Chapter- 16

Chemoresistance of Cervical Cancer Stem Cells: Challenges and Prospects

Susmita Mondal[1†*], Sutapa Saha[1], Saptarshi Chatterjee[2] and Biplab Bhowmik[1]

Abstract:

   Cervical cancer (CC) is one of the leading causes of death among women, with thousands of women diagnosed each year, particularly in developing countries where access to healthcare resources may be limited. Persistent infection with high-risk human papillomavirus (HPV) induces CC. While advancements in treatment modalities, such as chemotherapy, have improved outcomes for many patients, a significant challenge remains in the form of chemoresistance, particularly in the context of cervical cancer stem cells (cCSCs). cCSCs are a small subpopulation of cells within CC with self-renewal and aberrant differentiation capacity. Upregulation of biomarkers expression such as CD44, CD133, Sox2, ALDH1 and etc. is often associated with robustness of cCSCs. cCSCs possess higher invasion, metastasis and drug resistance ability thereby leading to poor prognosis and relapse. Therapeutic strategies to manage advanced CC typically involve surgery, radiotherapy and chemotherapy mostly using platinum-based drugs. However, acquired chemoresistance of cCSCs is the biggest challenge to therapeutic outcomes. There are several mechanisms involved in chemotherapy resistance in cCSCs, such as enhanced DNA damage repair mechanisms, which include nucleotide excision repair and homologous recombination, and promoting survival pathways like PI3K/AKT, Wnt, Notch. Elevated drug transporters like ABCG2 are one of the key feature for the resistance phenotype of cCSCs. Furthermore, epigenetic modulation and mutual interaction of cCSCs with tumour microenvironment play crucial role to avoid chemotherapeutic damage. This chapter aims to explore the mechanisms underlying chemoresistance in cCSCs and discuss potential therapeutic strategies to overcome this challenge.

Introduction:

   Cancer stem cells (CSCs) are a small subpopulation of tumour cells with self-renewal and multilineage-differentiation potential like normal stem cells. CSCs maintain tumour heterogeneity and contribute to tumour initiation, progression, and recurrence. CSCs are mostly quiescent cells with higher invasion, metastasis and drug-resistance capacity leading to poor prognosis (Prasetyanti & Medema, 2017; Das et al., 2021). Several studies identified CSCs population by the expression of certain biomarkers, which are analogous to normal stem cells.

Susmita Mondal
Department of Zoology, Diamond Harbour Women's University, Sarisha, West Bengal, India

E-mail: ✉ susmita.dhwu@gmail.com

Orcid iD: 🆔 https://orcid.org/0009-0003-8119-2197
Sutapa Saha
Department of Zoology, Diamond Harbour Women's University, Sarisha, West Bengal, India
Saptarshi Chatterjee
Department of Zoology, University of Burdwan, Bardhaman, West Bengal, India
Biplab Bhowmik
Department of Zoology, Diamond Harbour Women's University, Sarisha, West Bengal, India
*Corresponding Author: susmita.dhwu@gmail.com

The first CSCs population was isolated from leukemia with $CD34^+CD38^-$ expression. In solid tumour, CSCs were first identified in breast cancer ($CD44^+CD24^-$/lowLin$^-$), subsequently in brain, cervical, colon, pancreas, skin, lung cancers etc. (Saito et al., 2022).

Cervical cancer (CC) is the fourth most common gynaecological cancers and the second leading cause of death among women after breast cancer. CC are mostly induced by persistent human papillomavirus (HPV) infection, which is typically asymptomatic. Recent advancements of cytological screening and vaccination programs reduced the occurrence rate of CC at early stage (Burmeister et al., 2022). Advanced CC cases are normally treated using a combination of radiotherapy and chemotherapy. However, it remains a significant global health challenge, with chemoresistance posing a major obstacle to successful treatment. Even though many drugs, most importantly platinum-based drugs are used to treat CC, however, acquired chemoresistance lead to relapse (Zhu et al., 2016). Therefore, it is very important to understand the molecular mechanism of chemoresistance for developing CC treatments. Recent research has shed light on the role of CSCs in driving chemoresistance, offering new insights into potential therapeutic strategies. The heterogeneity of CC is achieved by the existence of cervical CSCs (cCSCs). Therapeutic targeting of cCSCs has the ability to reduce metastasis and relapse by preventing the generation of new CC clones (Huang & Rofstad, 2017). This chapter aims to provide an update on the role of cCSCs and the molecular mechanisms involved in therapy resistance.

