CANCER STEM CELLS IN CERVICAL CANCER AS BENEFICIAL GOALS AND BIOMARKERS: A COMPREHENSIVE

Pushpendra D. Pratap*, Syed Tasleem Raza*, Ale Eba, Muneshwar Rajput**, Alok Kumar Singh*****

Department of Biochemistry, Department of Biotechnology**, Department of Pathology****

King George's Medical University, Lucknow, Uttar Pradesh, India - 226003***.

Era's Lucknow Medical College and Hospital, Era University, Sarfarazganj Lucknow, U.P., India-226003*,**.

Received on : 10-10-2023
Accepted on : 31-10-2023

Address for correspondence

Dr. Pushpendra D. Pratap
Department of Biochemistry
Era's Lucknow Medical College &
Hospital, Era University, Lucknow-226003.
Email: pushppratap67@gmail.com
Contact no: +91-

ABSTRACT

The fourth most prevalent gynaecological malignancy affecting females globally is cervical cancer (CC). HPV (high-risk) infection has been related to the majority of CC cases. Owing to efficient screening through Pap smear and vaccination delivery, the commonness and death rate of CC have significantly decreased. Nevertheless, not all societies have access to this equally. A better therapeutic outcome may be achieved by targeting CSCs, which might play a significant impact in carcinogenesis, metastasis, recurrence, and radio / chemo –resistance of CC. The majority of tumours are made up of a tiny subset of tumour cells called CSCs that have the capability to self-renew and develop into a variety of tumour cell types. Cervical CSCs (CCSC) are challenging to recognise, which has prompted the hunt for other markers. The potential indicators of CSCs in CC are described in the current review. These CCSC indicators might be used as molecular goals to improve the effectiveness and lessen the negative effects of chemotherapy in HR-HPV-positive CC.

KEYWORDS: HPV, CC, CSC, CCSC.

INTRODUCTION

The second most frequent disease in the world, and most lethal evils for women is CC (1). It is ranked 4th prevalent type of cancer overall and recurrently affects the inferior portion of the cervix, damaging healthy epithelial tissues of cervix and bringing about abnormal variations in the deeper tissues (2). As per WHO, CC recognized as 4th most common malignancy with approximately 604,127 newly diagnosed cases and 341,831 deaths worldwide (2-3). Surprisingly, 90% of CC cases occur in low- and middle-income nations (4). In India, 365.71 million females above the age of 15 are thought to be a menace for CC. Approximately 132,000 fresh cases of CC are diagnosed annually in India, and 74,000 of those cases result in death, making up roughly 1/3rd of all CC fatalities globally. Indian females have an annual risk of CC of 2.5 percent and n annual risk of CC mortality of 1.4 percent (5). The foremost menace factor for the CC development is persistent infection with HR-HPVs (6). E6/E7, oncogenic viral proteins, are articulated 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. The primary biological variables linked to the emergence of CC are HPV16 and HPV18 (7). CC is still a significant worldwide health concern despite scientific advancements in primary as well as secondary deterrence (vaccine, HPV detection, and cure of precancerous lesions, correspondingly). The lack of effective vectors is the fundamental reason the clinical translation to humans is currently behind schedule. Therefore, the development of innovative agents is crucial for improving therapeutic outcomes. The impact of CCSCs as it is presently understood is covered in this review, as well as how they can serve as therapeutic objects to improve the therapy of CC.

CSCs are a tiny fraction of tumour cells with the capability to self-renew. Tumours' diverse cellular makeup results in extreme genetic and epigenetic variety, which generates a wide range of biological variables that can contribute to a deprived prognosis and low existence proportions (8). A crucial player in these processes is the cancer stem cell (CSC). The capability to create both differentiated and indistinguishable tissue-maintaining cells, as well as controlled self-renewal, characterises stem cells in

normal tissues. They support cell differentiation and tumour progression. CSC populations from various tumours, comprising CC, have been isolated and enriched using cell outward indicators and transcription elements such as ALDH1, CD44, Nanog, and Oct4 (9-10). Spherogenesis, resistance to cytotoxic medications, and ionising radiation are all factors that CSCs play in the tumorigenic potential of cancer (11).

