International Journal of Current Research in Physiology and Pharmacology
Volume 7, Issue 4; 2023
eISSN: 2523-6709 pISSN: 2523-6695

Stem Cells in Cervical Cancer: An Overview

Mohd Altaf Dar — Department of Pharmacology, CT Institute of Pharmaceutical Sciences, PTU, Jalandhar Punjab

Aslam Hamid Khan — Chandigarh college of Pharmacy Landran Mohali

Cervical cancer has emerged as the leading cause of women's cancer-related deaths despite screening and vaccination programs. Surgery and chemotherapy help patients with cervical cancer live longer, but they do not provide a permanent cure. Radical surgery is the only option in the advanced stage of cervical cancer, which also affects patients' ability to conceive. Sometimes it also causes the disease to return. As a result, new therapeutics must be developed immediately. According to the CSC hypothesis, a tumor has a hierarchical cellular structure with a small subset of cells called cancer stem cells that induce tumorigenesis. The CSCs' tumor-initiating capacity has been the subject of numerous studies. These CSCs are crucial in tumor metastasis, relapse, and radiotherapy resistance. Because they play a role at the beginning of the spread of the tumor, they are thought to improve outcomes. The most well-known gynecological danger is cervical carcinoma, which shows a high malignant growth death rate in females. As a result, research into cervical cancer has increasingly turned to stem cells from the disease. In this review, we have summarized CSCs and CCSCs as emerging key players in cervical cancer early diagnosis and as a therapeutic target in this cancer.

Keywords: Cancer, Cervical Cancer, Cancer Stem Cell, Cervical Cancer Stem Cell, Human Papilloma Virus

Introduction

Among all cancers that affect women, cervical cancer ranks fourth among the most common. 5,28,000 cases of cervical cancer have been identified, resulting in 266,000 deaths in 2012. Cervical cancer has largely been attributed to HPV infection [1-4]. Walboomers and others found HPV infection in 99.7% of cervical cancer specimens in 1999. Cervical cancer is not caused by all HPV (Human Papilloma Virus) infections; however, it takes between 10 and 15 years for HPV to cause cervical cancer. Multiple partners, early sexual activity, long-term use of oral contraceptives, tobacco use, and infection with Chlamydia trachomatis all contribute to the recurrence of HPV infection in the cervical cancer [5-7]. Ferlay and co. have shown that 87% of cervical cancer-related deaths in less developed countries, with only 25% occurring in India in 2012, have been attributed to socioeconomic factors. Routine evaluating techniques for the early discovery of precancerous sores in the cervix and presentation of antibodies against HPV have diminished the pace of cervical malignant growth-related passings in created nations. These HPV prevention measures were later deemed unworkable due to their high cost. The treatment for cervical cancer, which typically consists of chemotherapy and radiotherapy, is determined by the stage of the disease. On the other hand, cancer in its advanced stage necessitates surgical procedures. Numerous specialists have made sense of the impact of the disease's foundational microorganism hypothesis at the beginning of malignant growths. This hypothesis makes sense of particular examples of cells in growth, named disease immature microorganisms (CSCs). These cells have the ability to begin and build the

development of cancer. Cap and Dick (1997), first time, depicted the presence of malignant growth undifferentiated cells in intense myeloid leukemia. After that, the role of CSCs in solid tumors of the breast, colon, brain, pancreas, prostate, lung, and liver has been the subject of numerous experimental studies. CSCs share characteristics with somatic stem cells, such as self-renewing and differentiating into non-stem cancer cells [9-13]. Although it is common knowledge that genetic and environmental stimuli regulate normal stem cells, no evidence exists regarding the response of CSCs to these stimuli. Furthermore, it has been seen that CSCs show opposition towards chemotherapy and radiotherapy, so these cells have been known to assume a focal part in backslide of malignant growth. Therefore, until CSCs are removed, it is difficult to diagnose cancer, according to the CSCs hypothesis [14-16].