Epidemiology and risk factors of cervical cancer

Globally, cervical cancer accounts for an estimated ~604,127 new cases and 341,831 deaths in 2020 (Singh et al., 2023). It displays higher incident rates and ~90% mortality in low and middle-income countries specifically in Sub-Saharan Africa, Central America and South-East Asia (Hull et al, 2020). CC is the second most common cancer among Indian women, accounting for ~17% of all female cancer cases. An estimated 96,922 new cases and 60,078 deaths from cervical cancer were reported in India in 2020, highlighting the substantial burden of the disease (Singh et al., 2022). CC incidence varies across India, with higher incidence and mortality rates observed in rural areas. CC predominantly affects women in their reproductive years, with peak incidence observed between the ages of 35 and 55 years. Disparities in cervical cancer incidence and mortality are closely linked to socioeconomic factors, including access to healthcare services, education, and poverty levels. Lack of access to screening programs including Pap smears and HPV testing, vaccination, and timely treatment, contribute to higher mortality rates in underserved populations (Singh et al., 2022).

The primary causative factor for CC is the persistent infection with high-risk HPV types, particularly HPV-16 and HPV-18, accounting for nearly all cases. However, co-infection with human immunodeficiency virus (HIV) or any other immunosuppression adds up to the risk of HPV acquisition and cervical cancer development. Other risk factors for cervical cancer include first sexual encounters at early age, multiple sexual partners, prolonged use of oral contraceptives, smoking, cervix dysplasia (Chan et al. 2019).

Although most of the HPV infections are transitory and cleared spontaneously by the immune system, ~95% of malignant CC are resulted from high-risk HPV infection. Carcinogenic HPV (HPV 16 and 18) infected cells arise in the transition area between the exocervix and endocervix, which is known as the squamocolumnar (SC) junction, eventually lead to cervical intraepithelial neoplasia (CIN, ~90%) and carcinomas (Sravani et.al, 2023). CC are categorized primarily into two histological subtypes- Squamous cell carcinoma (70%) and adenocarcinomas (25%). Other less common types of CC include adenosquamous, small cell or neuroendocrine, serous papillary and clear cell carcinomas. These specific SC junction cells express junction-specific markers like CD63, anterior gradient 2, matrix metalloproteinase 7 and guanine deaminase. It has been hypothesized that CC develops from stem-like cells in the transition area of the cervical opening in the presence of the persistent infection with hrHPVs (Zhang et al., 2020).

Current management strategies for cervical cancer

Pap smear screening and HPV testing have been effective for the early detection of lesions in the cervix which lower the incident rate and mortality in high-resource countries. The immune system clears most of the early precancerous lesions, however, due to persistent hrHPV infection and having a weakened immune system lead to the progression of lesions into invasive cancer. Detection stages of CC by the International Federation of Gynaecology and Obstetrics (FIGO), is the most prognostic factor in order to plan the best treatment (Bhatla et al., 2018). Depending on the extent of the disease these patients are treated with cryotherapy, laser therapy, or loop electrosurgical excision procedure. Cryosurgery and laser surgery are applied to remove precancerous lesions (Khan et al., 2014). The early-stage CC (stage Ia1-Ib1) can also be successfully treated by primary surgery with 5-year survival rates of 85-95%. However, nodal metastasis, parametrial extension in early stage has significant risk of local relapse after primary radical hysterectomy. Locally advanced CC (stage Ib2-IVa) are usually prescribed with chemoradiotherapy and the death rate for these patients with lymph node metastasis has been improved by the addition of chemotherapy to the radiotherapy protocols. Radiation therapy (RT) is used in the treatment of non-metastatic CC to reduce the size of the tumour or to halt the growth of the cancer cells that remain after the surgery (Martin-Hirsch & Wood, 2011). In chemotherapy, the use of platinum-based drugs is the primary therapeutic option for advanced and recurrent cervical cancer. Cisplatin is a commonly used drug which covalently binds to DNA and induces cell cycle arrest, inhibits replication thereby leading to DNA damage and eventually apoptosis. In addition, cell cycle-specific drugs, including paclitaxel, vincristine, and 5-fluorouracil, have radiosensitization capabilities or synergize the cytotoxic effects of platinum drugs (Duenas-Gonzalez et al., 2019). However, chemoresistance remains a formidable obstacle in the treatment of cervical cancer, particularly in the context of cervical cancer stem cells (cCSCs).

Cervical Cancer Stem Cells

The traditional "clonal evolution" theory of carcinogenesis, proposes that CC arises due to a mechanism of uncontrolled and unlimited cellular proliferation in cells of clonal origin within a tumour, there is genetic heterogeneity in CC. Another theory suggest that the intratumoural genetic heterogeneity in CC is due to the existence of cervical cancer stem cells (cCSCs). cCSCs represent a small subpopulation of cells within cervical tumours that possess self-renewal capabilities and the capacity to differentiate into heterogeneous tumour cell populations. These cells are implicated in tumour initiation, progression, lymph node metastasis, poor response to chemo/radiotherapy, and pelvic recurrence, making them a critical target for therapeutic intervention (Di Fiore et al. 2022). Recent studies suggested that, the ability of CSCs to transdifferentiate into vascular endothelial cells and other tumour-associated stromal cells contribute to the heterogeneity of tumour (Huang et al., 2015).

