

Review Article

# Stem Cells in the Context of Cervical Cancer

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## Abstract

Cervical carcinoma exhibits a high mortality among females, particularly in less developed countries. 99.7% of cervical cancer occurs due to an HPV infection. Other factors also contribute to the progression of HPV to cervical cancer including using oral contraceptives long-term, tobacco use, partaking in sexual activity at an early age and having multiple partners, low-socioeconomic status and other sexually transmitted infections. The current standard of care does not provide a cure but rather just prolongs the patient's survival. Patients that have to undergo surgery are burdened by life-long consequences related to the child-bearing ability and the chances of recurrence are not fully eliminated. The theory of cancer stem cells states that most tumor cells die after transient differentiation, but a small number of tumor cells significantly contribute to oncogenesis due to their ability to proliferate and self-renew indefinitely. Developing a treatment that specifically targets these CCSCs could prevent the new tumors from developing since CCSCs may be at the root of metastasis. Recent discoveries in the field of targeted therapy have shown promise including, but not limited to, immune checkpoint inhibitors, anti-angiogenesis agents, poly (ADP-ribose) polymerase (PARP) inhibitors, targeted gene delivery and nanotechnology.

**Keywords:** Cervical Cancer; Cancer; Stem Cells

## Abbreviations

ADC: Antibody-Drug Conjugates; CSC: Cancer Stem Cells; CCSC: Cervical Cancer Stem Cells; CT: Computed Tomography; CTL: Cytotoxic T Lymphocytes; DLL4: Delta-Like Ligand 4; HPV: Human Papilloma Virus; HR-HPV: High-Risk Human Papilloma Virus; iPSC: induced Pluripotent Stem Cell; LEEP: Loop Electrosurgical Excision Protocol; MDR: Multidrug Resistance; MRI: Magnetic Resonance Imaging; NP: Nanoparticles; PARP: Poly (ADP-ribose) Polymerase; PD1: Programmed Death 1; PET: Positron Emission Tomography; P13K: P13-Kinases; SC: Squamo-Columnar; TZ: Transformation Zone

## Introduction

Cervical cancer is the fourth most common type of cancer in women [1]. In cervical carcinomas, heterogeneity is present [2]. This heterogeneity causes cervical cancer to respond poorly to chemotherapy and radiation [2]. Cells specifically located in between the endocervix and exocervix, at the Squamo-Columnar (SC) junction can lead to cervical intraepithelial neoplasia and carcinogenesis with more ease than other cells. 90% of cervical cancers arise from this area [2]. When the disease has progressed to advanced stages, surgery, chemotherapy and radiation are the standard of care [1]. Properties of CSCs include the ability to self-renew, decelerate cycling capacity and tumorigenicity and differentiate into multiple lineages [2]. Therapeutics for this disease may enhance drug resistance in tumors by eliminating non-stem cells in tumors and thus leaving the nutrients in the tumor microenvironment to be consumed by CSCs ultimately strengthening them [1]. The unstable and biologically complex nature of CCSCs make them difficult to target [2].

### *Epidemiology*

Cervical carcinoma exhibits a high mortality among females, particularly in less developed countries [2]. Cervical cancer is the fourth most common type of cancer in women [1]. HPV16 accounts for 50-60% of cervical cancer cases and HPV18 accounts for approximately 20% [3]. In 5 years, the likelihood of relapse and metastasis is approximately 40% [4].

### *Pathophysiology*

Cervical cancer is traditionally thought of as the result of uncontrolled cell proliferation [2]. 99.7% of cervical cancer occurs due to an HPV infection, however this is not always the case [1]. Other factors also contribute to the progression of HPV to cervical cancer including using oral contraceptives long-term, tobacco use, partaking in sexual activity at an early age and having multiple partners, low-socioeconomic status and other sexually transmitted infections [1].

