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ROLE OF CANCER STEM CELLS IN CERVICAL CANCER

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ABSTRACT

In spite of screening and vaccination programmes, cervical cancer has become a foremost reason of cancer related deaths in women. Chemotherapy and surgery is involve in prolong survival in the patients but not give the permanent cure to patients of cervical cancer. Radical surgery is the only option for the cervical cancer at their advance stage, which also affects the childbearing capacity of the patients. Sometime it also results in the recurrence of the disease. Therefore, there is an urgent requirement to develop novel therapeutics. Hypothesis of CSCs have reported about a tumor possesses hierarchical cellular structure containing small subset of cells named as cancer stem cells inducing tumorigenesis. Many studies have reported about the CSCs tumor – initiating capacity, These CSCs play an important roles in metastasis of tumor, relapse and chemo radio-resistance. They are considered for the better outcome because they involve in the initiation of tumor propagation. The most common gynaecological malignancy is cervical carcinoma and in females it shows a high cancer mortality rate. Therefore, cervical cancer stem cells has emerged as an keen player in investigation of cervical cancer. Herein, this review, we have summarized CSCs and CCSCs as an emerging key role player in early diagnosis of cervical cancer and as a therapeutic target in this cancer.

KEYWORDS: Cervical Cancer, Cancer Stem Cell, Cervical Cancer Stem Cell, Human Papilloma Virus.

CERVICAL CANCER

Cervical cancer is considered as the 4th most common cancer among all types of cancers in women. Ferlay et al. (2013) has noticed 5,28,000 cases of cervical cancer, in which 266,000 death were reported in 2012. HPV infection has been considered as crucial reason of cervical cancer.[1] Walboomers et al. has reported HPV infection in 99.7% of specimens of cervical cancer in 1999. All HPV (Human Papilloma Virus) infections do not lead to cervical cancer, but it takes a long time approximately10-15 years to cause cervical cancer by HPV infection.[2] There are several other factors such as multiple sexual partners, sexual activity at early stage, use of oral contraceptives for long time, use of tobacco and infection with Chlamydia trachomatis which aid to the succession of HPV infection in cervical cancer.[3] Ferlay et al. have revealed the socioeconomic feature of cervical cancer in 2012, it has been represented that 87% cervical cancer related deaths in less developed countries, in which only India has accounted for 25% in 2012.[1]

Routine screening procedures for the early detection of precancerous lesions in the cervix and introduction of vaccine against HPV have decreased the rate of cervical cancer related deaths in developed countries. These preventive procedures against HPV, later considered unapproachable due to their high cost. Stages of cervical cancer help in determining the treatment procedure comprising of chemotherapy and radiotherapy, while cancer at their advance stage demand surgical procedures.

Many investigators have explained about the effect of cancer stem cell theory in the origin of cancers. This theory explains about distinctive patterns of cells in tumor, named as cancer stem cells (CSCs). These cells possess the capability to start and to increase the growth of tumor.[4] Bonnet and Dick (1997), first time, described about the existence of cancer stem cells in acute myeloid leukemia.[5] After that, many experimental studies have been demonstrated the role of CSCs in solid tumor of different parts of body like breast[6], colon[7], brain[8], pancreas[9], prostate[10], lung[11] and liver.[12] CSCs show the similarity to somatic stem cells due to their same characteristics such as self-renewal properties and differentiation to non-stem cancer cells. Whereas it is well known that regulation of normal stem cells occur

under the genetic and environmental stimulus[13], however, there are still not any evidences about the response of CSCs towards these stimuli.[14] Additionally, it has been noticed that CSCs show the resistance towards chemotherapy and radiotherapy, so these cells have been known to play central role in relapse of cancer. So, according to CSCs hypothesis, cancer is hard to pin down until CSCs are removed.

ORIGIN OF CERVICAL CANCER

Three different types of cells involve in the composition of the cervix. These cells are such as hard squamous cells in the ectocervix, mucin secreting glandular cells in the endocervix and the last parts represent the metaplastic cells, present between the ectocervix and endocervix. This zone is also named as transformation zone or squamo-columnar junction. Ectocervix comprises of four different layers such as Basal, parabasal, intermediate, superficial. A process named as, exfoliation involves in the continuous removal of cells from the superficial layer.[15] Basal layers, having actively dividing immature epithelial cells, possessing stem like properties, involve in the regeneration of these cells. Endocervix cells possess cilia and secrete mucous, help in the movement of spermatozoa. Cervical cancer origin starts in the transformation zone. HPV infection occur in stem cells, possess different gene expression profile of the epidermis in the transformation zone.[16,17] Basal stem cell and terminally differentiated cells involve in the formation of cervical epithelium.[18] When injury occurs in the differentiated cells of cervical epithelium, basal stem cells start to proliferate and differentiate and finally replace the damaged cells. Differentiation ability of stem cells play a key role in the origination of viral particles.[19] Infection of virus instructs the cells to start symmetric division rather than asymmetric division. This process allows the cells for the proliferation and production of viral particles and finally inhibit their differentiation activity[18], High risk HPV involves in increased proliferative activity and help in the production of viral particles and prevent the differentiation processes. Infection of virus directly does not lead to cancer process, but it induces the proliferative activity of infected cells. This process leads to mutation and loss of DNA repair mechanisms activity, which finally results in the HPV infection to induce cancer process (fig: 1).