Cell surface markers such as CD44, CD 24, CD 49f, and CD 133 have been used to identify cervical cancer stem cells. Pluripotent transcription factors, for example, Sox2, Oct3/4, Nanog have been widely used to isolate and enrich CSC populations from different tumours including cervical cancer. Higher level of aldehyde dehydrogenase 1 (ALDH1) is also considered as an indication of stemness properties. High-risk HPV induces cervical carcinogenesis due to the overexpression of the viral oncoproteins E6 and E7 which in turn upregulates expression levels of stemness associated genes such as Oct3/4, Sox2, Nanog and fibroblast growth factor 4 to maintain the self-renewal capacity of CSCs. CSCs contribute to the tumourigenic potential of cancer and resistance to cytotoxic drugs and ionizing radiation leading to relapse (Organista-Nava et al., 2019). Understanding the underlying mechanisms driving chemoresistance in cCSCs is crucial for the development of effective therapeutic strategies to overcome this challenge. Here, we discussed the detailed mechanisms therapeutic resistance of cervical CSCs.
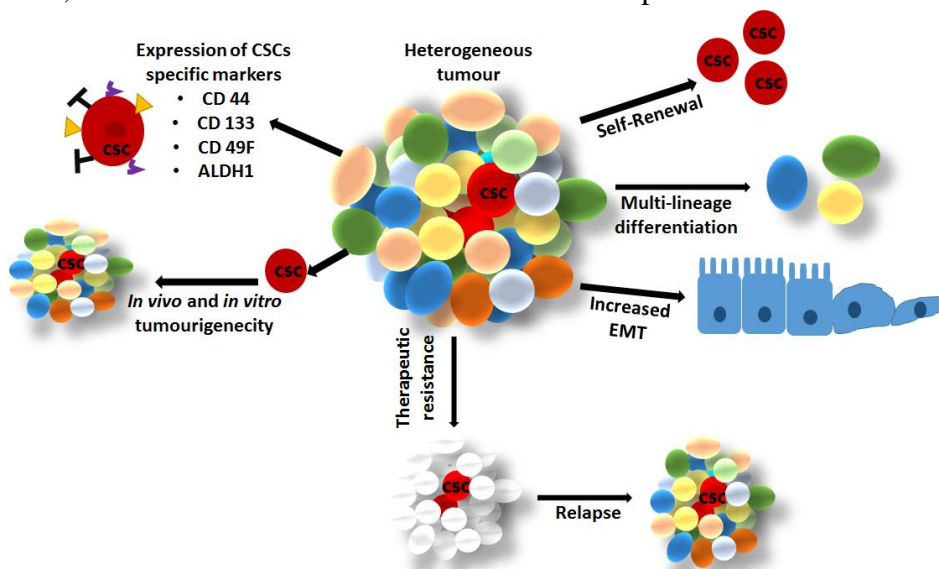

Figure 1. Properties of cervical cancer stem cells (cCSCs)

Mechanisms of therapeutic resistance of cCSCs

Cytotoxic anti-cancer therapies for CC involve both the combination of radiotherapy and chemotherapeutic drugs, such as platinum-based drugs, antimetabolites, or anthracyclines. Radiotherapies and certain chemotherapeutics induce cytotoxicity by means of direct DNA damage. Other group of chemotherapy such as paclitaxel, is the mitotic spindle poisons, and their mechanism of action is to exert toxic effects on the dynamics of microtubules thereby inhibiting cell division. Therapy resistances have been linked to CSCs and is considered one of the main possible causes of poor results for cervical cancer and other malignancies (Bailly et al., 2020). Thus, through the understanding of different cellular as well as genetic mechanisms involved in the development of treatment resistance by which the CSCs escape chemotherapy and radiotherapy, more effective treatments can be developed for CC.

