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Review Article

OVARIAN CANCER STEM CELLS IN CHEMORESISTANCE

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ABSTRACT

Ovarian cancer (OC) is the leading cause of mortality from cancers of female reproductive tract in the world. Despite decades of research, it is still associated with unacceptably high mortality rates. OC develops silently towards presentation with advanced disease, which is generally successfully treated with a combination of surgical de-bulking and chemotherapy. In spite of initial treatment success, an unacceptably high number of patients develop terminal, recurrent, chemoresistant disease. Clearly, patients require novel treatments that target the development of recurrent chemoresistant disease. One avenue through which this may be achieved is the targeting of 'Cancer Stem Cells' (CSCs), to which strong evidence points as the cell that is responsible for the development of chemoresistant recurrence.

Chemoresistance is the main challenge for the recurrent ovarian cancer therapy and responsible for treatment failure and unfavorable clinical outcome. Cancer stem cells play important roles in ovarian cancer chemoresistance. Cancer stem cells are rare chemotherapy resistant cells within a tumor which can serve to populate the bulk of a tumor with more differentiated daughter cells and potentially contribute to recurrent disease. To date, the study of CSC in ovarian cancer has been extremely challenging. Chemoresistance is a major limitation in the treatment of ovarian cancer. In our review, we focused our attention on the properties of ovarian cancer stem cells (CSCs); the putative ovarian CSC markers and the possible mechanisms of CSCs in ovarian cancer chemoresistance.

Keywords: Ovarian cancer; Ovarian cancer stem cells; Chemoresistance;Chemotherapy.

INTRODUCTION

Ovarian cancer (OC) is defined as any malignant tumour that develops in the ovarian tissues [1]. It is the leading cause of mortality from cancers of female reproductive tract in the world. In 2012, OC accounted for 151,900 deaths worldwide and there were 238,700 patients diagnosed with OC, according to the latest GLOBOCAN estimates [2]. Ovarian cancer is a highly lethal disease that lacks effective screening tests for early detection. Therefore, the majority of patients are diagnosed with advanced stages of the disease and have expected 5-year survival rates below 40% [3,4].

Based on the presumed cells of origin, ovarian cancer is commonly classified as epithelial ovarian carcinoma (EOC), ovarian germ cell tumour and sex cord-stromal tumour. EOC is believed to derive from epithelial cells that cover the outer surface of the ovary and alone accounts for 95% of all cancers in the ovaries [5]. Additionally, EOC is the most lethal group among ovarian cancers and the prime cause of death for patients with gynecological malignancies. Based on histopathology, immunohistochemistry, and molecular genetic analysis, at least five main types of EOC are currently distinguished: high-grade serous carcinoma (HGSC, 70%); endometrioid carcinoma (EC,10%); clear-cell carcinoma (CCC,10%); mucinous carcinoma (MC, 3%); and low-grade serous carcinoma (LGSC, <5%) [6]. Among these types, High-grade serous carcinomas (HGSC) are the most common and deadly form of ovarian carcinomas. On the contrary, ovarian germ cell tumours and sex cord-stromal tumours are rare events, accounting for only 2-3 and 1.2% of all ovarian cancers, respectively [7]. Ovarian germ cell tumours arise from primitive germ cells in the embryonic gonad [8], which tend to occur in teenagers and women in their twenties. Sex cord-stromal tumours are a morphologically diverse group of neoplasms composed of cells derived from gonadal sex cords, specialised gonadal stroma and fibroblasts [9]. Unlike germ cell tumours, sex cord-stromal tumours are more common in adult women and can be found in peri- and post-menopausal women.

Statistical analyses show that the incidence of ovarian cancer is much higher in industrial countries than in developing countries. The birth rates in industrial countries are low compared to developing countries [10]. There is strong evidence that reproductive factors including multiple pregnancies, breastfeeding, and use of oral conceptive pill (OCP) protect against ovarian cancer. With each pregnancy, the risk of developing ovarian cancer decreases by 10–16% and a pregnancy at the age of 35 years is twice as protective as at the age of 25 years [11, 12]. Also, a significant protective effect is seen in women that do breastfeeding for more than 18 months [13, 14]. Similarly, application of OCP for more than 3 years causes a 30–50% reduced risk of developing ovarian cancer [15]. In contrast to these protective factors, women with an early first period and a late menopause as well as women that receive drugs for the treatment of infertility (gonadotropin releasing- hormone antagonists or clomiphene) have an increased risk of developing ovarian cancers. The latter is thought to be caused by high concentrations of estrogen after stimulation of the sex-steroid hormone synthesis in the ovary [16]. Also, application of hormone replacement therapy (HRT) was

found to be a risk factor for ovarian cancer. An approximately 22% increased risk of ovarian cancer over 5 years was seen in postmenopausal women using unopposed estrogen as HRT.