E6 and E7 are oncoproteins that are constitutively expressed in cervical cancer cells [3]. In cervical carcinomas, heterogeneity is present [2]. This heterogeneity causes cervical cancer to respond poorly to chemotherapy and radiation [2]. Metastasis to the lymph nodes and recurrence is also a possibility due to the heterogeneous nature [2]. This could be due to cervical cancer stem cells dividing asymmetrically and being capable of transdifferentiation [2]. Cells specifically located in between the endocervix and exocervix, at the Squamo-Columnar (SC) junction can lead to cervical intraepithelial neoplasia and carcinogenesis with more ease than other cells. 90% of cervical cancers arise from this area [2]. The cells at this junction have a morphology and gene profile different from surrounding cells. They express SC junction specific markers which have also been found in multiple cervical malignancies [2]. The Transformation Zone (TZ) is a complex zone in which cervical carcinogenesis occurs [5]. This area is found on the vaginal surface of the cervix. The growth of vaginal microflora and overproduction of estrogen allow metaplastic squamous epithelium to replace the endocervical columnar epithelium. Another proposed pathophysiological mechanism is linked to stem cells found in the TZ. Viral oncogenes from the High-Risk Human Papilloma Virus (HR-HPV) could lead to malignant transformation of the stem cells in the TZ [5]. CSCs in CC avoid anti-cancer drugs by remaining in a semi-quiescent state [6]. Molecular mechanisms in cancer stem cells are regulated by Notch, Wnt and DNA repair pathways [7].

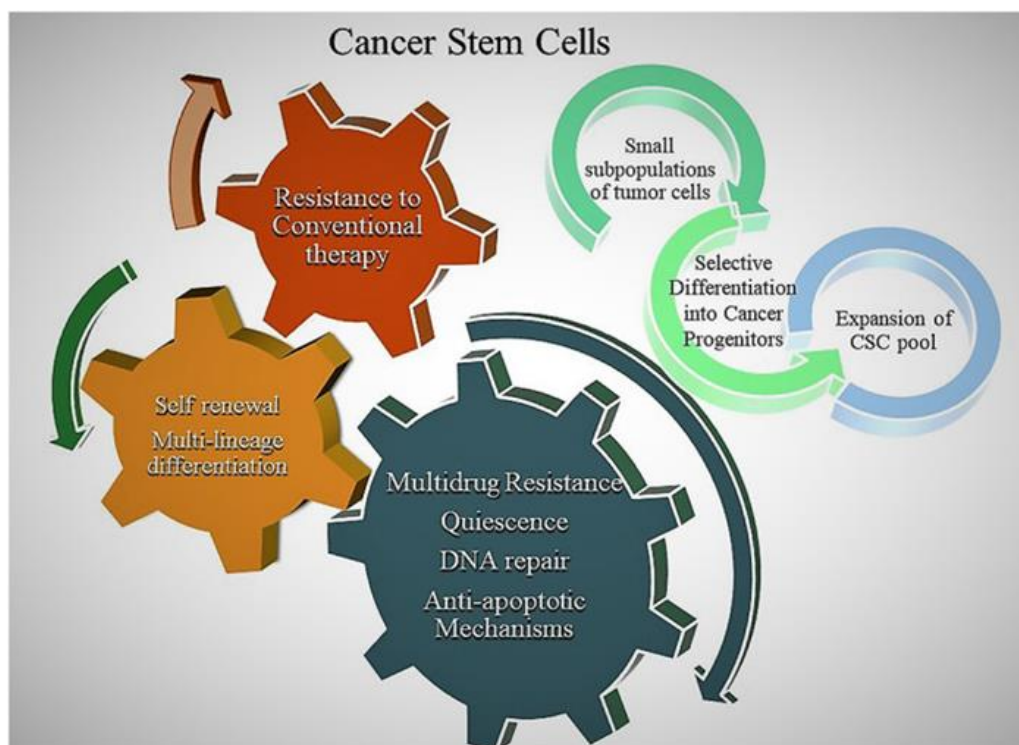
### *Current Standard of Care*

The current standard of care does not provide a cure but rather just prolongs the patient's survival [1]. Preventative measures include: a pap smear test recommended to women 21 and older, used to detect precancerous cells, HPV DNA testing and Gardasil vaccines [1]. Preventative practices, such as screenings and vaccines, are not easily accessible in less developed countries [1,8]. For this reason, 87% of deaths attributed to cervical cancer occur in less developed countries [1]. Furthermore, prophylactic HPV vaccines are ineffective against established cancers [3]. After diagnosis, pelvic exams and imaging techniques such as PET scans, MRIs, CT scans and X-rays are used [1]. During the early stages of cervical cancer, the abnormal cells can be removed using Loop Electrosurgical Excision Protocol (LEEP). When the disease has progressed to advanced stages, surgery, chemotherapy and radiation is the standard of care. Patients that have to undergo surgery are burdened by life-long consequences related to the child-bearing ability and the chances of recurrence are not fully eliminated [1]. Cisplatin-based chemotherapy is a specific type commonly used for cervical cancer [2]. Therapeutics for this disease may enhance drug resistance in tumors by eliminating non-stem cells in tumors and thus leaving the nutrients in the tumor microenvironment to be consumed by CSCs ultimately strengthening them [1]. Cell cycle-specific drugs can increase the radiosensitivity of CCSCs, thus making radiotherapy a more successful treatment [8]. These drugs including, vincristine, paclitaxel, 5-fluorouracil and gemcitabine, can also enhance the effects of platinum drugs [8].