Enhanced DNA Repair Mechanisms:

Radiation and some chemotherapeutic drugs trigger the DNA damage response which leads to cell cycle blockade followed by induction of apoptosis in sensitive cervical cancer cells. However, cCSCs exhibit upregulation of several DNA Damage Response (DDR) genes with roles in different DNA repair pathways, including nucleotide excision repair and homologous recombination, conferring resistance to DNA-damaging agents such as cisplatin. Radioresistant CSCs exhibited upregulation of homologous recombination (HR) gene such as RAD51 and HR/single-strand annealing pathway gene- RAD52 (Zhou et al. 2021). DNA damage sensor proteins, such as ataxia telangiectasia mutated (ATM) and ataxia telangiectasia mutated-RAD3-related (ATR) kinases form complexes with breast cancer 1 (BRCA1) and poly ADP-ribose polymerase (PARP-1) and promote DNA repair capability of cCSCs through CHK1/CHK2 phosphorylation or by activating anti-apoptotic signalling pathways, such as PI3K/Akt, WNT/β-catenin, and Notch signalling pathways (Marzagalli et al., 2021). Non-homologous end-joining genes like XRCC2 and Ku70/80, and genes related to reactive oxygen species (ROS) metabolism such as CYBA2 and SOD2 are also found to be upregulated in cCSC. Radio-resistant cCSCs with higher aldehyde dehydrogenase (ALDH)-1 activity exhibit preferential activation of the DNA damage checkpoint response and protect cells from elevated levels of ROS. Some studies have interconnected splicing/ RNA-binding proteins (RBPs) to the DDR response and CSC biology. The expression of the RBPs such as TRA2α/TRA2β which regulate CHK1 expression, are associated poor prognosis in cervical cancer. Transcriptomic data of cervical cancers also showed increased expression of SRSF6, an RBP gene, compared to normal tissues which corresponded with an increase in alternative splicing of DDR genes. SRSF1 binds to and stabilizes RECQL4 mRNA, a master regulator of genome stability, through regulating DNA replication and multiple DNA repair pathways (Gillespie et al., 2023).

Altered Drug Efflux Pumps:

Analysis of side population cells through flow cytometry is one of very popular methods to identify and isolate CSCs in different solid tumours, including CC. Overexpression of drug-

transporter proteins, including multidrug resistance (MDR) proteins of ATP-binding cassette (ABC) transporters family such as ABCB1 (P- glycoprotein), ABCC1, and notably ABCG2, facilitates the efflux of chemotherapeutic agents, reducing intracellular drug accumulation in cCSCs (Alisi et al., 2013). This enhancement of MDR proteins is one of the main protective mechanisms for CSCs in response to chemotherapeutic agents which facilitates the expulsion of cytotoxic drugs leading to higher resistance to chemotherapeutic agents and disease relapse. ABC transporters blocker such as fumitremorgin C and verapamil, have been used in ovarian cancer to sensitize CSCs (Di Fiore et al., 2022).

Activation of Survival Pathways:

Activation of PI3K/Akt and MAPK/ERK signalling pathways in cCSCs promotes cell survival and anti-apoptotic responses following chemotherapy-induced stress. P21-activated kinases (PAKs; serine/threonine kinases) have pivotal roles in tumour progression by regulation of the Ras-induced metabolism, cell proliferation, angiogenesis, and EMT (Navaei et al., 2022). Studies have showed that PAK4 is significantly upregulated in cervical cancer tissue samples which is involved in cancer progression and promotes the cisplatin through PI3K/AKT pathway. Secreted phosphoprotein 1 (SPP1) upregulation has been observed in cervical cancer tissues and suppression of SPP1 inhibited of PI3K/AKT pathway thereby reducing cisplatin resistance (Shu et al., 2015). Stem cell regulatory pathways such as Wnt/β-catenin, Hedgehog signalling, Notch signalling, and TGF β pathways are often upregulated in cervical CSCs and are associated with cancer progression, metastasis as well as therapy resistance (Manni et al., 2022).

DNA methylation:

Epigenetic mechanisms are key regulators of CSCs. DNA methylation helps cancer cells to regain stem CSC-specific features. Alteration of methylome profile can contribute to the progression and therapy resistance of CSCs. Consequently, agents targeting epigenetic programming such as DNA methyltransferase (DNMT) inhibitors are a class of potent anti-CSC compounds that are already being used in CC. Aberrant methylation of apoptotic signalling genes such as death-associated protein kinase (DAPK), and tumour necrosis factor receptor superfamily member 6 (FAS), results in acquired resistance to radio- and chemotherapy. The promoter hypomethylation of cancer/testis antigen gene, CAGE, results in cell cycle progression, angiogenesis, and drug resistance (French & Pauklin, 2021).

