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Review

Has the time come for therapy linked to cancer stem cells in ovarian cancer?

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Summary

Epithelial ovarian cancer (EOC) is the seventh most common cancer in women around the world and current therapies very rarely provide complete disease relapse. The cancer stem cell (CSC) concept has been the subject of broad recent studies. In this review the authors present basic identification methods on ovarian CSCs and current therapeutic approaches linked to this concept.

Key words: Ovarian cancer stem cells; Ovarian cancer.

Introduction

"Cancer is a problem of developmental biology" G.Barry Pierce *et al.,* 1978.

The concept of stem cells was already well known in the 19th century. although molecular methods were not available at that time. Pathologists observed some similarities between cancer tissue and embryonic tissue. This theory was formalized by Julius Conheim in 1889 who claimed that embryonic cells, which can become cancerous, lie in adult tissue [1, 2]. However, this theory could not be proved at this time due to the lack of research tools. The largest step in cancer stem cell (CSC) research was made by Dominique Bonnet and John E. Dick in 1997, who proved that acute myeloid leukemia is organized as a hierarchy by transplanting CSCs into mice [3]. A vast number of cancers are linked to CSCs. These are Wilms tumor, neuroblastomas, teratocarcinomas, adenocarcinomas, and skin and liver cancer [4]. Sharmila A. Bapat was the first who identified CSCs in ovarian cancer tissue [5]. In this review the authors attempt to answer the question whether the time has come for CSCs-based therapies in ovarian cancer treatment, since numerous papers have recently been published [6-8].

Ovarian cancer epidemiology and treatment overview

Epithelial ovarian cancer (EOC) is the seventh most common cancer in women around the world accounting for about 150,000 deaths annually [9]. The age standardized ratio for EOC in the world in 2008 was 6.1 varying from 0.9 in Mozambique, 1.2 in the Gambia, and 1.6 in Dominican Republic, to 14.9 in Fiji, 14.2 in Latvia, and 14.0 in Bulgaria [9]. Approximately 10% of EOC cases are attributed to the inheritance of a BRCA1 or 2 mutation [10], which increase the lifetime risk to 40-60 % [11, 12] compared with the general population risk of 1.8% [13]. EOC is often referred as the ''silent killer'' according to its asymptomatic clinical pattern [14], and the majority of patients with EOC are diagnosed in the advanced stage of disease [15]. Current optimal management of advanced-stage EOC includes maximal cytoreductive surgery and a platinum-based chemotherapy (carboplatin or cisplatin and paclitaxel) [16]. The most important prognostic factor in advanced EOC is the outcome of primary surgery [17, 18]. Median overall survival varies from 29.6 months for patients with residual tumors of more than 1 cm in diameter to 99.1 months in patients with complete resection [18]. Until today, no predictors are available indicating which patients will respond to chemotherapy, however, response rates are high and therefore all patients receive postoperative chemotherapy. The outcome of chemotherapy mainly depends on chemosensitivity, a factor currently not amendable to any influence by the therapist [18]. Unfortunately over 80% of patients with advanced ovarian cancer will relapse and despite a good chance of remission from further chemotherapy, they will usually die from their disease [19].

Ovarian cancer stem cells identification

Ovarian cancer stem cell identification is based on molecular markers. The markers currently known are presented below:

1) CD44

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Surface, transmembrane glycoprotein, that takes part in cell-cell and cell-matrix interactions, it regulates growth, differentiation and mobility of the cell [20]. CD 44+ cells are present in primary and metastatic ovarian carcinomas [21]. The expression of CD44+ is accompanied by more frequent disease relapse, shortening of disease free survival, and chemoresistance [22].

2) CD133 (prominin, AC 133) antibody

Transmembrane glycoprotein localized on cilia and microvilli. Its overexpression accompanies ovarian cancers and is linked to poor prognosis [23]. A high expression of CD133 correlates with chemoresistance, short disease free survival and shorter overall survival [24]. A murine anti-human CD133 antibody conjugated with monomethyl Auristatin F (a potentially cytotoxic drug) has stopped growth of hepatocellular and gastric cancer cell lines in *in vitro* studies [25].

3) CD117 (c-kit)

Tyrosine kinase receptor type III, that binds stem cells factor. It is a marker of embrional, haematopoietic, and mesenchymal cell lines. The expression of c-kit is observed in 40% of ovarian cancers and correlates with chemoresistance to conventional chemotherapy [26]. CD 117+ cancer cells have properties similar to stem cells, they can renew, differentiate, and have high oncogenic potential. They are considered as an attractive goal for targeted therapy [26, 27].