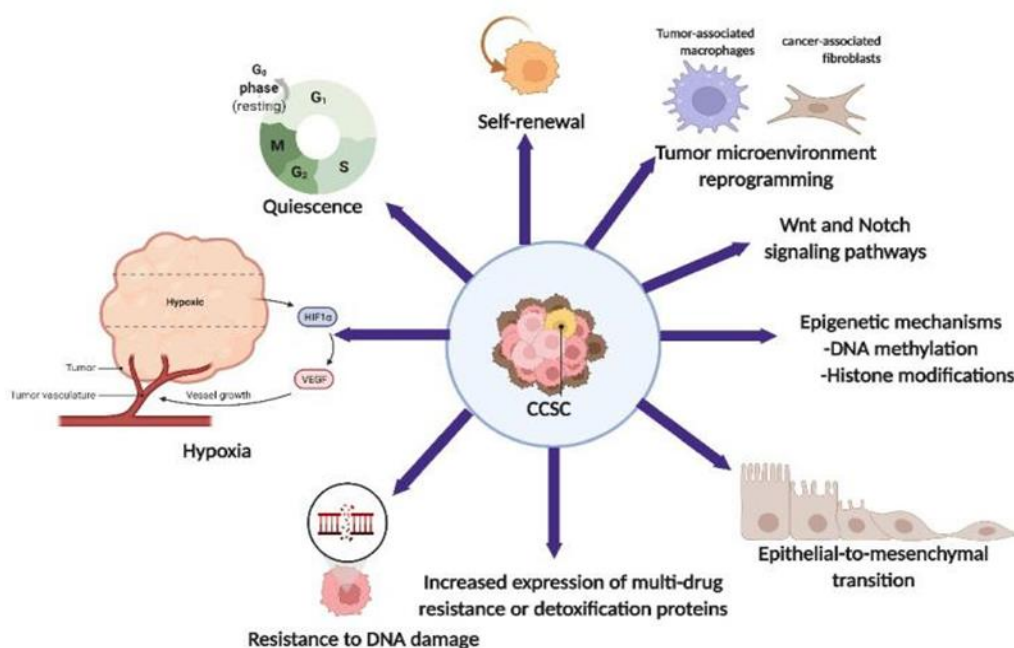
### *The Role of Stem Cells*

The theory of cancer stem cells states that most tumor cells die after transient differentiation, but a small number of tumor cells significantly contribute to oncogenesis due to their ability to proliferate and self-renew indefinitely [5]. This small population of cells are categorized as cancer stem cells. CSCs could also arise due to stem cells in normal tissues mutating or mature cells undergoing dedifferentiation [5]. Properties of CSCs include the ability to self-renew, decelerate cycling capacity and tumorigenicity and differentiate into multiple lineages [2]. CSCs also have their own niche, a protective and optimal environment for their growth [2]. When stressed, CSCs leave this niche and cause progression of cancer [2]. Asymmetric division and self-renewal allow phenotypically and functionally heterogeneous CSC populations to develop [2]. CSCs ability to initiate tumors make them a promising target for preventing cancer relapse [2]. CSCs are resistant to chemotherapy and radiotherapy which could be due to their quiescence, anti-apoptotic mechanisms, ability to repair DNA and multidrug resistance [5]. Cancer stem

cells are quite complex in regard to their phenotype and behavior which makes it difficult to isolate and purify them without losing these important complexities [2]. Thus far, cancer stem cells have been isolated from human breast cancer and identified in multiple myeloma, ovarian tumors, endometrial tumors, prostate tumors, brain tumors and lung tumors [5]. There are markers and assays available to perform this task, however these are not universal methods and usually possess limitations such as only being able to be implemented *in-vivo* studies [2,5]. The unstable and biologically complex nature of CCSCs make them difficult to target [2]. Developing a treatment that specifically targets these CCSCs could prevent the new tumors from developing since CCSCs may be at the root of metastasis [2]. An approach that can be utilized is monitoring the expression of specific stem cell markers in malignant cells (Fig. 1,2) [2].



