Cancer Stem Cells (CSCs): Emerging Concept and Strategy for Targeting Progression of Epithelial Ovarian Cancer

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The estimated new cases of ovarian cancer in the United States of America (USA) in 2014 is 21,980, and the estimated deaths is 14,270 [1]. It ranks 5th overall for cancer death in women, counting for 5% of all cancer deaths in women (lung, breast, colorectal, pancreatic are 1-4 respectively). At time of diagnosis, 15% of the total cases are localized, 18% are regional, and 61% are distant. In 2011, there were an estimated 188,867 women living with ovary cancer in the United States. The Standard treatment of ovarian cancer consists of surgical resection of disease followed by taxane and platinum-based chemotherapy which yields a partial response rate of about 80% and a complete response rate of 40%-60% in patients with advanced disease [1]. However, the recurrence rate is approximately 70% and five-year survival is 45% in patients with advanced disease [3-5]. It appears that the majority of ovarian cancer cells are initially chemosensitive as evidenced by the initial response rates. However, the high recurrence rates suggest development of chemoresistance. It is thought that some cells are not killed by chemotherapy, or they repopulate after exposure to chemotherapeutic agents. These cells have been described as ovarian cancer stem cells (CSCs).

The CSCs are progenitor cells [6,7], and its markers have been shown to be upregulated in cells growing in tumospheres. In ovarian cancer, this spheroid tumor cells are thought to be related to the spread of cancer and metastasis in the peritoneal cavity. CSCs have been shown to self-renew, differentiate, and metastasize [8]. In addition, it was observed that treatment with chemotherapeutic agents results in increased drug-resistant CSCs and this leads to recurrence. Certain types of blood cancers have normal stem cells, but normal ovarian stem cell are unknown [6].

Cancer Stem Cells Markers and its Significance

There are no specific ovarian CSCs markers and researchers rely on protein markers identified from other malignancies. These some of these proteins include CD44, CD133, CD117, ALDH1A1, and EpCAM. CD44 is a receptor that is involved in cell-cell and cell-matrix interactions and affects cellular growth, differentiation, and motility. It has been shown that CD44+/CD117+ cells had increased chemoresistance to taxane and platinum-based chemotherapy, and the ability to self-propagate [9]. It was noted that CD44+ cells were enriched in ovarian cancer patient ascites and once isolated and xenografted gave rise to tumor with both CD44+ and CD44- cells [10]. There are several strategies to target the CD44 receptor, which include binding to hyaluronic acid and osteopontin, a protein over-expressed in ovarian cancer, and contribute to receptor tyrosine kinase activation [11]. CD133 is a trans-membrane glycoprotein, and was shown that the amount of CD133 positive cells was higher in ovarian carcinoma than in normal ovarian tissue [12]. The ability of CD133+ cancer cells to generate both CD133+ and CD133- cells has been reported [13]. In addition, CD133 observed to be involved in increased tumor formation, increased chemoresistance, and the ability to recapitulate the original heterogeneous tumor [14]. CD117, also known as stem cell factor growth receptor. It has been shown to be involved in apoptosis, cell differentiation, proliferation, and cell adhesion [15]. CD117 was observed to have high expression in ovarian cancer cells [16], and cells expressing CD117 are highly tumorigenic in mouse models [17]. The Wnt/β-catenin pathway plays a role in the development of chemoresistance is activated by CD117 [18].
has been shown to have oncogenic signaling properties. Higher expression in ovarian cancer cell lines and decreased the formation of tumor spheres in CD133 and ALDH1A1 have a great ability to develop tumors in mouse models. miRNAs shown to prompt differentiation of human embryonic stem cells reported that p53 can activate two miRNAs (miR-34a and miR-145). These in triggering differentiation of epithelial ovarian cancer (EOC) to eliminate CSCs. Yin et al. Observed, that TWIST-1 played a marked role stemness property to eliminate CSCs. This was due to the inhibition of E-cadherin and ZEB2. To conclude, understanding the roles of CSCs in cancer therapy may improve the survival rate of ovarian cancer patients. The precision medicine dependent on different genomic characteristics of patients ought to be a more effective therapeutic method. In addition, the current advances in technology, such as next-generation DNA sequencing and mass spectrometry- based proteomics, would enhance the development and implementation of ovarian cancer precision medicine.

References

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