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" Molecular Markers of Cervical Cancer Stem Cells "

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ABSTRACT:
Cervical cancer remains the leading cause of cancer-related mortality among women, despite the existence of screening and vaccination programs. While treatments such as surgery and chemotherapy can extend the lives of patients, they do not offer a permanent cure. Radical surgery is often required for advanced-stage cervical cancer, but this comes with the risk of impairing fertility and potential recurrence of the disease. Hence, there is a critical need to develop new therapeutic strategies. According to the Cancer Stem Cell (CSC) theory, tumors are organized hierarchically, with a small group of cells known as cancer stem cells playing a significant role in tumor development. These CSCs are key contributors to tumor metastasis, recurrence, and resistance to radiation therapy, highlighting their importance in the initial stages of cancer spread. Among the most significant gynecological cancers, cervical cancer is known for its high mortality rate. Consequently, research into cervical cancer has increasingly focused on stem cells associated with the disease. This review explores the role of CSCs and Cervical Cancer Stem Cells (CCSCs) as important factors in the early detection and potential therapeutic targets for cervical cancer.

KEYWORDS:
Cervical Cancer, Cancer Stem Cells, Cervical Cancer Stem Cells, Human Papillomavirus (HPV), Tumorigenesis, Radiation Resistance.

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I. INTRODUCTION:

Cervical cancer ranks as the fourth most prevalent cancer among women worldwide. In 2012 alone, approximately 528,000 new cases were reported, leading to an estimated 266,000 deaths. A significant proportion of these cases have been linked to infections caused by the Human Papillomavirus (HPV) [1–4]. In a pivotal study conducted in 1999, Walboomers and colleagues detected HPV DNA in 99.7% of cervical cancer samples, firmly establishing the virus as a major etiological factor. However, not all HPV infections progress to cervical cancer. The transformation from infection to malignancy typically spans 10 to 15 years and is influenced by various risk factors, including early sexual debut, multiple sexual partners, prolonged use of oral contraceptives, smoking, and co-infection with *Chlamydia trachomatis* [5–7]. Research by Ferlay and collaborators indicated that about 87% of cervical cancer-related fatalities occurred in low- and middle-income countries, with India alone accounting for roughly 25% of these deaths in 2012. These disparities are often attributed to socioeconomic challenges. In wealthier nations, the introduction of routine screening programs and HPV vaccines has significantly reduced cervical cancer mortality. However, in resource-limited settings, the high cost of vaccination programs has hindered their widespread implementation. Treatment strategies for cervical cancer depend on the stage at diagnosis, with early-stage cancers generally managed through radiotherapy and chemotherapy, while advanced stages may require surgical intervention. Recent studies have increasingly focused on the cancer stem cell (CSC) theory, which proposes that a subset of cancer cells with stem-like properties drive tumor initiation, progression, and recurrence. Cap and Dick first identified CSCs in acute myeloid leukemia in 1997. Since then, their presence has been confirmed in solid tumors, including those of the breast, brain, pancreas, liver, lung, colon, and prostate. CSCs possess the ability to self-renew and differentiate, similar to normal stem cells, but they also exhibit notable resistance to conventional treatments like chemotherapy and radiation [9–13]. Unlike somatic stem cells, the exact mechanisms by which CSCs respond to genetic and environmental cues remain poorly understood. Their resilience makes them key contributors to cancer relapse, emphasizing the importance of targeting CSCs in order to achieve lasting cancer remission [14–16].

II. LITERATURE OF PAPER:

Sharmila A. Bapat-2008: This book provides an in-depth exploration of cancer stem cells (CSCs), including their identification, characteristics, and potential as therapeutic targets. While it covers CSCs across various cancer types, it offers valuable insights into the molecular markers.