Origin of Cervical Cancer

Three distinct kinds of cells include in the structure of the cervix. These cells are, for example, hard squamous cells in the ectocervix, mucin-discharging glandular cells in the endocervix and the last parts address the metaplastic cells present between the ectocervix and endocervix. This zone is additionally named a change zone or squamo-columnar intersection. Ectocervix includes four unique layers, for example, Basal, parabasal, transitional, shallow [17-19]. A cycle named as, shedding includes in the nonstop expulsion of cells from the shallow layer. Basal layers, having effectively separating youthful epithelial cells, having stem like properties, include in the recovery of these cells. Endocervix cells have cilia and discharge mucous, help in the development of spermatozoa. HPV disease happens in immature microorganisms have different quality articulation profiles of the epidermis in the change zone. Basal foundational microorganisms and terminally separated cells include the cervical epithelium arrangement. At the point when an injury happens in the separated cells of cervical epithelium, basal foundational microorganisms begin to multiply and separate lastly supplant the harmed cells [22-24]. The separation capacity of undifferentiated cells assumes a vital part in the start of viral particles. A disease of infection educates the cells to begin symmetric division as opposed to hilter kilter division. This cycle permits the cells for the multiplication and creation of viral particles lastly, repress their separation action. High-gamble HPV includes expanded proliferative movement and helps in the creation of viral particles and forestalls the separation processes. Contamination of infection straightforwardly doesn't prompt the disease process. However, it instigates the proliferative action of tainted cells. This cycle prompts change and loss of DNA fix components movement, which at long last outcomes in the HPV contamination to actuate malignant growth process. This reality uncovered the idea that undeveloped cells assume a focal part in Cervical malignant growth sooner than the idea of CSCs. Consequently, it might infer that HPV tainted foundational microorganisms lead to the malignant growth of undifferentiated organisms. Different flagging pathways connected with stem like properties of cells, for example, Score, Hedgehog, Wnt, BMI associated with the cervical disease.

Cancer-causing HPV contamination has a causal connection with cervical carcinogenesis. In any case, when the cervix is tainted with cancer-causing HPV, HPV-related CINs and cervical carcinomas are typically created inside a particular cell populace that is situated in the ectoendocervical squamocolumnar (SC) intersection of the cervix [30-32]. They are normally not created in the columnar cells situated inside the endocervix and squamous cells inside the ectocervix. The HPV-related CINs and cervical malignant growths keep up with the hereditary profile of the intersection cells, showing their cell order. Ancestor cells situated in the intersection region contaminated with cancer-causing HPV are probably going to become pre-threatening neoplastic undifferentiated organisms that can proliferate dangerous neoplastic immature microorganisms (CCSCs), which engender cervical carcinoma clones. Restoratively focusing on these cells might forestall the spread of HPV-related CINs and cervical carcinomas.

Cancer Stem Cells

Malignant growth foundational microorganisms are a modest number of gatherings of cancer cells, having attributes of tumorigenesis, self renewal, multilineage separation potential, and slow cycling

limit. In the ongoing year, explores have given progressed techniques to recognise cancer cells and their descendants in vivo, which persuaded about the endurance of CSCs . CSCs partition lopsidedly and bring about two different girl cells. One duplicate of this cell makes the whole genome of mother cells and the other duplicate of the little girl cell, showing the likeness to foundational microorganisms. CSCs involve self-recharging limits and have a capacity for cancer commencement. Because of hilter kilter division of CSCs, cancer cells have a mix of CSCs and their descendants, in view of the critical phenotypic trademark and heterogeneity in elements of CSCs. Subsequently, CSCs assume a focal part in the beginning phase of malignant growth, disease backslide and metastasis that is the reason CSCs have been considered to work on the endurance of patients of malignant growth and furthermore to forestall disease backslide processes. CSCs are quiet cells and live in CSC specialty. Its outcome is the security from harm from hostile to cancer treatments. An ideal equilibrium is found between enactment, self-restoration and separation processes for CSCs to stay in CSCs specialty. In the pressure condition, CSCs enact and select into different tissues to separate and change into dangerous cells. Late explores on in-vitro and in-vivo examinations have announced many undifferentiated cell explicit markers to perceive CSCs. There have been numerous CSCs markers recognised as malignant growth restorative targets. Though, the perplexing science of CSCs has arisen as a test. A related trouble emerges that cancer cells show differences among various patients, exhibiting that CSCs markers are well defined for their individual growths.