Ovarian cancer is still the deadliest of all gynecologic malignancies in women worldwide. This is attributed to two main features of these tumors, namely, (i) a diagnosis at an advanced tumor stage, and, (ii) the development of chemoresistance. Although the majority of women experience a variety of non-specific symptoms in the year before diagnosis, the disease is not commonly recognized until the tumor reaches an advanced stage. OC is highly curable at stage I when it is confined to the ovaries, with an expected 5-year survival rate of 89% [17]. However, due to the absence of specific symptoms and the lack of an effective screening strategy, approximately 75% of women present at an advanced stage disease, where the cancer has spread within peritoneal cavity and the overall survival (OS) rates are only 17-36% [17]. For the early stage OC patients, surgery can completely remove tumor and then give patients a full recovery. For the advanced stage OC patients, cytoreductive surgery followed by platinum/taxane acts as a standard therapy, resulting in a 75% high initial response rate [18]. In spite of initial treatment success, an unacceptably high number of patients (70%) develop terminal, recurrent, chemoresistant disease [19]. Chemoresistance is a major limitation in the treatment of ovarian cancer. Clearly, patients require novel treatments that target the development of recurrent chemoresistant disease. One avenue through which this may be achieved is the targeting of 'Cancer Stem Cells' (CSCs), to which strong evidence points as the cell that is responsible for the development of chemoresistant recurrence. As ovarian cancer stem cells (OCSCs) are responsible for tumor initiation, invasion, metastasis, and chemo-resistance, new stratagems that selectively target ovarian CSCs are critically significant.

OVARIAN CANCER STEM CELLS (OCSCs) AND CHEMORESISTANCE

Stem cells, as classically defined, are cells with a capacity for self-renewal and generation of daughter cells that can differentiate into all the way down different cell lineages found in the mature tissue [20]. Stem cells always undergo asymmetric cell divisions, with each cell generating two cells; one that is identical to itself in stemness and another which is committed to a certain lineage. The daughter cell with stem cell like properties maintains its own compart-ment over time, while its sister cell undergoes a series of cell divisions [21]. Self-renewal allows stem cells to persist during the entire the lifetime of the organism, while their differentiation potential allows them to perform functions like tissue genesis, tissue maintenance, and regeneration following stress or injury [21]. Recently, specific subpopulations of cells with stem-like properties, termed cancer stem cells (CSC), have been identified in solid tumors of various origins. As in other malignant tumors, cancer stem cells in ovarian cancer are responsible for tumorigenesis and tumor growth.

CSC models:

Although there exists a long-lasting debate regarding the origin of CSCs, it is widely accepted that

tumors are composed of phenotypically and functionally heterogeneous cells and CSCs are only a small subset of tumors cells. The stochastic model, hierarchy model and the dedifferentiation model are the three major theories as to how CSCs arises. The earlier CSC model is a static one. According to stochastic model, tumor cells are biologically equivalent but behave variably due to stochastic influences (intrinsic and extrinsic factors). The core of this theory is that behaviors of tumor cells cannot be predicted and every tumor cell is thought to have the potential to behave the activity of CSCs [22]. The hierarchy model, which is the most universal accepted hypothesis, supports that tumors consist of distinct cell classes with differing functional abilities and behaviors on the basis of different intrinsic characteristics. Based on this model, CSCs are the only subpopulation possessing self-renewal and giving rise to non-tumorigenic progenies that make up the bulk of tumor [22]. However, data emerging in the last couple of years has revised the model to a dynamic one, where the hierarchical feature of the CSCs turns out to be more transient than once thought. That is, new progenies acquire the ability of self-renewal through de-differentiation of progenitor cells, as well as reversal of terminally differentiated cells [23]. The implications of CSCs and their offspring gaining self-renewal suggest the necessity to evolve current cancer treatments to target both bulk terminal differentiated cells and those with self-renewal potential [24] .