III. ORIGIN OF CERVICAL CANCER:

The cervix is composed of three primary types of epithelial cells: squamous epithelial cells located in the ectocervix, mucus-secreting glandular cells lining the endocervix, and metaplastic cells situated at the junction between the ectocervix and endocervix. This transitional area, known as the squamo-columnar junction or transformation zone, plays a critical role in cervical biology. The ectocervical epithelium is stratified into four layers: basal, parabasal, intermediate, and superficial layers [17–19]. The superficial layer continuously sheds cells, while the basal layer, containing undifferentiated epithelial cells with stem-like characteristics, replenishes the lost cells through regeneration. Cells of the endocervix are characterized by the presence of cilia and mucus secretion, aiding in the transportation of sperm. HPV (Human Papillomavirus) infections often target the stem-like cells located in the transformation zone, which possess unique gene expression profiles different from other epidermal cells. The cervical epithelium is structured with basal stem-like cells at the base and terminally differentiated cells at the surface. When injury occurs in the cervical epithelium, basal cells activate, proliferate, and differentiate to repair the damage [22–24]. These stem-like cells play a crucial role in the initial stages of HPV infection. Normally, stem cells divide asymmetrically, but upon HPV infection, this division shifts to a symmetric pattern, enhancing proliferation and viral particle production while suppressing cellular differentiation. High-risk HPV strains promote this abnormal proliferative behavior and inhibit differentiation, setting the stage for oncogenic transformation. The viral infection itself is not immediately cancerous but rather induces sustained proliferation of infected cells, eventually disrupting DNA repair mechanisms and contributing to malignant transformation. This understanding suggests that cervical cancer development begins with stem-like cells long before the cancer stem cell (CSC) model was widely accepted. It is hypothesized that HPV-infected progenitor cells initiate the transformation into malignant stem-like cells. Several signaling pathways associated with stemness—such as Notch, Wnt, Hedgehog, and BMI1—have been implicated in the pathogenesis of cervical cancer. Oncogenic HPV infection has a well-established causal relationship with cervical cancer development. However, it has been observed that cervical intraepithelial neoplasias (CINs) and invasive carcinomas most commonly originate from a specific population of cells at the squamo-columnar (SC) junction of the cervix [30–32]. These lesions rarely arise from the columnar epithelium of the endocervix or the squamous cells of the ectocervix. Instead, the SC junctional cells retain a unique genetic and cellular profile that is preserved in HPV-associated CINs and carcinomas, supporting the hypothesis that these cells act as progenitors. Once these SC junctional precursor cells are infected by high-risk HPV types, they may transform into pre-neoplastic stem-like cells and eventually give rise to cervical cancer stem cells (CCSCs), which drive tumor progression. Therefore, therapeutic strategies that specifically target this cell population could be key to preventing the development and spread of HPV-induced cervical precancerous and cancerous lesions.

IV. CANCER STEM CELLS:

Cancer stem cells (CSCs) are a small subpopulation within tumors that exhibit key characteristics such as the ability to self-renew, initiate tumor formation, differentiate into multiple cell types, and maintain a slow-cycling state. Recent advancements in research have enabled the in vivo identification of CSCs and their progeny, providing strong evidence for their role in tumor persistence and progression. One of the defining features of CSCs is their asymmetric division. This process results in two daughter cells: one that retains the stem-like properties of the original CSC and another that resembles differentiated cancer cells. This division ensures a balance between maintaining the CSC pool and generating diverse cancer cell populations. The ability of CSCs to self-renew and initiate tumor growth makes them central to cancer development, recurrence, and metastasis. Due to their unique biological behavior and heterogeneity, CSCs contribute significantly to therapy resistance. They often reside in specialized microenvironments known as CSC niches, which protect them from conventional anti-cancer therapies. Within these niches, a tightly regulated balance of activation, self-renewal, and differentiation is maintained. However, under stress conditions—such as those induced by chemotherapy—CSCs may become activated, migrate to different tissues, and differentiate into aggressive cancer cells. Both in vitro and in vivo studies have led to the identification of specific markers associated with CSCs. These markers are being investigated as potential therapeutic targets. Nevertheless, the complex and diverse biology of CSCs remains a major challenge. Tumor heterogeneity across patients also complicates treatment strategies, as CSC markers tend to vary between cancer types and even among individuals with the same type of cancer. This variability underscores the need for personalized approaches to effectively target CSCs and improve patient outcomes.