Epithelial-Mesenchymal Transition (EMT):

The epithelial-to-mesenchymal transition (EMT) is a reversible process, by which epithelial cells can convert into a mesenchymal phenotype, with altered expression of polarity, adhesion molecules, and morphology of cells. EMT activation is associated with metastasis, and treatment resistance by inducing cancer cells to exhibit stem cell-like features, which promote invasion of surrounding tissues and the underlying drug resistance. However, in most cases, the

molecular mechanisms of EMT transition and EMT-associated therapeutic resistance in CC are not clear. EMT transcription factors, such as SLUG, SNAIL, and TWIST can confer stem-like features in cancer cells (Phi et al., 2018). Study reported that, in cervical cancer, TGF-β/Smad3 pathway activation by TWIST induces EMT (Fan et al., 2015). Chronic treatment of epidermal growth factor (EGF) increases the expression of fibronectin, a mesenchymal marker. In cervical cancer treatment with EGF induces mesenchymal phenotypes. In cervical cancer, EMT increases the CSC subpopulation and leads to chemoresistance and radio-resistance. Hence, inhibiting epithelial to mesenchymal transition in CC cells sensitizes them to drugs and radiation (Qureshi et al., 2015).

Tumour Microenvironment Interactions:

The tumour microenvironment (TME) comprises of tumour cells and several non-cancerous cells like fibroblasts, stromal cells, endothelial cells, immune cells (such as macrophages, microglia, and lymphocytes), as well as the constituents of extracellular matrix. The interaction between TME and cancer cells is crucial for the establishment of a CSC niche which supports quiescence property and promote tissue invasion. Highly angiogenetic cancers like advanced CC, CSCs can differentiate into functional endothelial cells to form blood vessels known as vascular mimicry (Di Fiore et al., 2022). Angiogenic factors released from CSCs promote vascular growth and enhance tumour growth. On the other hand, endothelial cells provide angiocrine-signalling to regulate CSC behavior. Interactions between cCSCs and components of the tumour microenvironment, such as cancer-associated fibroblasts, tumour-associated macrophages, and extracellular matrix proteins, create a protective niche that shields cCSCs from the cytotoxic effects of chemotherapy. The microenvironment could stimulate signalling pathways, such as Notch and Wnt and create an inequity between self-renewal and differentiation CSCs. These disproportion enable CSCs for higher evasion, metastasis and anoikis (Phi et al., 2018; Madhu et al., 2022, 2023).
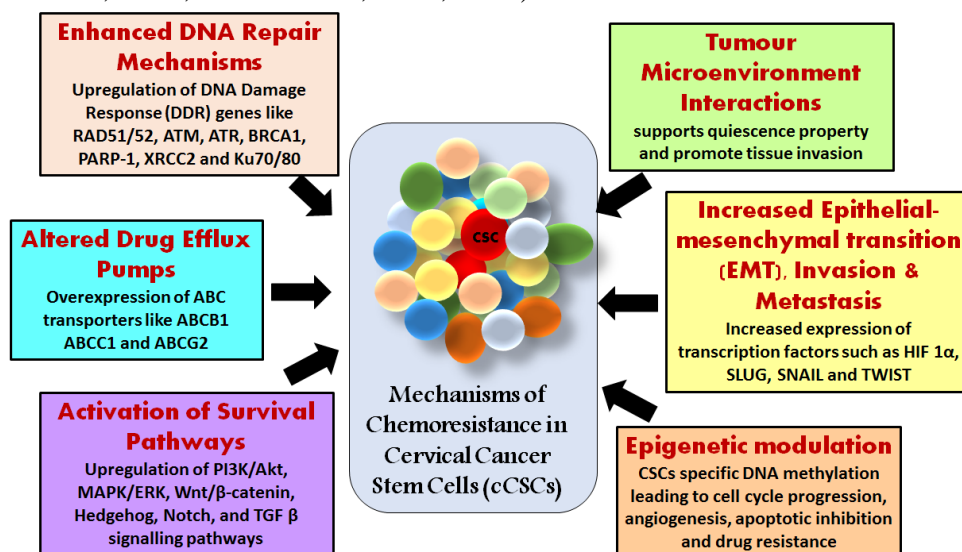

Figure 2. Mechanisms of chemoresistance in cervical cancer stem cells (cCSCs)

Hypoxic TME is associated with increased cancer aggression, progression, metastasis and significantly impair tumour response to anti-cancer therapies. Hypoxia-inducible factors 1 and 2 (HIF1/2) are activated in hypoxic TME which bind to promoter regions containing the hypoxia-response element (HRE) of several downstream genes associated with angiogenesis, apoptosis, metabolic regulation, and pH balance. Activated PI3K/ATK pathway further activate HIF1/2 creating a feedback loop to promote CSCs (Heddleston et al., 2010). Studies have shown that hypoxia promotes radioresistance of cCSC from HeLa and SiHa cell lines by activating the DNA damage checkpoint response and improved DNA repair (Yao et al., 2020).

