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CERVICAL CANCER STEM CELL

Nursing

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ABSTRACT

Cervical Cancer is one of the most aggressive malignant tumor diseases, accounting for a large proportion of all cancer cases. Patients with cervical cancer have very poor prognosis, with short survival time and high recurrence rates after therapy. This is associated with the existence of cancer stem cells (CSCs), which is well supported by a large number of previous studies. Here, we describe the signaling pathways and mechanisms (mainly Wnt, notch and hedgehog pathways) involved in cancer stemness. This will help develop new therapies against CSCs and improve the prognosis of cancer cervical patients.

KEYWORDS

cervical cancer, stem cell, WNT, notch, hedgehog, cancer stemness, prognosis

The term "cancer" describes a group of diseases that are characterized by uncontrolled cellular growth, cellular invasion of adjacent tissues, and the potential to metastasize if not treated at a sufficiently early stage [1,2]. These cellular aberrations are produced by the accumulation of genetic modifications, either through changes in the underlying genetic sequence or through epigenetic alterations[3,4]. Tumors and other structures that result from aberrant cell growth contain heterogeneous cell populations with diverse biological characteristics and potentials. The cancer stem cells (CSCs) have been identified in many different types of tumors, including cervical cancer [4]. The CSCs are at a less-differentiated state than corresponding cancer cells. Similar to other stem cells, CSCs possess the capacity for asymmetrical division in addition to symmetrical division.

In fact, the heterogeneity of cancerous tissues is such that researchers will likely identify differences in the genetic profiles of different tissue samples from the same specimen. Cancer heterogeneity may be associated with the CSC content. Histologically, tumors with a high percentage of CSCs may be poorly differentiated, undifferentiated or mixed tumors. While scientists can classify organ or tissue-specific cancers into subcategories that may inform treatment decisions and provide predictive information, the remarkable complexity of cancer biology continues to confound treatment efforts.

Treatments vary according to the type and severity of the cancer. Surgery, radiation therapy, and systemic treatments such as chemotherapy or hormonal therapy are traditional approaches designed to remove or kill rapidly-dividing cancer cells. These methods have limited clinical use.

Several agents that target specific proteins implicated in molecular pathways associated with cancer were developed for clinical use in recent years. These include trastuzumab, a monoclonal antibody that targets the protein HER2 in breast cancer [5] gefitinib and erlotinib, which target the epidermal growth factor receptor (EGFR) in lung cancer [6] imatinib, which targets the BCR-ABL tyrosine kinase in chronic myelogenous leukemia[7] the monoclonal antibody bevacizumab, which targets the vascular endothelial growth factor in colorectal and lung cancer [8] and cetuximab and panitumumab, which target EGFR in colorectal cancer [8]. Cisplatin-based chemotherapy is a commonly used cervical cancer therapy. These agents have shown that a targeted approach can be successful, although they have been effective only in patients with certain cancer subclasses.

The treatments mentioned above have been successful mainly in localized cancers, but most have failed in the treatment of metastatic tumors [9–11]. The CSC as a cell within a tumour that possesses the capacity to self-renew will result in the formation of tumours. What this hypothesis suggests is that tumour-initiating cells possess enough stem-like characteristics to warrant a comparison with stem cells, since the observed experimental and clinical behaviour of metastatic cancer cells are highly reminiscent of the classical properties of stem cell. Intra-tumour genetic heterogeneity in cervical carcinoma is associated with a poor chemo/radio-therapy response, lymph node metastasis and pelvic recurrence.

One explanation for the heterogeneity in cervical carcinoma is the existence of CCSCs. The CSC hypothesis suggests that cancer does not simply appear spontaneously; rather, cancerous cells, like their non-cancerous counterparts, originate from other living cells. Stem cell-like populations have been characterized using cell-surface protein markers in breast[17], colon[18], brain[19], pancreas[20,21], cervix[22] and prostate[23] tumours.