Cervical Cancer Stem Cells

In-vitro and in-vivo investigations have been invited to explain stem cell markers to identify cancer stem cells due to the experimental restriction of the functional assay [2, 15, 45, 46]. As a result, identifying CSC-specific markers has become a feasible method for identifying CSCs, but molecular assays are insufficient. As a new marker for the treatment of cervical cancer, stem cell markers for CSCs have just come to light. Here, we discussed the CCSC markers that are currently being investigated as potential study targets.

Cancer Stem Cell Markers

Humans have the POU class 5 homeobox 1 gene, which codes for the transcription factor OCT4 (OCT3 and 3/4). It preserves stem cells' pluripotency and is crucial for embryonic development. OCT4 is overexpressed in cervical cancer tissue compared to nearby normal tissues [49-51]. Studies on cervical cancer cells have shown that excessive exposure to OCT4 is associated with poorly differentiated cervical cancer cells and positive lymph node metastases. Clinical studies have clarified the association between OCT overexpression and radiation resistance, and they have later come to the conclusion that OCT4 expression is a separate risk factor for cervical cancer patients' survival. OCT4 is involved in the promotion of tumours, according to an in vitro study.

CD-133

CD-133, a 120KDa pentaspanning transmembrane glycoprotein, is encoded by the human gene prominin 1 (PROM1) . It has been frequently employed as a CSC marker in several tumours, including melanoma, lung, colon, liver, breast, brain, and ovarian cancers. CD-133 serves as a particular marker for cervical cancer stem cells in targeted therapy for CSCs. Numerous investigations on cervical cancer have revealed that CD-133, which indicates radiation resistance in cells, is present in cervical-stem-like cells.

CD49F

Known as CD49f, the integrin alpha 6 (ITGA6) gene encodes this cell surface protein. Human embryonic stem cells and mesenchymal stem cells are the main sources of it. Certain CCSC models exhibit significant CD49f expression, demonstrating a radiation resistance.

ALDH1

The cytoplasm contains aldehyde dehydrogenase 1, which is involved in metabolic processes. Aldehydes are dehydrogenated through its catalysis. It possesses the capacity for tumorogenesis and self-renewal, primarily in breast cancer. Additionally, it has been discovered that CSCs containing the ALDH1 stem cell marker are linked to effective patient-derived xenografts in primary breast cancer. In patient tissues, expression of ALDH1 reveals a dismal survival rate. Additionally, increased cell migration, proliferation, and sphere formation levels are associated with overexpression of ALDH1 in cervical cancer cells, demonstrating ALDH1's steaminess in this disease.

ABCG2

The subfamily G member 2 (ABCG2) of the ATP binding cassette is a drug efflux membrane transporter ABC (ABC) component. ABCG2 is also known as the breast cancer resistance protein (BRCP) . It causes a lot of chemical substances to be released from cells and contributes to multidrug resistance (MDR) in different malignancies . It acts as a molecular marker for the side population phenotype, one of the key properties of CSCs. Axitinib and Icotinib are two medications that specifically target and inhibit ABCG2, which makes cells more resistant to chemotherapy. As a result, ABCG2 has been regarded as a CSC marker for cancer treatment. In cervical cancer, the redox sensing protein Nrf2 is involved in controlling ABCG2 transcription. Indefinite cell proliferation and apoptosis inhibition are two traits that cells with Nrf2 and ABCG2 overexpression share with stem cells [69-71].

SOX2

Both embryonic development and the explanation of stem cell destiny involve a crucial transcription factor called SOX2. Cervical cancer displays SOX2 overexpression when compared to healthy cervix tissue. Additionally, SOX2 overexpression has been linked to cervical carcinoma that is not well differentiated [72-74]. The significance of SOX2 as a diagnostic for undifferentiated cervical carcinoma was thus made obvious. Numerous in vitro and in vivo investigations have shown that overexpression of SOX2 is associated with enhanced cervical cancer cell proliferation and tumorigenesis. Radiation therapy is ineffective in cervical squamous carcinoma patients whose tumour cells show a high amount of SOX2 [72, 75, 76].