METHODOLOGY

Search Strategy: We conducted a thorough search of databases such as PubMed, Scopus, and Web of Science, identifying papers published up to the time of our knowledge. Keywords included in our search were "ALDH1," "CD44/CD26," "ALDH1," "CD133," "Cervical carcinoma," and "immunohistochemistry." We only included peer-reviewed studies in English.

Inclusion and Exclusion Criteria: Studies that investigated ALDH1, CD44/CD26, Oct 3, and/or CD133 immunoexpression in cervical carcinoma, provided data on clinicopathological characteristics, prognosis, or therapeutic implications, involved human subjects, and were published in peer-reviewed journals met our inclusion criteria.

Finding the molecular pathways pertaining to stemness has required a great deal of research, which is not surprising considering the significance of CSCs in the etiology of cancer. Similar to regular stem cells, CSCs possess genetic traits and pathways that are usually associated with proliferation (12). The atypical appearance of transcription factors OCT3/4, SOX2, NANOG, and c-Myc (13), along with the activation of the Hedgehog, β-catenin, Notch, and PI3K signaling pathways (14), provide a representative set of characteristics that uphold the stem cell phenotype in CSC and promote interventions. On the other hand, disruptions of SC self-renewal and DNA damage processes have been linked to mutations impacting the tumour suppressor genes TP53, PTEN, and INK4A-ARF locus. (12).

There are a number of hypotheses about how CSCs originated because SCs and CSCs are similar. Somatic cells and SCs can also be affected by DNA mutations; as a result, crucial changes can object SCs and create CSCs with a great tumor-genicity. The probability of DNA alterations in malignant progenitor cells that object stemness genes and convert precursor cells into CSC is another option (15). CSCs might, however, be latent up until the start of carcinogenesis (16, 17), leaving them in place. As previously indicated, CSCs play a role in encouraging cancer spread because of their ability to migrate and invade distant tissues. Tumor-associated CSCs have been linked to poor outcomes and high rates of metastasis, according to prior research (16, 18, 19). Metastatic cells are thought to primarily originate from EMT. Transcriptional regulators with high levels of expression in CSCs, including SNAI1, SNAI2, TWIST1, and BMI1, are responsible for this cell's metamorphosis. Epithelial adhesion and apical-basal polarity are lost as a result of the EMT, allowing altered cells with CSC properties to enter the circulatory system (20).

Cancer Stem Cells In Cervical Cancer

Squamous and columnar cervical neoplasia are the outcomes of HPV infection in the TZ of the cervical epithelium. These cells are thought to be the SCs of the cervical epithelium; they are the targets of the virus because they display the external markers CD44, CK17, CD49f, and CD133 on the cell membrane (9, 18, 21).

Target cells become infected with HR-HPV when viruses connect to cell surface receptors, internalising the virus as a result. Endosomes and endo/lysosomes release viral DNA, which is then transferred to the cell nucleus (22, 23). Following that, the synthesis of viral oncoproteins (including E6 and E7) begins. The endogenous tumour suppressor proteins pRb and p53, respectively, are inhibited by E7 and E6, which encourage the propagation of infested SCs (24). Sox2 and Oct3/4 repression is stopped by the degradation of pRb (25). Similar to how HRHPV E6's degradation of p53 results in higher levels of Nanog expression, this is true (26).

Experimental methods, such as the separation of tumour cell subpopulations, the detection of outward indicators, and the relocation of these compartments into the suitable animal models, are commonly used in research to discover CSCs in CC (27). To distinguish and separate CSCs from tumour cell populations, the outward indicators CD26, CD34, CD44, CD90 and CD133, are utilised. These cells also have the capacity to spread, invade, and defy chemotherapy (28). The following have all been utilized to identify CCSCs as potential markers of cervical epithelial stem cells: ALDH1, MSI1, SOX2, and CD49f (21). Other markers like as CK-17, CD44, CD133, and Oct3 & 4 have also been utilized to detect CCSCs, in addition to SOX2, MSI1, ALDH1, and CD49f (29). This subgroup's existence could be useful in predicting the prognosis and chemoresistance of patients with cervical cancer. Furthermore, CCSCs may be therapeutic targets for new medications that improve chemotherapy's efficacy for people whose tumors are resistant to it.