4) ALDH1 (aldehyde dehydrogenase 1)

Recently ALDH1 was reported as a CSC marker in ovarian carcinoma [28]. More than 50% of patients with ovarian cancer had an elevated expression of ALDH1 which was linked to poor prognosis (shorter overall survival) [29]. The expression of ALDH1 in combination with CD44 (ALDH1+CD44+), or CD133 (ALDH1+CD133+) [29-31] in ovarian cancer was correlated with shorter progression free survival (PFS) and shorter overall survival. However, other studies showed that the expression of ALDH1 was linked to better prognosis [32].

5) BMI1 (B lymphoma Mo-MLV insertion region 1 homolog)

A protein, polycomb family member that modifies chromatin proteins and plays an important role in embryonic development and cancer progression [33]. It regulates functions of the p16 and p19 cell cycle inhibitors and has ubiquitin complex ligase activity. The elevated expression of BMI1 in patients with ovarian carcinoma was linked with poorer prognosis [34].

6) Nestin

Protein of neurofilaments, expressed by neuroepithelial stem cells. Overexpression of nestin correlates with staging and pathological grading, as well as with poor prognosis in ovarian cancer [35].

7) Oct- 4 (POU5F1)

Octamer binding transcription factor 4, Oct-4 also known as POU5F1 (POU domain, class 5, transcription factor 1). Oct-4 is a homeodomain transcription factor, member of the POU family. It plays a key role in the self-renewal of embryonic stem cells and might be used as a germinal cell marker [36]. Elevated expression of Oct-4 in ovarian carcinoma correlates with staging and PFS [37].

Marker	Highlight
CD44+	More frequent disease relapse, shortening of disease free survival, and chemoresistance
CD133+	Linked to poor prognosis
CD117 (c-kit)	Expression of c-kit is observed in 40% of ovarian cancers and correlates with chemoresistance to conventional chemotherapy
ALDH1	Coexpression with CD44+ or CD133+ in ovarian cancer is correlated with shorter PFS
BMI1	Regulates functions of the p16 and p19 cell cycle inhibitors and has ubiquitin complex ligase activity
Nestin	Expression correlates with staging and pathological grading
Oct-4 (POU5F1)	Correlates with staging and PFS

Mechanisms of chemoresistance and radioresistance

Although standard operative treatment and adjuvant chemotherapy successfully reduce tumor mass in EOC, about 80% of advanced EOC patients will relapse. The probable cause of therapy failure is the presence of ovarian CSCs. This small population of cells constitutes approximately 2% of tumor mass, and is directly linked to chemoresistance, metastasis, and might also be responsible for tumor origin [7, 38-40]. Below, there are several mechanisms that may be responsible for chemo- and radioresistance of CSCs:

1) Lack of apoptosis regulated by p53 suppressor gene and Bmi-1 oncogene.

Mutations in the p53 suppressor gene are presented in about 50% of ovarian carcinomas; the loss of apoptotic function correlates with multidrug resistance [41, 42]. The expression of the *Bmi-1* oncogene is linked to stem cell renewal, its silencing enhances chemotherapy sensitivity. This is why *Bmi-1* is considered in targeted therapy in chemoresistant ovarian carcinoma [43].

2) Increase of CSCs levels during progression of disease

In vivo and in vitro research on ovarian epithelial cell lines OVCAY33 and mesenchymal HEY cell lines showed that after exposure to cisplatin and paclitaxel (or both), cells after chemotherapy were enriched with a subpopulation with high expression of CSCs (Oct-4 and CD117), and mice in this experiment generated larger tumor mass [44]. Similar observations of elevated CSC levels both *in vitro* and *in vivo* studies were made [39, 45, 46]. This research suggests the clinical progression of ovarian carcinoma during chemotherapy [47, 48].

3) Presence of inactive, dormant cells

Zhou e*t al.* [49] were the first to prove that cisplatin administration in animal models lead to the elevation of dormant cell levels; most of them were in the G0/G1 phase of

the cell cycle and showed high elevation of the following markers: Oct-4, Nestin, CD117, and CD44 which are specific for CSCs. These CSCs are probably responsible for disease relapse.

4) Over-expression of drug resistance genes - the effect of cytostatic pump-out mechanism

One of the factors causing chemoresistance of ovarian carcinoma cells is the overexpression of the ABC family proteins in CSCs, which is responsible for the pump-out mechanism. These proteins are the product of the multidrug resistance gene MDR1 – glycoprotein P (P-gp), multidrug resistance - associated protein-1 (MRP1 protein), and breast cancer resistance protein (BCRP), also known as ABCG2 [38, 50-52].