**Figure 1:** Significant properties of cancer stem cells are depicted [4].



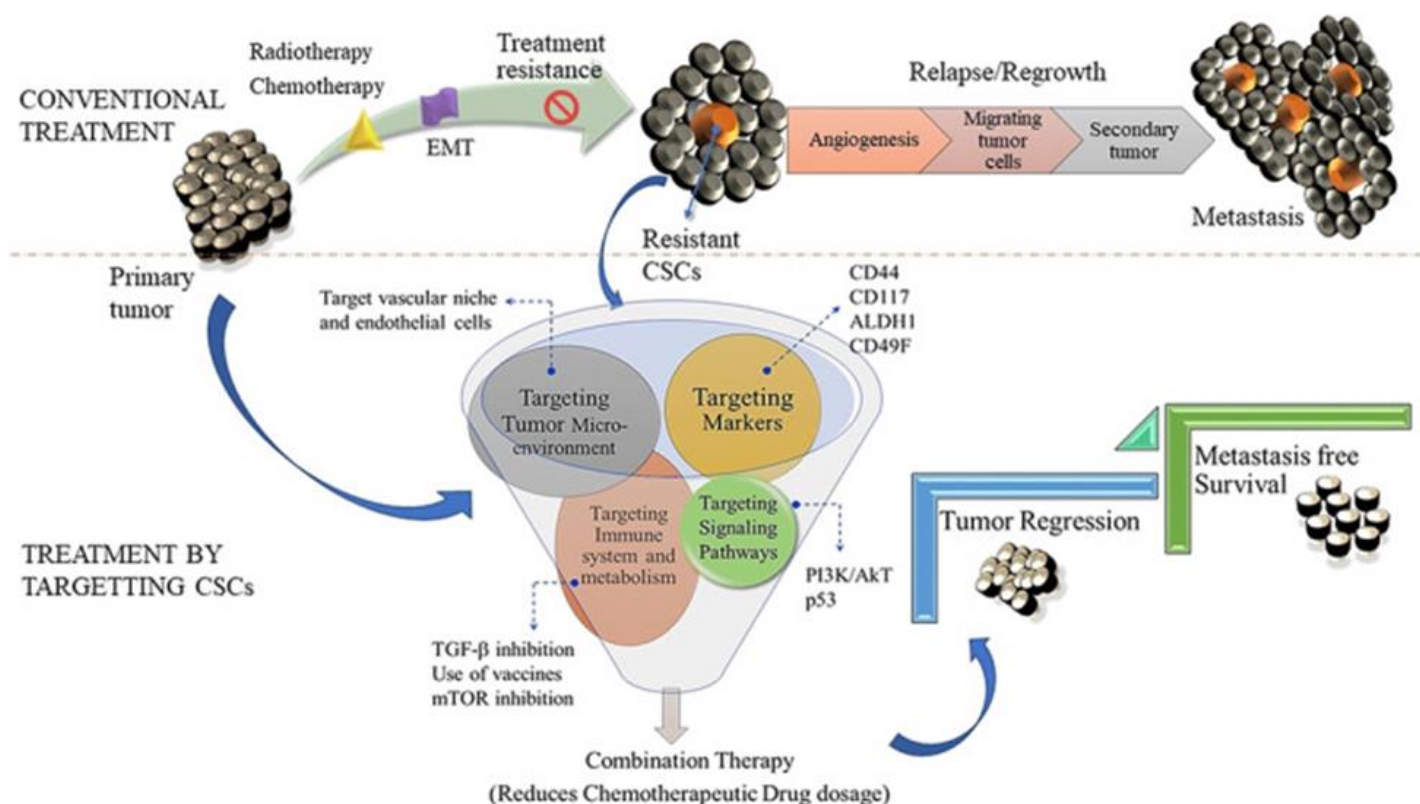
**Figure 2:** Properties and pathways involved in the proliferation of cervical cancer stem cells are shown [8].