Accumulating evidence indicates that CSCs have close relationship with OC progression, metastasis, therapeutic resistance and tumor recurrence. The concept of CSCs has opened new areas of research in carcinogenesis, but has more immediate translational potential of uncovering new treatment targets. Ovarian CSCs (OCSCs) have been isolated from established OC cell lines, ascites, and primary and metastatic tumors [25-28]. They share several characteristics with normal stem cells, including the ability to form anchorage-independent spherical aggregates, express stem cell markers, undergo membrane efflux, form clones in culture and in addition, exhibit enhanced tumorforming ability [29].

The putative ovarian CSC markers:

A number of cell surface markers have proved useful for the isolation of subsets enriched for OCSCs including CD44, CD133, CD117, CD24, ALDH1A1 and EpCAM.

CD44: CD44 is a surface molecule which mediates cell adhesion and migration by binding extracellular matrix components such as hyaluronic acid, osteopontin, or activating receptor tyrosine kinases, which are related to tumor progression and metastatic progression [30, 31]. CD44 is involved in cell–cell interactions, cell adhesion and migration, but it constitutes also a receptor for hyaluronic acid, activating a variety of receptor tyrosine kinases in many cancer types. According to this role, it drives some mechanisms favoring an increase in the proliferation and survival rates of tumor cells, by the activation of the MAPK and PI3K/AKT pathways. CD44 was well documented to be a common CSC marker in many cancers such as breast cancer, head and neck squamous cell carcinoma, pancreatic cancer, colon cancer, as well as OC (ovarian cancer), and proved to

be correlated with therapeutic resistance. CD44 expression has been associated with poor prognosis and resistance to chemotherapy.

CD133: CD133, a pentaspan membrane glycoprotein, has been identified as a CSC marker for various cancers [32]. It is also known as Prominin-1. In EOC, CD133 has emerged as one of the most promising CSC markers based on in vitro cell lines, in vivo animal xeongrafts and human primary tumor experiments.

CD117: CD117, also known as c-Kit or stem cell growth factor receptor, is a proto-oncogene encoded by the KIT gene.

It is a type III receptor tyrosine kinase involved in cell signal transduction. It is involved in various cellular processes, including apoptosis, cell differentiation, proliferation, and cell adhesion. CD117 was found to have high expression in OC cells [28]. It has been also suggested that CD117 in ovarian carcinoma was associated with poor response to chemotherapy. The activation of Wnt/β-catenin-ATP-binding cassette G2 pathway was required for cisplatin/paclitaxel-based chemoresistance caused by CD117 in ovarian CSCs [33].

CD24: CD24 is a glycosylphosphatidylinositol-linked cell surface protein expressed in various solid tumors. Expression of CD24 represented a marker of poor prognosis in ovarian cancer. A study demonstrated that CD24 could localize in the cytoplasm of ovarian serous tumors, while normal epithelium and serous cystadenomas expressed CD24 marker in the apical membrane.Thus, the cytoplasmic expression of CD24 could be used as a specific marker to predict survival rates and recurrence of cancer. Gao et al. have successfully isolated CD24+ CSCs from ovarian tumor specimens and identified CD24 as a putative CSC marker in EOC [34]. In this study, CD24 cells were shown to proliferate slowly, were more resistant to chemotherapy, and demonstrated enhanced tumorigenicity potential compared to CD24- cells.

ALDH1A1: A valid marker detected in several malignant and normal tissues is aldehyde dehydrogenase-1A1(ALDH1A1). It belongs to the aldehyde dehydrogenase (ALDH) family of proteins. ALDH1A1 is an intracellular enzyme that participates in cellular detoxification, differentiation, drug resistance, through the oxidation of intracellular aldehydes, and management of the differentiation pathways. It is not only a stemness marker, but it also play an important role in the biology of tumor initiating cells. ALDH1A1 was associated with chemo-resistance in the ovarian CSC too [35]. It has been demonstrated that mouse/human hematopoietic/neural stem and progenitor cells have high ALDH1 activity. High ALDH1 activity, associated with poor clinical outcome, has been reported in breast cancer cells, ovarian cancer cells and glioblastomas. ALDH activity is commonly detected using an ALDEFLUOR assay.