However, identifying markers that unequivocally characterize a population of CSCs is still a challenging task, even when there is evidence that putative CSCs exist in a given solid tumour type. For example, cellular analysis suggests the presence of stem-like cells in hepatocellular carcinoma [24]. Definitive markers that allow to characterize these putative CSCs have yet to be identified, but several potential candidates were proposed recently [25,26]. In other cancers in which CSCs have yet to be identified, researchers are beginning to find links between established stem-cell markers with malignant cancer cells. For instance, the proteins Nanog, nucleostemin, and musashi-1, which are highly expressed in embryonic stem cells and are critical for maintaining their pluripotency, are also highly expressed in malignant cervical epithelial cells[27]. These specific squamo-columnar junction cells exhibit unique morphology and gene profiles, which distinguish them from the adjacent endocervical and ectocervical epithelium. For instance, they express squamo columnar junction-specific markers, keratin 7 (Krt7), anterior gradient 2 (AGR2), cluster differentiation 63 (CD63), matrix metalloproteinase 7 (MMP7) and guanine deaminase (GDA), it suggests that these proteins may play a role in the carcinogenesis and progression of cervical cancer. Given the similarities between tumour-initiating cells and stem cells, researchers are seeking to determine whether CSCs arise from stem cells, progenitor cells, or differentiated cells present in adult tissue.

Cancer Cells Arise from Stem Cells. Stem cells are distinguished from other cells by two characteristics: (1) they can divide to produce copies of themselves, or self-renew, under appropriate conditions and (2) they are pluripotent, or able to differentiate into most, if not all, mature cell types. If CSCs arose from normal stem cells present in adult tissue, the formation of tumours would not require cell dedifferentiation. In that scenario, cancer cells could self-renew by using the existing stem-cell regulatory pathways. The ability to self-renew gives stem cells long lifespans compared to mature,

differentiated cells [30,31]. It has been hypothesized that the limited lifespan of a mature cell makes it less likely to live long enough to undergo the multiple mutations necessary for tumour formation and metastasis.

Cancer Cells Arise from Progenitor Cells. The differentiation pathway from a stem cell to a differentiated cell usually involves one or more intermediate cell types. These intermediate cells, which are more abundant in adult tissue than stem cells, are called progenitor or precursor cells. They are partly differentiated cells present in fetal and adult tissues that usually divide to produce mature cells. However, they retain a partial capacity for self-renewal. This property, when considered together with their abundance in adult tissue compared to stem cells, has led some researchers to propose that progenitor cells could be a source of CSCs [32,33].

Cancer Cells Arise from Differentiated Cells. Some researchers have suggested that cancer cells could arise from mature, differentiated cells that somehow dedifferentiate to become more stem cell-like. In that scenario, the dedifferentiation process and the subsequent self-renewal of the proliferating cells would have to be driven by the required oncogenic genetic mutations. This model leaves open the possibility that a relatively large population of cells could have tumorigenic potential, a small subset of which would actually initiate the tumour.

The Notch Pathway. Its role in control of stem cell proliferation has now been demonstrated for several cell types including hematopoietic, neural and mammary stem cells. Components of the Notch pathway have been proposed to act as oncogenes in mammary, cervix and other tumors. A particular branch of the Notch signaling pathway that involves the transcription factor Hes3 has been shown to regulate a number of cultured cells with cancer stem cell characteristics contained from cervical cancer patients (Figure 1).

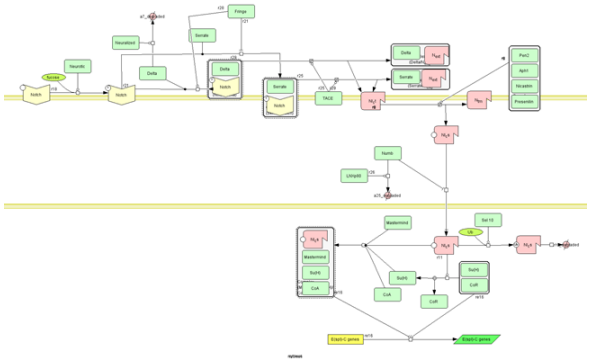

Figure 1 .Notch is a transmembrane receptor that mediates local cell-cell communication and coordinates a signaling cascade. It plays a key role in modulating cell fate decisions throughout the development of invertebrate and vertebrate species. A number of human diseases have been associated with mistakes of Notch function[47].

Sonic hedgehog and Wnt. These developmental pathways are also strongly implicated as stem cell regulators. Both Sonic hedgehog (SHH) and Wnt pathway are commonly hyperactivated in tumors and are requires to sustain tunor growth. However, the Gil transcription factors that are regulated by SHH take their name from cervical cancer, where they are commonly expressed at high levels (Figure 2).

