

# Cancer Stem Cells (Csc's): 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 tumorspheres. 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 growth factor 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/ $\beta$ -catenin pathway plays a role in the development of chemoresistance is activated by CD117 [18].

ALDH1A1 contains 19 enzymes that function as cell protectors from carcinogenic aldehydes [19]. Landen et al. [20] showed its association with chemoresistance in ovarian carcinoma. Cells that are double positive for CD133 and ALDH1A1 have a great ability to develop tumors in mouse models [21]. It has been observed that metformin decreased the population of ALDH+ cells in ovarian cancer cell lines and decreased the formation of tumor spheres in patient tumors [22]. EpCAM (CD326) is a transmembrane glycoprotein, and has been shown to have oncogenic signaling properties. Higher expression of EpCAM has been observed in metastatic ovarian tumors [23], and it is involved in epithelial to mesenchymal transition leading to metastasis [24]. CD24 is a cell membrane glycoprotein, and it was noted that the movement of CD24 from the cell membrane to the cytoplasm in borderline ovarian tumors was associated with micro-invasion and omental implants, and shorter survival time in adenocarcinoma of the ovary [25]. Moulla et al. [26], showed that the transition from membrane to cytoplasmic CD24 expression was associated with a more aggressive phenotype in borderline tumors.

### Therapeutic Approaches of Ovarian CSCs

The elimination of ovarian CSCs has been challenging in part due to heterogeneity, so the efficacy of any single drug is limited. Combined treatments that target CSCs will be a novel direction in the future; however drug treatment for CSCs may increase the risk of toxicity, as CSCs share common features with normal stem cells. The therapeutic strategies in ovarian CSCs include the following

#### 1. Nonsurface Markers

Cell surface markers (CD 133, CD 44, CD 24, and CD 117) have been used to isolate putative CSCs. The development of antibody-drug conjugates has recently achieved marked success [27]. The development of specific therapies that target biomarkers of ovarian CSCs may improve oncogenic outcome and patient's survival [28]. EpCAM is highly expressed in different tumor types, including colon, lung, pancreas, breast, head and neck, and ovary [29]. Down regulation of EpCAM may cause loss of cell-cell adhesion and promote epithelial mesenchymal transition (EMT) [30]. Catumaxomab, a monoclonal antibody against EpCAM is a trifunctional antibody, which can bind three different cell types, including tumor cells, T cells, and accessory cells (dendritic cell, macrophages, and natural killer cells) [31]. It has been used in phase III clinical trials in patients with malignant ascites [32]. In addition, two stem cell markers, Lin28 and Oct4, could serve as targeted therapy due to their roles in the maintenance of pluripotency in ovarian cancer [33]. Moreover, over expression of the Müllerian inhibiting substance (MIS) type II receptor has been reported in ovarian cancer cell lines [34]. MIS observed to inhibit the cell population with stem-like characteristics in ovarian cancer cell lines [35].

#### 2. Differentiation of Ovarian CSCs

To eliminate CSCs is to induce their differentiation, resulting in loss of their stemness property [36]. One must emphasize that, the understanding of regulation of differentiation processes is essential for designing new agents to eliminate CSCs. Yin et al. observed that TWIST-1 played a marked role in triggering differentiation of epithelial ovarian cancer (EOC) [37]. It was reported that p53 can activate two miRNAs (miR-34a and miR-145). These miRNAs shown to prompt differentiation of human embryonic stem cells [38]. It has been suggested that miRNAs may be a therapeutic target for cancer treatment [39]. In addition, retinoic acid, and its analogs are the most common differentiation agents. The all-trans-retinoic acid (ATRA)

can inhibit the proliferation and induce the differentiation via inhibition of Wnt/ $\beta$ -catenin pathway in head and neck squamous carcinoma CSC [40]. The clinical study of ATRA has shown an increased survival rate of patients with acute promyelocytic leukemia, but successful cases are limited in solid tumors [41]. Reduction of the growth of ovarian CSC via Carboplatin combined with three novel retinoid compounds was observed [42]. Moreover, linoleic acids can trigger adipocyte-like differentiation in many types of cancer cells, including ovarian cancer cell line SKOV3 [43].

#### 3. Niches of CSCs

Niches are microenvironments where CSCs reside, containing cell-cell, cell-extracellular matrix, and soluble factors that support the growth, progression, and metastasis of CSCs [44]. Bone-marrow-derived mesenchymal stem cells (MSCs) and derived cell types have been shown to secrete prostaglandin E2 and release various cytokines, which is important for the formation and progression of a tumor [45]. In addition, MSC affected metastatic ability and chemoresistance in two ovarian cancer cell lines: OVCAR3 and SKOV3 [46]. It was observed that tumorigenic ability of ovarian tumor cells was dependent on niches derived from human embryonic stem cells [47]. The hypoxic niches were beneficial for acquisition of stem-like properties of ovarian cancer cells [48].

#### 4. MicroRNAs (miRNAs)

They regulate gene expression at posttranscriptional level. Thus, miRNAs are involved in diverse biological processes, such as development and tumorigenesis [49]. The expression profile of miRNAs noted to be different between normal stem cells and CSCs (50, 51). MiR-214 was demonstrated to have the property of self-renewal and chemoresistance in ovarian CSCs [52]. In addition, miR-199a prevented tumorigenesis in xenograft model [53]. Moreover, the expression of miR-200a could reduce migrating ability of CD133+ ovarian CSCs. This was due to the inhibition of E-cadherin and ZEB2 [54]. To conclude, understanding the roles of CSCs in cancer therapy may improve the survival rate of ovarian cancer patients. It is worth-noting that, it would be difficult to effectively treat all advanced ovarian cancer patients. As, ovarian CSCs are heterogeneous, which leads to different sensitivities to the therapy used. It is reasonable to suggest, that combination therapy is the major direction for ovarian cancer treatment. 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- (MS-) based proteomics, would enhance the development and implementation of ovarian cancer precision medicine.

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