignant cervical tumour cells are the main objectives of this study.

Keywords: Cancer progression, Cervical cancer, Cervical intraepithelial neoplasia (CIN) lesions, HPV infection, Microarray, microRNA, qPCR.

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I. INTRODUCTION

As per WHO, CC recognized as 4th most common malignancy with approximately 604,127 newly diagnosed cases and 341,831 deaths worldwide (1, 2). Surprisingly, 90% of CC cases occur in low- and middle-income nations (3). In India, 365.71 million women over the age of 15 are thought to be at risk for CC. Approximately 132,000 new cases of CC are diagnosed annually in India, and 74,000 of those cases result in death, making up roughly one-third of all CC deaths worldwide. Indian females have an annual risk of CC of 2.5 percent and n annual risk of CC mortality of 1.4 percent (4).

SCC, which accounts for 70–80% of cases, and AC, which occurs in 10%–25% of cases, are the two clinical subtypes of cervical tumours (5). Malignant adenoma, clear cell carcinoma (CCC), endometrioid carcinoma (EC), PAC, ACC, ASC, and UDC are a few other uncommon cervical tumours that indicate a wide range of histological types. These tumours account for >1% of freshly diagnosed cases (5).

The foremost menace factor for the CC development is persistent infection with HR-HPVs (6). E6 and E7, oncogenic viral proteins, are expressed by HR-HPVs and are accomplished of composing a variety of molecular pathways that may lead to the development of malignant illness. Merely a few females with morphologic manifestation of infection by HR-HPV proceed to invasive illness, despite the fact that HR-HPV infection is a required cause of CC (6). Intraepithelial lesions, which are frequently histologist categorized as CIN grade 1-3, can develop as a result of persistent infections. In 30 years, almost 1/3rdof CIN3 cases progress to invasion (7). CIN1 and CIN2, which usually recur, are thought to be morphologic manifestations of HPV infection, respectively (8). Only a portion of the mechanisms underlying carcinogenesis are known. As a result, more tumour advocate elements must be active. Understanding of these characteristics is essential for initial detection and may aid in more effective CC therapy and prognosis.

The majority of research focuses on the genomic dysregulation of host-cell proteins linked to accelerating cervical tumorigenesis. Exploration has recently focused on ncRNAs, particularly miRNAs and they are small, double-stranded, 19 to 24 nucleotides long and highly conserved (9). They undesirably regulate coding genes expression by forming hybrids with complementary or nearly complementary sequences found in the 3′-UTR of target mRNAs. Such binding specifically prevents translation or promotes mRNA breakdown (10). MiRNAs are crucial regulators of numerous cellular pathways linked to the emergence of cancer because of their roles.

II. MIRNA AND CANCER

The majority of miRNAs play a role in the control of basic processes in biology, including cell cycle (11), apoptosis (12), proliferation (13), inflammation (14), differentiating themselves (15), and immune response (16). MiRNAs perform a wide variety of functions, and when these functions are dysregulated, it has significant effects on cellular outcomes and contributes to the emergence of a variety of diseases, encompassing tumours(17), autoimmune ailments (18), disorders of the brain (19), cardiovascular diseases (20).

III. CERVICAL CANCER MIRNA SIGNATURE

In tumours, aberrant miRNA expression is frequently seen (21). The dysregulated miRNA, comprising the up-regulated and the down-regulated, was associated with ICC development.MiR-21, one of the up-regulated miRNAs, has been linked to the progression of CIN and ICC (22, 23, 24). One of the most frequently expressed miRNAs in mammals, miR-21, has a demonstrated association with several cancers (25). Both E6 and E7 may be responsible for enhanced miR-21 expression. Ras-MeK-ERK pathway, which PTEN tumour suppressor, a target of miR-21, regulates, can feed back on viral E6 and E7 (26).

Additionally, the over expressed miRNA in the aetiology of cervical tumorigenesis encompasses miR-9, miR-10a, miR-16, miR-20b, miR-25, miR-27a, miR-31, miR-92a, miR-92b, miR-93, miR-106a, miR-146a, miR-155, miR-185, and miR-196a, miR-200a, and miR-378 (27, 28, 29).

In tissues infected by hr-HPV and CIN2 or CIN3, miR-218 was shown to be the miRNA that was most significantly down regulated (30, 31). Additionally, miR-29a expression diminished in CIN and ICC (32). By inhibiting the CDC42-PAK1 signalling pathway, the miR-29a has been demonstrated to reduce cell migration and proliferation, which protects against CC (33). Additionally, miR-23b, miR-34a, miR-99a, miR-100, miR125b, miR-145, miR193b, miR-203, miR-375, miR-424, and miR-497 have been found to be down regulated in CC (34, 35).

IV. MIRNA AS A BIOMARKER IN EARLY STAGE FOR CC

The current gold standard for detecting HPV-associated dysplasia and CC is histopathology and cytology (Pap smear). These techniques are effective and affordable, but they rely largely on interpretation, specimen recollection, technician training, and their sensitivity is only approximately 50% (36). The addition of HPV testing to cervical cytology, which offers 60–70% more protection against ICC than Pap-smear alone, is one of the most recent revisions to cervical cancer screening recommendations (37).

However, more perceptive methods are required for prompt and accurate diagnosis. For screening of CC, diagnosis, and follow-up, a liquid biopsy-based approach may theoretically constitute a useful additional (or alternative) paradigm (38).Initial stages of cervical tumorigenesis are typically asymptomatic, and the symptoms of advanced CC are universal and shared by a number of illnesses, necessitating the urgent need for markers that show the presence of CD in the early stages (39). MiRNAs might be thought of as cervical cancer prognostic biomarkers because they are very stable ncRNA species compared to mRNAs and some IncRNAs and have a comparatively high average half-life (5 days on average) (40).

Park et al. investigated the prospective clinical significance of specific miRNAs in tissue specimens of cervix and showed the likely of miR-21 and miR-155 in combination with an assay of HPV E6/E7 mRNA as biomarkers for the diagnosis and management of both HPV+ and HPV- LSILs and cervical tumours (41).

V. CONCLUSION

Considering whether miRNA signatures may be linked to present and forthcoming CIN menace in the context of ICC screening may require combining them with additional biomarkers. To decrease CC mortality and achieve successful care, the clinical repercussions of miRNA-based diagnostic as well as therapeutic techniques are essential.

Therefore, more research is needed to understand how miRNAs contribute to the development of CC and the mechanisms by which they control cellular processes that promote tumorigenesis. These researches may offer sufficient support for the use of miRNAs as CC therapy agents, prognostic biomarkers, and diagnostic biomarkers.

VI. ABBREVIATIONS

- CC: cervical cancer
- ncRNAs: non-coding RNAs
- miRNAs: microRNAs
- HPV: Human papilloma virus
- Hr-HPV: High risk Human papilloma virus
- SCC: Squamous cell carcinoma
- AC: Adenocarcinoma
- CCC: Clear cell carcinoma
- EC: Endometrioid carcinoma
- PAC: Papillary adenocarcinoma
- ACC: Adenoid cystic carcinoma
- ASC: Adenosquamous carcinoma
- UDC: Undifferentiated carcinoma
- CIN: Cervical intraepithelial neoplasia
- CD: Cervical dysplasia

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