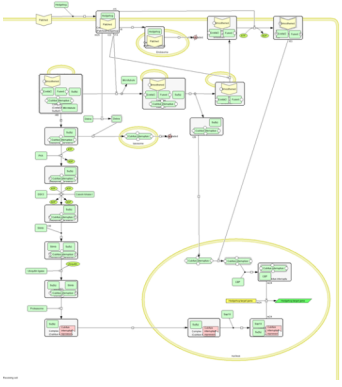

Figure2. This is the current model for the Hedgehog signaling pathway. The best data for mechanism of signaling has been worked out in Drosophila, so this model based largely on Drosophila data. Hedgehog target genes vary from tissue to tissue, so the identities of individual target genes have not listed. The main difference between the Drosophila and mammalian Hedgehog signaling pathways is the fact that there are three mammalian homologs of Cubitus interruptus, Gli1, Gli2 and Gli3. Some or all of the mammalian homologs may be proteolytically processed, but the data are controversial. There are two mammalian Ptc genes and three mammalian Hedgehog genes as well[47].

A degree of crosstalk exists between the two pathways and their activation commonly goes hand. This a trend rather than a rule. For instance, in cervicalcancer hedgehog signaling appears to antagonize Wnt. Sonic hedgehog blockers are available, such as cyclopamine. There is also a new water soluble cyclopamine that may be more effective in cancer treatment. There is also DMAPT, a water soluble derivate of parthenoide (induce oxidative stress, inhibits NFkappaB signaling) for AML (leukemia), and possibly myeloma and cervical cancer. Finally, the enzyme telomerase may qualify as a study subject in CSC physiology. If it is possible to eliminate the cancer stem cell, then a potential cure may be achieved if there are no more CSCs to repopulate a cancer (Figure 3).

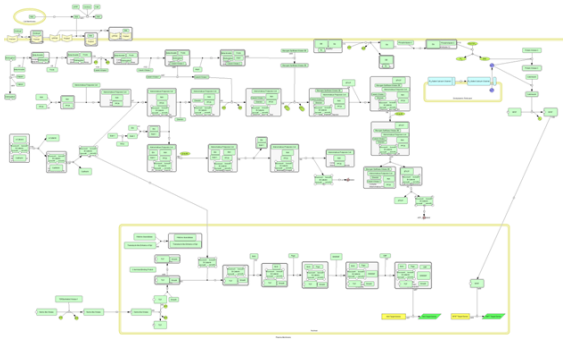

Figure 3 .The secreted protein Wnt activates the heptahelical receptor Frizzled on nieghboring cells. Activation of Frizzled causes the recruitment of additional membrane proteins which in turn result in 1) the activation of the protein Dishevelled via phosphorylation and 2) the activation of a heterotrimeric G protein of unknown type. Activation of Dishevelled results in the down-regulation of the Beta-Catenin destruction complex which causes ubiquitination of Beta-Catenin and its ultimate degradation via the proteasome. Inhibition of the Beta-Catenin destruction complex yields a higher cytosolic concentration of Beta-Catenin, which enters the nucleus, binds various transcriptional regulatory molecules including the TCF/LEF class of proteins, and results in the transcription of TCF/LEF target genes. Activation of the heterotrimeric G-protein pathway in turn activates Phospholipase C which in turn catalyzes the catalysis of PI(4,5)P2 into DAG and Ip3[47].

Conclusion

Hence, there is an urgent need to develop better methods for isolation of CSCs in cervical cancer. Since the proportion of CSCs is associated with the severity of the disease, the women undergoing routine cervical cancer screening will benefit tremendously if the screening procedure includes detection of CSCs. This would not only help in the early detection of the disease, but also provide preliminary evidence about the status of the disease.

The cancer, it is governed by an intricate interplay of molecular signals and can often resist systemic treatments. Paradoxically, the uncontrolled cellular growth that characterizes cancer may hold the key to understanding how it spreads throughout the body. It has long been suggested that tumours form and proliferate through the actions of a small population of unique cells. The observation that metastatic cancer cells exhibit an experimental and clinical behaviour that is highly reminiscent of the classical properties of stem cells has led researchers to search for and characterize "cancer stem cells" believed to be implicated in the development of cancer.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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