Osteopontin (OPN)

Malignant and tumour stromal cells produce osteopontin (OPN), an extracellular matrix protein with chemokine-like properties. It is crucial for metastasis and tumour cell movement. Because OPN is elevated in response to hypoxia, it is recognised as an endogenous hypoxic marker. OPN binds to areas of hypoxic tumour tissue [77-80]. A stronger OPN expression reflects tolerance to hypoxic radiation. OPN controls HIF1-dependent VEGF expression in hypoxic environments to promote tumour angiogenesis. Additionally, OPN is overexpressed in human cervical cancer patients with low survival rates. Higher blood and serum levels of OPN expression are associated with a worse prognosis for cervical cancer patients.

BMI1

BMI1 preserves stem cell properties by inhibiting genes linked to differentiation. The expression of BMI1 was discovered to be increased in cervical cancer cell lines SiHa, HeLa, C33a, and CaSki as compared to the healthy epithelial cells [82-84]. Studies on the tissue of uterine cervical cancer have similarly identified up-regulated expression. This report has also demonstrated a favourable connection with tumour size and lymph hub metastasis.

KLF4

KLF4 is essential for differentiation when it is overexpressed in the cervical epithelium's basal cells . The expression of KLF4 declines with cervical cancer progression. P27Kip1 binds to the promoter regions (435 and -60) of KLF4 to prevent ectopic KLF4 expression, which prevents the development of tumours and limits cell proliferation.

UTF1

UTF1 plays a critical role in ensuring the fate of cells during underdeveloped development. Wu and colleagues found that decreased UTF1 expression is associated with the advancement of cervical cancer. Hypermethylation of the advertiser was linked to diminished UTF1 articulation. Interestingly, it functions similarly to UTF1 in that it activates p27Kip 1, which binds to regions 517 and 388 of the promoter to inhibit cancer in vivo and in vitro as well as cell proliferation.

Future Prospective

The field of CSC research has gained huge headway lately. In this field, there are still a ton of things that haven't been covered. The beginning of CSCs has not been plainly settled. Epidermal immature microorganism contamination with HPV might bring about cervical malignant growth. Be that as it may, cervical disease, for the most part, doesn't appear until quite a while sometime later. Gupta and co. have expressed that one significant restriction of CSC is that they can't venture into an unadulterated populace because of their inborn capacity to recapture the qualities of tests from which they were taken out [95-97]. It gives the technique for their separation an inordinate measure of weight. Moreover, there are various ways to deal with isolating CSCs that select just a few CSCs. While not indistinguishable, the CSC populace shares a few qualities. The circle development examination shows a slight expansion in CD 133 action in HeLa cell line CSCs, though the SP measure shows a critical increment. It has been seen that upregulation in CD 133 impacts the review's results. Thus, further developed strategies for CSC partition are desperately required. Since the seriousness of the infection is related to the quantity of CSCs, it could be useful for ladies going through routine cervical malignant growth screening to recognise CSCs. In addition to the fact that it is useful for early sickness recognition, it likewise gives fundamental data about the illness' seriousness. Various proofs have exhibited the capability of CSCs in sickness repeat and chemoresistance metastasis, so broad exploration of them in cervical disease is desperately required. The evaluating methodology and helpful procedures for cervical malignant growth patients work on because of a superior comprehension of the systems of cervical disease foundational microorganisms.

Conclusion

Cancer is linked to a small percentage of CSCs with epithelial-mesenchymal phenotypes and non-stem cells with epithelial features. CSCs have been thought of as a clever goal in illness therapy due to their propensity for carcinogenesis and self-renewal. Numerous investigations have revealed the presence of CSCs in cervical tumours. These researches have talked about the functional state and function of the stem/progenitor cell population in cervical cancer as early diagnostic and improved treatment targets for cervical cancer, as well as indicators for CSC isolation ABCG2, SOX2, CD133, CD49f, and ALDH1 have been found.

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