5) Hyaluronic acid (HA) in extracellular matrix and its role in chemoresistance

HA is the main component of the extracellular matrix and also plays a key role in chemoresistance. HA has a specific interaction with the CD44 external membrane receptor, which is a member of multifunction transmembrane proteins that are present on stem cells. This interaction stimulates the binding of the cytoskeleton protein – ankiryne and MDR1 (P-gp) building up a complex, that causes the chemotherapeutic agent to be pumped out of the cell. The synergistic pathway is based on the HACD44 and Nanog protein complex regulating the self-renewal of stem cells, their growth and chemoresistance attributes. Moreover the HACD44 complex can bind with the STAT3 protein – which is part of the Janus kinase STAT transduction pathway responsible for both normal and cancer cells biological processes. This complex might also cause the overexpression of MDR1/Pgp – chemoresistance and cancer progression [53, 54].

6) Aldehyde dehydrogenase activity (ALDH1A1)

Intracellular enzyme oxygenating aldehydes, active in cell differentiation processes is linked to chemoresistance of ovarian CSCs. Overactivity and expression was found in cancer cells resistant to platinum and taxane treatment. ALDH1A expression in patient samples negatively correlated with PFS. Silencing of ALDH1A using nanoliposomal siRNA (small interfering RNA) made platinum and taxane resistant cell lines susceptible to chemotherapy, reducing the tumor size in mice. ALDH1A1 is an important enzyme in identification of chemoresistant cell lines – it might be an important molecular target for future therapies [55, 56]. Possible mechanisms of chemoresistance: lack of apoptosis regulated by suppressor gene p53 and Bmi-1 oncogene, increase of CSC levels during progression of disease, presence of inactive, dormant cells, over-expression of drug resistance genes - the effect of cytostatic pump-out mechanism, HA in extracellular matrix (stimulation of MDR1), and aldehyde dehydrogenase (ALDH1A1) activity.

Future therapies

Research on stem cells is beginning to play a key role. According to Massard *et al.* [50], therapies targeting CSCs should be based on transduction pathways such as the conservative pathways Wnt, Notch or the sonic hedgehog homolog (Shh) protein activated pathway influening the survival of CSCs, ABC family protein transporters or specific properties of CSCs. Most concepts of therapy linked to CSCs involve their elimination by use of molecular targeted inhibitors towards CSC signalling pathways or their external membrane receptors.

Shah *et al.* [7] found that a therapeutic problem might be the heterogeneity of ovarian cancer based on genome analysis. This histological diversity, "mixed" types of cancers, shows that cancer cells have a common stem cell that is able to differentiate numerous CSCs to many phenotypes which are difficult molecular targets. Some experiments have already been performed with salinomycin and *Clostridium perfringens* endotoxin (CPE).

Salinomycin is an antibiotic produced by *Streptomyces albus.* It induces apoptosis in ovarian CSCs both *in vitro* and *in vivo* using MAPKp38 pathway activation. It is a cascade pathway activated by phosporylation responsible for cell growth, differentiation, and apoptosis. One of its family members is kinase 38 [57]. Parajuli *et al.* [58] found that salinomycin destroys ovarian CSCs by increasing the level of death receptor DR5 and activation of caspase 8, an executing enzyme of apoptosis in cisplatin resistant ovarian carcinoma cells.

Another interesting study was made with the use of Clostridium perfringens endotoxin (CPE). CSCs with CD44+ marker have a high expression of gene coding claudine 4 – protein responsible for cell membrane integrity in chemoresistant ovarian cancer. Claudine 4 has a natural affinity towards CPE. It was used as chemotherapeutic drug both *in vitro and in vivo*; the results were promising: in about 50% of examined mice, there was a 100% tumor mass reduction. The authors claim that the use of this endotoxin might be a strategy for the destruction of ovarian CSCs [59]. Another compound, Verrucarin J, is being tested in Louisville. It is isolated from the Myrothecium fungus family and seems to target ovarian cancer stem cells [60].

Recently, miRNA microarray panels have been tested [61]. Also, a whole set of 17 transcription factors (named as pivot-TFs) is under study [62]. Another new study of the Vav3.1 truncated isoform (modulator of GTP-hydrolases of the Rho/Rac family, which is involved in cell proliferation) seems to be linked with a higher FIGO stage and residual disease [63]. Hopefully these new advances will shed new light on better diagnosis and treatment of ovarian cancer.

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