V. CERVICAL CANCER STEM CELLS:

Due to limitations associated with functional assays, both in vitro and in vivo studies have increasingly focused on identifying reliable stem cell markers to detect and characterize cancer stem cells (CSCs) [2, 15, 45, 46]. As a result, the identification of CSC-specific markers has become a practical approach for recognizing these cells. However, while molecular assays are helpful, they often fall short of fully characterizing CSCs. In the case of cervical cancer, a number of novel CSC markers—specific to cervical cancer stem cells (CCSCs)—have

recently gained attention as promising targets for diagnosis and therapy. This section outlines key markers currently under investigation.

VI. CANCER STEM CELL MARKERS IN CERVICAL CANCER:

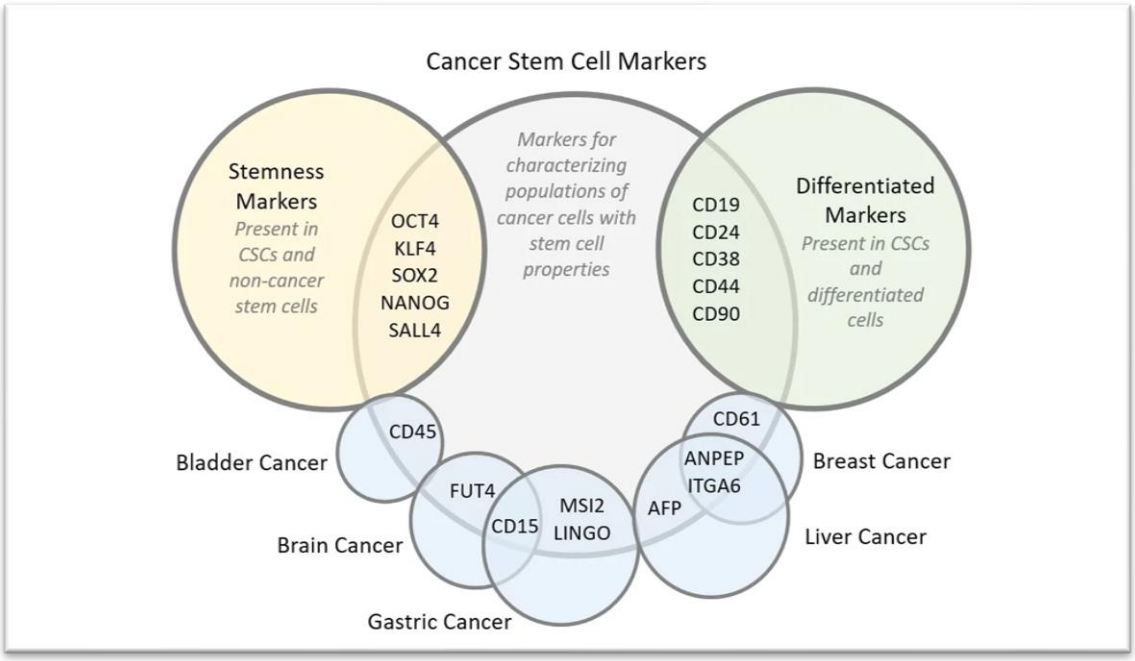

FIGURE : 1 : CANCER STEM CELL MARKERS

6.1.OCT4:

The POU class 5 homeobox 1 gene encodes the transcription factor OCT4 (also known as OCT3/4), which plays a vital role in maintaining the pluripotency of embryonic stem cells. In cervical cancer, OCT4 expression is significantly higher in tumor tissues compared to adjacent normal tissues [49–51]. Overexpression of OCT4 has been associated with poor differentiation, lymph node metastasis, and decreased survival rates in cervical cancer patients. Furthermore, clinical studies suggest that OCT4 contributes to resistance against radiation therapy, making it an independent prognostic factor. Experimental studies also confirm OCT4's involvement in promoting tumorigenesis in cervical cancer cell lines.[11][17][19]