Targeting cervical CSCs to overcome chemoresistance

CSC-targeted therapy has been a popular topic for research in past few years to improve and prevent cancer relapse. However, very few studies related to cCSC-specific targeted therapies have been carried out so far. In general, strategies combining conventional chemotherapy with molecules targeting cCSC-specific pathways such as Notch, Wnt, Hedgehog, hold promise in overcoming chemoresistance. Inhibition of key stemness regulatory molecules like Oct4, Sox2, and Nanog has been shown to sensitize cCSCs to chemotherapy and reduce tumour recurrence (Huang & Rofstad, 2017). As previously mentioned, ALDH protects cCSCs from elevated ROS levels and promotes chemo-and radio-resistance. Several ALDH inhibitors such as CM307 and 673A have shown efficacy in pre-clinical models of gynecologic malignancies, therefore, have potential for improving patient outcomes in CC (Muralikrishnan et al., 2020). The inhibitors of ABC transporter in combination with chemotherapy is in pre-clinical study in CC (Shukla et al., 2011). Nanocarriers loaded with chemotherapeutic agents can enhance drug delivery to cCSCs while minimizing systemic toxicity. Gold and silver nano-particles conjugated with chemotherapeutic agents showed efficacy against human glioma, breast cancer and oral cancer stem cells in vitro. Harnessing the immune system to target cCSCs via immune checkpoint inhibitors or chimeric antigen receptor (CAR) T-cell therapy represents an emerging approach in combating chemoresistance (Huang & Rofstad, 2017). Disrupting interactions between cCSCs and the TME through targeting ECM remodelling enzymes, immune checkpoint inhibitors, and CAFs may enhance the efficacy of chemotherapy. Therefore, combinatorial approaches incorporating conventional chemotherapeutic agents with targeted therapies, immunotherapy, or epigenetic modifiers hold promise for overcoming chemoresistance and improving treatment outcomes in cervical cancer patients. There are also certain limitations for CSC-targeting therapies. CSCs are usually present at very low in numbers (0.1-10%) and their biological characteristics are quite similar to normal stem/progenitor cells, therefore, making the task more challenging to specifically target CSC.

Conclusion:

Understanding the molecular mechanisms underlying chemoresistance in cCSCs is crucial for the development of effective therapeutic strategies. Targeting cCSC-specific pathways, utilizing nanotechnology-based drug delivery systems, modulating the tumour

microenvironment, exploring combination therapies, and exploring immunotherapeutic approaches offer promising avenues for overcoming chemoresistance and improving outcomes in cervical cancer patients and reduce the burden of cervical cancer worldwide.

References:

Alisi, A., Cho, W. C., Locatelli, F., & Fruci, D. (2013). Multidrug resistance and cancer stem cells in neuroblastoma and hepatoblastoma. *International journal of molecular sciences*, *14*(12), 24706–24725. https://doi.org/10.3390/ijms141224706

Bailly, C., Thuru, X., & Quesnel, B. (2020). Combined cytotoxic chemotherapy and immunotherapy of cancer: modern times. *NAR cancer*, *2*(1), zcaa002. https://doi.org/10.1093/narcan/zcaa002

Bhatla, N., Aoki, D., Sharma, D. N., & Sankaranarayanan, R. (2018). Cancer of the cervix uteri. *International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics*, *143 Suppl 2*, 22–36. https://doi.org/10.1002/ijgo.12611

Burmeister, C. A., Khan, S. F., Schäfer, G., Mbatani, N., Adams, T., Moodley, J., & Prince, S. (2022). Cervical cancer therapies: Current challenges and future perspectives. *Tumour virus research*, *13*, 200238. https://doi.org/10.1016/j.tvr.2022.200238

Chan, C. K., Aimagambetova, G., Ukybassova, T., Kongrtay, K., & Azizan, A. (2019). Human Papillomavirus Infection and Cervical Cancer: Epidemiology, Screening, and Vaccination-Review of Current Perspectives. *Journal of oncology*, *2019*, 3257939. https://doi.org/10.1155/2019/3257939

Das, J., Das, M., Doke, M., Wnuk, S., Stiffin, R., Ruiz, M., & Celli, J. (2021). A small molecule inhibits pancreatic cancer stem cells. *Int. J. Exp. Res. Rev.*, 26, 1-15. https://doi.org/10.52756/ijerr.2021.v26.001

Di Fiore, R., Suleiman, S., Drago-Ferrante, R., Subbannayya, Y., Pentimalli, F., Giordano, A., & Calleja-Agius, J. (2022). Cancer Stem Cells and Their Possible Implications in Cervical Cancer: A Short Review. *International journal of molecular sciences*, *23*(9), 5167. https://doi.org/10.3390/ijms23095167