This fact revealed the concept that stem cells play central role in Cervical cancer earlier than the concept of CSCs. Thus, it may conclude that HPV infected stem cells give rise to cancer stem cells. Different signaling pathways related to stem like properties of cells such as NOTCH[19], Hedgehog[20], Wnt[21], BMI[22] involved in the cervical cancer.

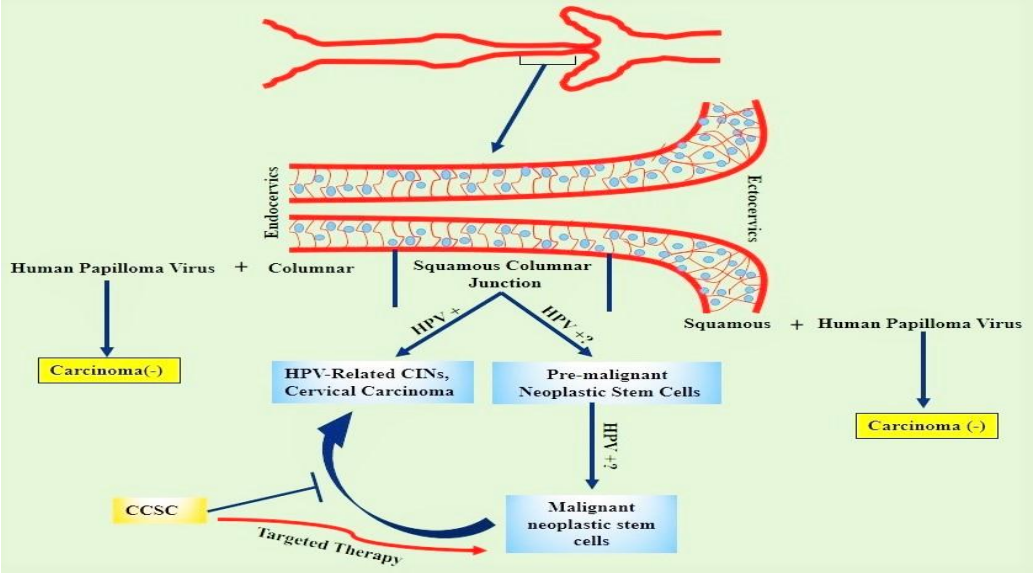

Figure 1: Description of Cervical cancer and CCSCs: Relation of carcinogenic HPV infection with causal effect on cervical cancer- HPV related infection occur in ectoendocervical squamocolumnar junction of the cervix progresses in the cervical cancer but it does not occur in columnar cells of endocervix and squamous cells of the ectocervix. (Modified from the review of Huang R et al. 2016)

Carcinogenic HPV infection has a causal relation with cervical carcinogenesis. However, when the cervix is infected with carcinogenic HPV, HPV-related CINs and cervical carcinomas are usually generated within a specific cell population that is located in the ectoendocervical squamocolumnar (SC) junction of the cervix. They are typically not generated in the columnar cells located within the endocervix and squamous cells within the ectocervix. The HPV-related CINs and cervical cancers maintain the genetic profile of the junction cells, indicating their cellular hierarchy. Progenitor cells located in the junction area infected with carcinogenic HPV are likely to become pre-malignant neoplastic stem cells that can propagate malignant neoplastic stem cells (CCSCs), which propagate cervical carcinoma clones. Therapeutically targeting these cells may prevent the propagation of HPV-related CINs and cervical carcinomas.

CANCER STEM CELLS

Cancer stem cells are small number of groups of tumour cells, having characteristics of tumorigenesis, self-renewal[23], multilineage differentiation potential, slow cycling capacity.[24-26] In recent year, researches have provided advanced method to identify tumor cells and their progeny in vivo, which convinced about the survival of CSCs.[27-29] CSCs divide asymmetrically and give rise to two different daughter cells. One copy of this cell make the entire genome of mother cells and the other copy of daughter cell, show the similarity to stem cells. CSCs comprise of self-renewal capacity and have ability for tumor initiation.[30] Due to asymmetrical division of CSCs, tumor cells possess combination of CSCs and their progenies, because of the significant phenotypic characteristic and hetrogenity in functions of CSCs.[31] Hence, CSCs play a central role in the starting stage of cancer, cancer relapse and metastasis.[32,33], that's why, CSCs have considered as to improve the survival of patients of cancer and also to prevent cancer relapse processes.[34-36] CSCs are quiescent cells and reside in CSC niche, its result in the protection from damage from anti-tumor therapies.[34,37-39] An optimal balance is found between activation, self-renewal and differentiation processes for CSCs remain in CSCs niche.[40,41] In the stress condition, CSCs activate and recruit into other tissues to differentiate and transform into malignant cells (19).