SOX2 and OCT4

transcription factors are encoded by SOX2, a member of the SOX gene family that affect cell fate and differentiation and are active during embryonic development. When SOX2 expression in healthy and sick cervix tissues was investigated in "tumour spheres," differentiated cells confirmed the protein's involvement in the development of cancer, suggesting that SOX2 might be a potential therapeutic target molecule (30). OCT4 inhibits apoptosis and encourages cancer in vitro (31). In CC cells, high OCT4 expression is linked to positive lymph node metastases and low differentiation. Elevated OCT4 expression is linked to resistance to chemotherapy and radiation and poses a separate risk for the survival of cancer patients (31).

Aldehyde Dehydrogenase 1

An effective CCSC marker is ALDH1, an enzyme implicated in the early phases of SC synthesis and retinol oxidation. Its expression in tissues from invasive squamous carcinoma and adenocarcinoma was investigated using immunohistochemistry (IHC). It was found that HeLa, CaSki, and SiHa cells were reactive to ALDH1. ALDH1-expressing cervical cancer cells have a high rate of cellular proliferation and carcinogenesis. (32). Moreover, studies conducted in vivo have demonstrated that cells with elevated ALDH expression levels possess a high propensity to tumor, suggesting that ALDH functions as a stemness factor in cervical cancer (32).

Recent years have seen a significant amount of research conducted on CSC-targeted therapy in an attempt to improve current cancer treatment approaches and prevent cancer relapse. Unfortunately, there haven't been many studies done on some CCSC-focused medications up to this point. Generally speaking, we'll discuss CSC-targeted medications, which could shed some light on prospective CCSC-targeted treatment approaches. While many CSC targeting approaches are being investigated, the majority of therapeutic targets have been CSC-specific markers and signaling pathways.

CONCLUSION

Several studies have attempted to deepen our knowledge of the molecular pathophysiology of CC and the progression of virus-related infections into an aggressive malignancy. However, more recent research have sought to identify the variables and molecular changes that are associated with the stemness and expansion of CC. The bulk of these investigations have attempted to confirm that the HPV infection is the cause of CC. In this regard, accumulating data point to the CCSCs as an innovative, ultimate, and intentional critical component to be taken into account in the progress of cancer, the emergence of chemotherapeutic resistance, and the regression of cancer. The most widely recognised theory for the development of CCSCs proposes that SCs are transformed by HPV infection via their oncoproteins. Nevertheless, a sizable numeral of proteins have as their primary function the preservation of stemness in sound cells. However, proteins including SOX2, OCT4, NANOG, Klf4, and Nestin are too important for keeping CSCs stem-like. To find new targets connected to the stemness of CC cells, numerous research teams are working very hard right now. Consequently, Considerations include genes, proteins, and signaling pathways.. In this regard, the data presented in this review compiles a number of viable candidates to carry out the challenging duty of CCSC development control. The Hedgehog, PI3K, Wnt, or Notch signalling pathways could thus be blocked in CCSC by targeting CD44, CD133, and CD49f as excellent targets for therapeutic intervention.

ABBREVIATIONS

ALDH 1: Aldehyde dehydrogenase 1

CD44: Cluster differentiation 44

CSCs: Cancer stem cells

CCSCs: Cervical cancer stem cells

CC: Cervical cancer

HPV: Human papilloma virus

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Orcid ID:

Pushpendra D. Pratap - https://orcid.org/0000-0002-7660-448X

Syed Tasleem Raza - https://orcid.org/0000-0003-1248-8974

Ale Eba - https://orcid.org/0000-0002-9469-8619

Muneshwar Rajput - https://orcid.org/0000-0001-5251-3498

Alok Kumar Singh - https://orcid.org/0000-0001-5251-3498

How to cite this article:

Pratap P.D., Raza S.T., Eba A., Rajput M., Singh A.K. Cancer Stem Cells In Cervical Cancer As Beneficial Goals And Biomarkers: A Comprehensive. Era J. Med. Res. 2023; 10(2): 51-55.