Duenas-Gonzalez, A., & Gonzalez-Fierro, A. (2019). Pharmacodynamics of current and emerging treatments for cervical cancer. *Expert opinion on drug metabolism & toxicology*, *15*(8), 671–682. https://doi.org/10.1080/17425255.2019.1648431

Fan, Q., Qiu, M. T., Zhu, Z., Zhou, J. H., Chen, L., Zhou, Y., Gu, W., Wang, L. H., Li, Z. N., Xu, Y., Cheng, W. W., Wu, D., & Bao, W. (2015). Twist induces epithelial-mesenchymal transition in cervical carcinogenesis by regulating the TGF-β/Smad3 signaling pathway. *Oncology reports*, 34(4), 1787–1794. https://doi.org/10.3892/or.2015.4143

French, R., & Pauklin, S. (2021). Epigenetic regulation of cancer stem cell formation and maintenance. *International journal of cancer*, *148*(12), 2884–2897. https://doi.org/10.1002/ijc.33398

Gillespie, M. S., Ward, C. M., & Davies, C. C. (2023). DNA Repair and Therapeutic Strategies in Cancer Stem Cells. *Cancers*, *15*(6), 1897. https://doi.org/10.3390/cancers15061897

Heddleston, J. M., Li, Z., Lathia, J. D., Bao, S., Hjelmeland, A. B., & Rich, J. N. (2010). Hypoxia inducible factors in cancer stem cells. *British journal of cancer*, *102*(5), 789–795. https://doi.org/10.1038/sj.bjc.6605551

Huang, R., & Rofstad, E. K. (2017). Cancer stem cells (CSCs), cervical CSCs and targeted therapies. *Oncotarget*, *8*(21), 35351–35367. https://doi.org/10.18632/oncotarget.10169

Huang, Z., Wu, T., Liu, A. Y., & Ouyang, G. (2015). Differentiation and transdifferentiation potentials of cancer stem cells. *Oncotarget*, *6*(37), 39550–39563. https://doi.org/10.18632/oncotarget.6098

Hull, R., Mbele, M., Makhafola, T., Hicks, C., Wang, S. M., Reis, R. M., Mehrotra, R., Mkhize-Kwitshana, Z., Kibiki, G., Bates, D. O., & Dlamini, Z. (2020). Cervical cancer in low and middle-income countries. *Oncology letters*, *20*(3), 2058–2074. https://doi.org/10.3892/ol.2020.11754

Khan, M. J., & Smith-McCune, K. K. (2014). Treatment of cervical precancers: back to basics. *Obstetrics and gynecology*, *123*(6), 1339–1343. https://doi.org/10.1097/AOG.0000000000000287

Madhu, N.R., Sarkar, B., Biswas, P., Roychoudhury, S., Behera, B.K., & Acharya, C.K. (2023). Therapeutic potential of melatonin in glioblastoma: Current knowledge and future prospects. Biomarkers in Cancer Detection and Monitoring of Therapeutics, Volume-2. Elsevier Inc., pp. 371-386. ISBN 978-0-323-95114-2. https://doi.org/10.1016/B978-0-323-95114-2.00002-9

Madhu, N.R., Sarkar, B., Roychoudhury, S., Behera, B.K. (2022). Melatonin Induced in Cancer as a Frame of Zebrafish Model. © Springer Nature Singapore Pte Ltd. 2022, S. Pathak et al. (eds.), Handbook of Animal Models and its Uses in Cancer Research, pp. 1-18. ISBN: 978-981-19-1282-5 https://doi.org/10.1007/978-981-19-1282-5_61-1

Manni, W., & Min, W. (2022). Signalling pathways in the regulation of cancer stem cells and associated targeted therapy. *MedComm*, *3*(4), e176. https://doi.org/10.1002/mco2.176

Martin-Hirsch, P. L., & Wood, N. J. (2011). Cervical cancer. *BMJ clinical evidence*, *2011*, 0818.

Marzagalli, M., Fontana, F., Raimondi, M., & Limonta, P. (2021). Cancer Stem Cells-Key Players in Tumor Relapse. *Cancers*, *13*(3), 376. https://doi.org/10.3390/cancers13030376

Muralikrishnan, V., Hurley, T. D., & Nephew, K. P. (2020). Targeting Aldehyde Dehydrogenases to Eliminate Cancer Stem Cells in Gynecologic Malignancies. *Cancers*, *12*(4), 961. https://doi.org/10.3390/cancers12040961

Navaei, Z. N., Khalili-Tanha, G., Zangouei, A. S., Abbaszadegan, M. R., & Moghbeli, M. (2022). PI3K/AKT signalling pathway as a critical regulator of Cisplatin response in tumor cells. *Oncology research*, *29*(4), 235–250. https://doi.org/10.32604/or.2022.025323