Recent researches on in-vitro and in-vivo studies have reported many stem cell specific markers to recognize CSCs. There have been many CSCs markers identified as cancer therapeutic targets. Whereas, the complex biology of CSCs have emerged as a challenge.[42-44] An associated difficulty arises that tumor cells show dissimilarity among different patients, demonstrating that CSCs markers are specific to their respective tumors.[45]

CERVICAL CANCER STEM CELLS

The experimental limitation of functional assay have invited the in-vitro studies and in-vivo studies to illustrate about stem cell markers to identify cancer stem cells. Hence, the identification of CSCs specific markers become an attainable approach to identify CSCs, whereas molecular assays are not enough to identify CSCs.[46] Recently stem cell markers for cervical CSCs have been emerged as a novel marker to cure cervical cancer. Herein, we described about the markers for CCSCs, currently they act as potential targets in CCSC studies.

CANCER STEM CELL MARKERS

Oct-4

Human containing the gene POU class 5 homeobox 1 (POU5F1) encodes transcription factor, named OCT4 (OCT3 and 3/4.). It maintains the pluripotency of stem cells and also play a central role in embryonic development.[47,48] Cervical cancer tissue show the over-expression of OCT4 in comparison to adjoining normal tissues.[49] Studies on cancerous cells of cervical cancer have revealed that over- expession of OCT4 is linked with low-differentiated grade of cervical cancer cells and positive lymph node metastasis. Clinical trial have explained the positive correlation between over-expression of OCT linked with radiotherapy resistance and later it have been concluded that expression of OCT4 is an independent risk factor for survival of cervical cancer patients.[49,50] Additionally, an invitro study confirmed that OCT4 involves in the promotion of tumor progression and also inhibits apoptosis of cancerous cell.[51]

CD-133

Human gene prominin 1 (PROM1) encodes a 120KDa pentaspanning transmembrane glycoprotein CD-133.[52] It has been widely used as CSC marker in several tumors[53], such as melanoma[54,55], lung[56] colon[57], liver[58,59], breast[60], brain[61], ovarion[62-64] cancers. In CSCs targeted therapy, CD-133 acts as a specific Cervical Cancer Stem Cells markers. Many studies on cervical cancer have shown that cervical-stem like cells comprise of CD-133, which shows the resistance towards radiation.[65,66]

CD49F

Integrin alpha 6 (ITGA6) gene encodes a cell surface protein, named as CD49f. It is mainly found in human embryonic stem cells and mesenchymal stem cells.[67,68] Moreover, some CCSC models presents high expression of CD49f shows resistivity towards radiotherapy.[65]

ALDH1

Aldehyde dehydrogenase 1 is found in the cytoplasm, involve in metabolic processes. It catalyses the dehydrogenation of aldehydes. It has the ability of self-renewal and tumorogenesis,[69] mainly in breast cancer.[70,71] Moreover, CSCs comprising ALDH1 stem cell marker is found to be associated with successful patients derived xenografts in primary breast cancer.[72] Expression of ALDH1 shows poor survival rate in tissues of patients.[73] Additionally in cervical cancer cells, overexpression of ALDH1 is linked with elevated level of cell proliferation, migration, sphere formation and tumor progression[74], showing ALDH1 shows stemness character in cervical cancer.

ABCG2

ATP- binding cassette sub-family G member 2 (ABCG2), belong to ATP binding cassette (ABC) which is drug efflux membrane transporter. ABCG2 is also known as breast cancer resistance protein (BRCP). It acts as multidrug resistance (MDR) in various types of cancer and pumps out a large number of chemical compounds from cells.[75] It acts as molecular marker in a side population phenotype, which is a main characteristic feature of CSCs.[76,77] Different therapeutic such as Axitinib[78] and Icotinib[79] target and inhibit the activity of ABCG2, which induces cellular sensitivity against chemotherapy. As a result, ABCG2 has been considered as CSC marker for cancer treatment.[80] In cervical

cancer, Nrf2, the redox sensing factor involves in the regulation of ABCG2 at transcriptional level. Overexpression of Nrf2 and ABCG2 in cells show the similar character as stem cells such as infinite cell proliferation and apoptosis inhibition.[81]