6.2.CD133:

CD133, also known as prominin-1, is a 120-kDa pentaspan transmembrane glycoprotein encoded by the *PROM1* gene. Widely recognized as a CSC marker in various cancers such as brain, colon, liver, breast, lung, melanoma, and ovarian tumors, CD133 has also been identified in cervical cancer stem-like cells. Its expression correlates with treatment resistance, particularly to radiation, making it a valuable target in CSC-directed therapies.[18][27][34]

6.3.CD49f:

CD49f, encoded by the *ITGA6* gene, is an integrin alpha-6 subunit found predominantly in human embryonic and mesenchymal stem cells. Elevated expression of CD49f has been detected in specific CCSC models, and its presence is linked to increased resistance to radiation. This highlights its potential utility as a biomarker for identifying aggressive and treatment-resistant cervical cancer stem cells.[43]

6.4.ALDH1:

Aldehyde dehydrogenase 1 (ALDH1) is a cytoplasmic enzyme involved in the detoxification of intracellular aldehydes through oxidative metabolism. It plays a critical role in cellular homeostasis and has been widely recognized for its involvement in tumorigenesis and self-renewal, especially in breast cancer. Research indicates that CSCs expressing ALDH1 are capable of generating effective patient-derived xenografts in primary breast tumors. In clinical samples, high ALDH1 expression is often associated with poor patient prognosis and reduced overall survival. In the context of cervical cancer, ALDH1 overexpression promotes enhanced cell migration,

proliferation, and sphere formation, reinforcing its potential as a functional marker of cervical cancer stemness.[47]

6.5.ABCG2:
ATP-binding cassette sub-family G member 2 (ABCG2), also known as breast cancer resistance protein (BCRP), is a membrane-bound drug transporter involved in the efflux of a wide range of chemotherapeutic agents. As a key contributor to multidrug resistance (MDR), ABCG2 is frequently overexpressed in various cancers. It is also considered a hallmark of the "side population" phenotype—an important functional characteristic of CSCs. In cervical cancer, ABCG2 expression is regulated by the redox-sensitive transcription factor Nrf2, which contributes to sustained cell proliferation and resistance to apoptosis—both typical features of CSCs. Targeted therapies using inhibitors like Axitinib and Icotinib have shown potential in sensitizing ABCG2-positive cells to chemotherapy, thereby validating ABCG2 as a promising CSC marker for therapeutic intervention.[5][45][85]

6.6.SOX2:
SOX2 (SRY-box transcription factor 2) is a key regulatory protein essential for maintaining the pluripotency of embryonic stem cells and guiding stem cell differentiation. In cervical cancer, SOX2 is markedly overexpressed compared to healthy cervical tissue. Its elevated levels are especially prevalent in poorly differentiated cervical carcinomas, highlighting its potential as a diagnostic marker. Experimental studies have demonstrated that SOX2 overexpression correlates with increased tumor cell proliferation and oncogenic potential in both in vitro and in vivo models. Furthermore, high SOX2 levels are linked with resistance to radiotherapy, particularly in patients with cervical squamous cell carcinoma, indicating its role in treatment failure and disease progression.[14][58][90]

6.7.OSTEOPONTIN (OPN):
Osteopontin (OPN) is an extracellular matrix protein produced by both malignant cells and tumor-associated stromal cells. It possesses chemokine-like properties and plays a significant role in tumor metastasis and cell migration.[18] OPN is considered an endogenous marker of hypoxia, as its expression increases under low oxygen conditions. It binds to hypoxic regions within tumors, where it contributes to tumor progression by facilitating a radiation-tolerant environment. OPN also regulates hypoxia-inducible factor 1 (HIF1)-dependent vascular endothelial growth factor (VEGF) expression, promoting angiogenesis in tumors. In cervical cancer, OPN is overexpressed and its higher levels in blood and serum correlate with poor survival rates, making it a potential prognostic marker for cervical cancer.[20][28][64]