Organista-Nava, J., Gómez-Gómez, Y., Garibay-Cerdenares, O. L., Leyva-Vázquez, M. A., & Illades-Aguiar, B. (2019). Cervical cancer stem cell-associated genes: Prognostic implications in cervical cancer. *Oncology letters*, *18*(1), 7–14. https://doi.org/10.3892/ol.2019.10307

Phi, L. T. H., Sari, I. N., Yang, Y. G., Lee, S. H., Jun, N., Kim, K. S., Lee, Y. K., & Kwon, H. Y. (2018). Cancer Stem Cells (CSCs) in Drug Resistance and their Therapeutic Implications in Cancer Treatment. *Stem cells international*, *2018*, 5416923. https://doi.org/10.1155/2018/5416923

Prasetyanti, P. R., & Medema, J. P. (2017). Intra-tumor heterogeneity from a cancer stem cell perspective. *Molecular cancer*, *16*(1), 41. https://doi.org/10.1186/s12943-017-0600-4

Qureshi, R., Arora, H., & Rizvi, M. A. (2015). EMT in cervical cancer: its role in tumour progression and response to therapy. *Cancer letters*, *356*(2 Pt B), 321–331. https://doi.org/10.1016/j.canlet.2014.09.021

Saito, S., Ku, C. C., Wuputra, K., Pan, J. B., Lin, C. S., Lin, Y. C., Wu, D. C., & Yokoyama, K. K. (2022). Biomarkers of Cancer Stem Cells for Experimental Research and Clinical Application. *Journal of personalized medicine*, *12*(5), 715. https://doi.org/10.3390/jpm12050715

Shu, X. R., Wu, J., Sun, H., Chi, L. Q., & Wang, J. H. (2015). PAK4 confers the malignance of cervical cancers and contributes to the cisplatin-resistance in cervical cancer cells via PI3K/AKT pathway. *Diagnostic pathology*, *10*, 177. https://doi.org/10.1186/s13000-015-0404-z

Shukla, S., Ohnuma, S., & Ambudkar, S. V. (2011). Improving cancer chemotherapy with modulators of ABC drug transporters. *Current drug targets*, *12*(5), 621–630. https://doi.org/10.2174/138945011795378540

Singh, D., Vignat, J., Lorenzoni, V., Eslahi, M., Ginsburg, O., Lauby-Secretan, B., Arbyn, M., Basu, P., Bray, F., & Vaccarella, S. (2023). Global estimates of incidence and mortality of cervical cancer in 2020: a baseline analysis of the WHO Global Cervical Cancer Elimination Initiative. *The Lancet. Global health*, *11*(2), e197–e206. https://doi.org/10.1016/S2214-109X(22)00501-0

Singh, M., Jha, R. P., Shri, N., Bhattacharyya, K., Patel, P., & Dhamnetiya, D. (2022). Secular trends in incidence and mortality of cervical cancer in India and its states, 1990-2019: data from the Global Burden of Disease 2019 Study. *BMC cancer*, *22*(1), 149. https://doi.org/10.1186/s12885-022-09232-w

Sravani, A.B., Ghate, V. & Lewis, S. Human papillomavirus infection, cervical cancer and the less explored role of trace elements. *Biol Trace Elem Res* 201, 1026–1050 (2023). https://doi.org/10.1007/s12011-022-03226-2

Yao, T., Weng, X., Yao, Y., Huang, C., Li, J., Peng, Y., Lin, R., & Lin, Z. (2020). ALDH-1-positive cells exhibited a radioresistant phenotype that was enhanced with hypoxia in cervical cancer. *BMC cancer*, *20*(1), 891. https://doi.org/10.1186/s12885-020-07337-8

Zhang, X., Lv, Z., Xu, X., Yin, Z., & Lou, H. (2020). Comparison of adenocarcinoma and adenosquamous carcinoma prognoses in Chinese patients with FIGO stage IB-IIA cervical cancer following radical surgery. BMC cancer, 20(1), 664. https://doi.org/10.1186/s12885-020-07148-x

Zhou, H. M., Zhang, J. G., Zhang, X., & Li, Q. (2021). Targeting cancer stem cells for reversing therapy resistance: mechanism, signalling, and prospective agents. *Signal transduction and targeted therapy*, *6*(1), 62. https://doi.org/10.1038/s41392-020-00430-1

Zhu, H., Luo, H., Zhang, W., Shen, Z., Hu, X., & Zhu, X. (2016). Molecular mechanisms of cisplatin resistance in cervical cancer. *Drug design, development and therapy*, *10*, 1885–1895. https://doi.org/10.2147/DDDT.S106412

HOW TO CITE