EpCAM: The epithelial cell adhesion molecule (EpCAM) is a glycosylated membrane protein expressed in different solid tumors, including colon, lung, pancreas, breast, head and neck and ovary [36]. EpCAM has been used as an important OCSC marker. By evaluating the expression of EpCAM at both RNA and protein levels in 4 normal fresh-frozen ovaries and 96 EOC biopsies (50 primary ovarian carcinomas, 34 metastatic, and 12

recurrent ovarian tumors, respectively), Bellone et al. found that EpCAM was significantly expressed in EOC tissues compared to the normal ovary tissues, and metastatic/recurrent tumours were found to express higher levels of EpCAM than primary ovarian carcinomas.

Using existing CSC makers to define OCSC is an important step to uncover OC chemoresistant mechanisms, find useful therapeutic targets and develop new treatment modalities to cure metastatic, recurrent OC. However, none of these current CSC markers are exclusively expressed by OC tissues, highlighting that it is imperative to use combinatorial makers or delineate more specific markers and techniques to detect OCSCs.

The possible mechanisms of CSCs in ovarian cancer chemoresistance:

Although the standard combination of surgery and chemotherapy can effectively reduce tumor mass, most patients, eventually with residual ovarian CSCs, acquire chemoresistance. The CSC theory supports that even if a small number of CSCs remains in situ after therapy, disease recurrence can occur [37]. The mechanism of CSCs in OC chemoresistance and recurrence is complex and not fully understood. It is possible that decreased chemotherapy responsiveness of CSCs may be partly due to the slow proliferation rate, cell cycle arrest, the high expression of ATP transporters, efficient DNA protection and repair mechanisms, the activation of some CSC-related signaling pathways, inactivation of cell death pathways, and the inherent epigenetic aberrations.

CSCs are known to possess highly elaborated efflux systems for cytotoxic agents, of which ABC (ATP-binding cassette) family of membrane transporters are the most important ones. In return, there is strong collective evidence that increased expression and the activity of ABC family of membrane transporters, especially ABCG2, also correlates with cancer stem-like phenotype [38]. Ricci et al demonstrated that higher levels of ABCG2 efflux pump in OCSC-like cells were linked with increased resistance to taxol and VP16 therapy in OC cells which were obtained from primary ovarian carcinoma samples [39]. It was reported that Wnt/β-catenin-ABCG2 signaling pathway was activated and enhanced chemoresistance was observed in OCSCs, and β-catenin small interfering RNA (siRNA) reversed the drug sensitivity of OCSCs significantly.

Moreover, up-regulated DNA protection and repair and inactivation of apoptosis may also be responsible for chemoresistance in OCSCs. Srivastava et al reported that an elevated expression of DNA polymerase η (Pol η) was observed in OCSCs isolated from both OC cell lines and primary tumors, and down-regulation of Pol η enhanced the cisplatin-induced apoptosis in CSCs both in vivo and in vitro [40], indicating that CSCs may have intrinsically enhanced translation DNA synthesis. On the other hand, a study demonstrated that p53 protein aggregation was associated with the inactivation of the p53-mediated apoptosis and platinum resistance in OC cells with CSC properties.

Therapeutic approaches of ovarian CSCs:

CSCs are implicated in cancer metastasis, recurrence, and therapeutic resistance. Targeting CSCs may possess many advantages by eradicating the root of tumor and managing their malignant behaviors. The current CSC targeting therapy in OC are mainly focused on the employment of OCSCs markers and the signaling pathways related to CSCs. In addition, targeting several CSC markers may achieve a better clinical result than only targeting one CSC marker. An ideal agent should be able to selectively target CSCs over normal SCs. Without this selectivity, the effectiveness of treatment might be limited by systemic toxicity. It is also likely that treatment of patients with CSC-targeted therapies will require new clinical end points for monitoring therapeutic efficacy.

CONCLUSION

Ovarian cancer is a disease for which at the time of initial treatment we can obtain complete clinical remission in the majority of patients. Unfortunately, most patients will relapse and succumb to their disease. This clinical course is in line with the cancer stem cell model. Cancer stem cells (CSCs) play important roles in ovarian cancer chemoresistance through various mechanisms. Chemoresistance is the main challenge for the recurrent ovarian cancer therapy and responsible for treatment failure and unfavorable clinical outcome. Understanding the roles of CSCs in cancer therapy may markedly improve the survival rate of ovarian cancer patients. More importantly, identification of the ovarian cancer stem cell would provide a critical step in advancing the development of novel therapeutic strategies in the management of ovarian cancer.

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