6.8.BMI1:
BMI1 (B lymphoma Mo-MLV insertion region 1) is a key regulator of stem cell self-renewal, primarily by suppressing genes involved in cellular differentiation.[74] Elevated BMI1 expression has been observed in various cervical cancer cell lines, such as SiHa, HeLa, C33a, and CaSki, compared to normal epithelial cells. Further investigations into uterine cervical cancer tissues have confirmed increased BMI1 expression, which correlates with larger tumor size and lymph node metastasis. These findings suggest that BMI1 is involved in cervical cancer progression and may serve as a potential therapeutic target.[56]

6.9.KLF4:
Kruppel-like factor 4 (KLF4) is a transcription factor critical for maintaining cellular differentiation, particularly in the basal cells of the cervical epithelium. In the context of cervical cancer, KLF4 expression decreases as the disease progresses. The transcriptional activity of KLF4 is regulated by the protein P27Kip1, which binds to KLF4's promoter regions, preventing ectopic KLF4 expression. This suppression is important for limiting cell proliferation and inhibiting tumor growth, indicating that the loss of KLF4 expression may contribute to cervical cancer progression.[5][11][19]

6.10.UTF1:
Undifferentiated embryonic cell transcription factor 1 (UTF1) plays a crucial role in the regulation of cell fate during development. Research has shown that reduced expression of UTF1 is linked to cervical cancer progression. This downregulation is often associated with the hypermethylation of the UTF1 promoter. Interestingly, UTF1 behaves similarly to P27Kip1, activating its expression and binding to the promoter regions of P27Kip1 to inhibit cancer cell proliferation both in vitro and in vivo. The loss of UTF1 function, therefore, appears to contribute to cervical cancer development.[1][24][75]

VII. FUTURE PROSPECTS:

The field of Cancer Stem Cell (CSC) research has made significant progress in recent years, but there remain numerous unanswered questions. One of the main challenges is the unclear origin of CSCs. It is believed that epidermal stem cell infection with Human Papillomavirus (HPV) could lead to cervical cancer; however, the disease typically develops years after the initial infection. Gupta and colleagues have highlighted a major limitation of CSC research, which is the difficulty in isolating a pure population of CSCs due to their inherent ability to revert to the characteristics of the original cell samples from which they were derived. This complicates efforts to study CSCs in a more focused and efficient manner. Additionally, various methods for isolating CSCs have proven to be selective, isolating only a small subset of CSCs, though this population shares several key characteristics. Recent studies have shown that CSCs, such as those in the HeLa cell line, exhibit slight increases in CD133 activity, with significant changes observed using the side population (SP) assay. The upregulation of CD133 can impact the results of these studies, indicating a need for more refined methods for CSC isolation. Improving these techniques is critical, as the number of CSCs in a tumor correlates with disease severity. Therefore, detecting CSCs could be valuable not only for early cervical cancer diagnosis but also for assessing the severity of the disease. Furthermore, substantial evidence has demonstrated that CSCs play a key role in disease recurrence, chemoresistance, and metastasis. As a result, further research into the behavior and mechanisms of CSCs in cervical cancer is essential. A deeper understanding of CSCs will lead to improved diagnostic methods and treatment strategies, potentially enhancing the outcomes of cervical cancer patients and paving the way for more targeted therapies.

VIII. CONCLUSION:

Cancer is associated with a small subset of Cancer Stem Cells (CSCs) that exhibit epithelial-mesenchymal phenotypes, as well as non-stem cells displaying epithelial characteristics. CSCs have gained attention as promising therapeutic targets due to their roles in carcinogenesis and self-renewal. Numerous studies have identified the presence of CSCs in cervical tumors, providing valuable insights into the functional status of stem/progenitor cell populations in cervical cancer. These findings highlight the potential of CSCs as early diagnostic markers and therapeutic targets, offering new avenues for treatment. Key markers for CSC isolation, such as ABCG2, SOX2, CD133, CD49f, and ALDH1, have been identified as crucial in understanding the behavior and targeting of CSCs in cervical cancer.

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