## Major Findings in Recent Studies

Therapy targeting cancer stem cells is a highly investigated area that could prevent relapse and improve the current treatments [2]. Recent discoveries in the field of targeted therapy have shown promise including, but not limited to, immune checkpoint inhibitors, anti-angiogenesis agents, Poly (ADP-ribose) Polymerase (PARP) inhibitors, targeted gene delivery and nanotechnology [2,8]. Targeting cancer stem cells with Nanoparticles (NP) have been created with the intention to inhibit stem cell-related functions [8]. Limitations of nanoparticle use include bioavailability and side effects [8]. Targeted gene delivery has been investigated further and shown promising preclinical results regarding tumor targeting and minimizing toxicity [8]. Efficient vectors are lacking, preventing clinical translation [8]. Furthermore, dual-targeting strategies have been investigated in which the outer-layer of a drug consists of anti-tumor therapeutics to kill cancer cells and the inner layer consists of Antibody-Drug Conjugates (ADCs) to target CSCs specifically [2,8]. In murine xenograft models with human breast and ovarian cancer cells, a dual inhibitor of mTORC1/2 and class 1 P13-kinases (P13K) was able to inhibit tumor-initiating capacity. Additionally, targeting Delta-Like Ligand 4 (DLL4) and Programmed Death 1 (PD1) showed potential to be a cancer therapeutic [2]. In addition, anti-cancer activity has been noted in multiple compounds isolated from microorganisms and plants [8]. BRM270 can be extracted from seven different plants and used medicinally [9]. Studies have shown that BRM270 can decrease tumorigenesis in several different ways. In stem-like cells with Multidrug Resistance (MDR), BRM270 can suppress Nf-kB signaling [9]. In the specific case of CCSCs, BRM270 has been shown to restrict SOX<sub>2</sub> and prevent CCSC proliferation [9]. Tumor initiation and metastasis of CC is negatively impacted by BRM270 as well [9]. The Wnt/B-catenin pathway plays a vital role in maintaining the CSC phenotype of CCSCs [9]. This pathway can be downregulated by BRM270. Unlike chemotherapy, BRM270 does not affect healthy cells, but rather specifically targets cancer cells [9]. Phytochemicals, like BRM270, may possess advantages over synthetic anti-cancer drugs and should be further investigated as a therapeutic for CC [6,9]. Cervical cancer has increased levels of ALDH1 expression [10]. ALDH1 can contribute to radio-resistant cells in CC and this effect can be induced by hypoxia [10]. Further, ALDH1 can play a role in the Wnt/B-catenin pathway and cause multidrug resistance [10]. Targeting ALDH1 may give rise to new therapeutics for CC [10]. Some compounds that possess the ability to do so include: limonin, zoledronic acid and PM01183 [10]. These compounds could interfere with the stemness of CC cells and contribute to overcoming chemoresistance [10]. These compounds are still under investigation in early-stage clinical trials, further research is needed [10]. An experiment was done with the intention to prevent the onset of cervical cancer in which induced Pluripotent Stem Cell (iPSC)-derived HPV16 E6 specific Cytotoxic T Lymphocytes (CTLs) were generated [3]. However, the use of a universal iPSC derived CTLs is restricted by the presence of a variety of major histocompatibility complexes in patients [3].

## Discussion

Cervical carcinoma exhibits a high mortality among females [2]. Preventative measures include: a pap smear test, HPV DNA testing and Gardasil vaccines; however, these are not easily accessible in less developed countries [1,8]. CSCs are a small population of tumor cells that significantly contribute to oncogenesis due to their ability to proliferate and self-renew indefinitely [5]. Therapy targeting cancer stem cells is a highly investigated area that could prevent relapse and improve the current treatments [2]. Recent discoveries in the field of targeted therapy have shown promise. Targeting cancer stem cells with Nanoparticles (NP) have been created with the intention to inhibit stem cell-related functions [8]. Furthermore, dual-targeting strategies have been investigated in which the outer-layer of a drug consists of anti-tumor therapeutics to kill cancer cells and the inner layer consists of Antibody-Drug Conjugates (ADCs) to target CSCs specifically (Fig. 3) [2,8,10].



**Figure 3:** Conventional treatment and treatment by targeting cancer stem cells are compared above. In conventional treatments, resistance and metastasis pose a great risk. By targeting specific properties of CSCs such as specific markers or pathways, metastasis free survival could be attained [4].

## Conclusion

Anti-cancer activity has been noted in multiple compounds isolated from microorganisms and plants. Compounds targeting ALDH1 such as, limonin, zoledronic acid and PM01183, may give rise to new therapeutics for CC. These compounds are still under investigation in early-stage clinical trials, further research is needed. The unstable and biologically complex nature of CCSCs make them difficult to target. Developing a treatment that specifically targets these CCSCs could prevent the new tumors from developing since CCSCs may be at the root of metastasis and thus further research in this area is vital.

## Conflict of Interest

The authors declare no conflict of interest in this publication.

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