SOX2

SOX2, a key transcription factor, plays a crucial role in explaining fate of stem cell as well as involve in the embryonic development.[82,83] Over-expression of SOX2 have been observed in cervical carcinoma in comparison to normal cervix tissue.[84-86] Additionally, Over-expression of SOX2 is found to be associated with poorly differentiated cervical cancer.[85] This fact revealed that SOX2 acts as marker of undifferentiated cervical cancer. Many in-vitro and in-vivo studies have been reported that over-expression of SOX2 is linked with increased proliferative activity of cells and tumourigenisis[84] in cervical cancer.[87] High expression of SOX2 in tumor cells of cervical squamous patients of cancer shows resistance towards radiation therapy.[88]

OSTEOPONTIN (OPN)

Malignant and tumour stromal cells secrete a chemokine-like extracellular matrix protein named as Osteopontin (OPN). It plays a central role in migration of tumour cells and metastasis.[89,90] Hypoxia up-regulates OPN, so it is considered as an endogenous hypoxic marker.[91] OPN binds to hypoxic regions in tumor tissue. Higher expression of OPN shows resistance towards hypoxic radiation.[92] In the hypoxic condition, OPN modulate HIF1α dependent VEGF expression for the promotion of tumors angiogenesis.[93] Over-expression of OPN is also responsible for poor survival in human cervical cancer.[92] OPN is also found in blood serum shows higher expression level results in the lower survival rate in cervical cancer patients.[94]

BMI1

BMI1 maintains the stem cells characteristics by the repression of differentiation specific genes.[95] Cervical cancer cell lines (SiHa, HeLa, C33a, CaSki) have shown the up-regulated expression of BMI1, when they were compared with normal epithelial of cervical cancer line. Study on uterine cervical cancer tissue have also been reported up-regulated expression. This report has also been shown positive correlation with tumor size and metastasis of lymph node.[96]

KLF4

KLF4 plays a crucial role in differentiation, when it is over-expressed in basal cells of cervical epithelium. Progression of cervical cancer decreases expression of KLF4. P27Kip1 binds to promoter region (-435 and -60) and reduces the growth of cell and inhibits the formation of tumor via the ectopic expression of KLF4.[97]

UTF1

During embryonic development UTF1 plays main role in cell fate determination. Wu et al. found down regulated expression of UTF1 is linked with progression of cervical cancer.[98] Decreased expression of UTF1 was involved in hypermethylation of promoter.[99] Interestingly, similar to UTF1 involved in the activation of p27Kip 1, which bound to region-517 and 388 of promoter to inhibit tumorigenesis in vivo and cell proliferation in-vitro.

FUTURE PROSPECTIVE

Since the past few years, incredible progress have been done in the research area of CSCs. There are a lot of things, still which have not covered in this field. No clear evidence have been identified about the origin of CSCs. Sometimes, HPV infection in epidermal stem cells may or may not lead to cervical cancer. But it takes several years to show the symptoms of cervical cancer. Gupta et al. has reported a major constraint about CSC that they cannot grow as pure population because they have the intrinsic property to regain the characteristics of samples from which they have been removed.[100]

It gives unjustified importance to method of their isolation. Additionally, there are many methods used to separate CSCc in which only small set of CSCs have been picked. The population of CSCs shows similar characteristics but they are not identical. Sphere formation assay shows minor increase in CD-133 activity in CSCs of HeLa cell line while SP assay have shown marked. Up-regulation in CD-133[101] has been observed that methods of isolation also affect the results of study. Therefore, there is a pressing requirement of better methods for separation of CSCs. As it has been noticed that, amount of CSCs is linked with the severe stage of disease, identification of CSCs may be advantageous for the women undergoing routine screening of cervical cancer. It is not only beneficial for early detection of disease, but also provide primary fact about the grade of disease. Many evidences have been shown about the function of CSCs in diseases recurrence and chemoresistance metastasis so there is an urgent need to study them in broad detail in cervical cancer. The better understanding of mechanisms of cervical cancer stem cells improves the screening procedures and therapeutic approaches, which finally results in the improved outcome in the patients of cervical cancer.

CONCLUSION

Cancer comprises of small subset of CSCs possess epithelial–mesenchymal phenotypes and non-stem cells with epithelial traits. CSCs have recognized as a novel target in treatment of cancer due to its ability of self-renewal and tumorigenesis. Many evidences have shown the existence of CSCs in cervical tumors. These studies have been explained about the functional status and contribution of stem/progenitor cell population in cervical cancer. Several markers such as ABCG2, SOX2, CD133, CD49f and ALDH1 have been identified for CSC isolation as well as early diagnostic and better therapeutic targets in cervical cancer.

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