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MINI REVIEW ARTICLE

Ovarian Cancer Stem Cells: Newer Horizons

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Abstracts
The ovarian cancer is one of the frequent cancers among women being diagnosed after cervical and breast cancer. The CA ovary is dreaded because even after successful treatment of the primary malignancy, the disease comes back and becomes resistant to conventional management. The prognosis in ovarian cancer management is mostly unsatisfactory, maybe because of the presence of ovarian cancer stem cells (OCSC). The hypothesis is that OCSC causes the recurrence of the ovarian malignancy. The OCSC can be identified by the presence of different markers and marker combinations. The assumptions are that CD44+, CD24+, CD117+, CD133+ and ALDH1+ could be the markers of ovarian cancer stem cells. The epithelial ovarian malignancy if proved as a stem cell disease, then it changes the entire management scenarios. Maybe, this will be the first step in managing the ovarian malignancy in the future.

Keywords Ovarian · Stem cells · Aggressiveness · Cancer · Recurrence

Introduction

The ovarian cancer is one of the frequent cancers among women being diagnosed after cervical and breast cancer. The prevalence is 10–15 for every 100,000 women, being the fifth most virulent malignancy among women [1].

Though there is good response to primary management, patients of ovarian cancer have recurrence and then the disease becomes resistant to chemotherapy [2]. This recurrence is due to genetic mutations and some tumor-propagating cells which survive the surgery and primary chemotherapy [3]. These surviving few cells behave like stem cells.

It is proposed that these small percentage of ovarian cancer stem cells are responsible for disease recurrence and decreased efficacy of chemotherapeutic agents [4]. The apoptosis is impaired but the repair mechanism persists. All these micro-modulations suppress immunity and contribute to recurrence of the cancer and poor prognosis.

The presence of ovarian cancer stem cells (OCSC) is now considered responsible for the poor outcome in the management of ovarian cancer. They are also thought to contribute to treatment failure.

OCSC

Nowadays, it is believed that OCSC are an important reason for ovarian cancer recurrence.

The hypothesis states that OCSC get transformed into cancer cells and cause recurrence. The aggressiveness of the ovarian cancer is due to stem cells and their transformation into progenitor cells [5]. The OCSC are present in small numbers, but they have capacity of lifelong regeneration and an asymmetric differentiation.

They also have the capacity to lie quietly for long periods and resist the effects of chemotherapy and radiotherapy [6].

The Challenge for Research

For the brain and breast CA, their cancer stem cells lineage is being mapped. As a result, the specific cancer stem cells and their progeny can be identified in the hematopoietic system with the help of the surface markers. But, there is a deficiency in the knowledge of stem cell population in the

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ovarian cancer stem cells and normal cells of the ovary. The ovarian surface epithelium (OSE) has regenerative capacity and can produce OSE cells, granulosa cell and germ cell [7].

In the beginning of the treatment, the patients do respond to surgical management, chemotherapy and radiotherapy. But when recurrence occurs, then they become resistant to all sorts of treatment and ultimately they succumb to the disease [8]. The treatment of an ovarian cancer remains challenging for the patients, the treating physicians, surgeons as well as the scientists involved in the research. Besides, the greater challenging situation is to isolate and identify those stem cells of ovarian malignancy which presents problems for management.

The following markers and marker combinations have been suggested as ovarian cancer stem cells. The markers identified are **CD44 + (hyaluronic acid receptor), CD24 + CD117 + (c-kit) CD133 + (prominin) and ALDH1 + .**.

CD 133

The CD 133, a glycoprotein popular as prominin-1, is attached to the membrane. It is the surface marker for identification of brain CA, colorectal CA, breast CA, neck and head CA, liver CA and ovarian cancer. There are efforts to investigate whether there is an expression of CD 133–1 and CD 133–2 in the normal ovary, benign and malignant tumors of ovary. The two epitopes of CD 133, e.g., CD 133 C and CD 133 K, are described in primary ovarian tumors, but not in the normal ovary and malignant ovarian tumors [9].

The tumor vasculature is very important for tumor cell survival. This vascularity is maintained by CD133C cells. The OCSC recruit CD 133C cells, so that neovascularity can be generated and maintained among the cancer cells. That is why, CD133C is an important marker for poor outcome for the ovarian malignancy. In the patients of ovarian cancer, the presence of CD133C predicts that the disease-free survival years are reduced.

CD44C/CD117C

The CD 44C/CD 117C cells extracted from ovarian cancer cells have an association with stem cell of other cancer [10], and they confirm to all the properties of the stem cells of other cancers.

The CD44 and CD117 are also seen among normal surface epithelium of the ovary [11].

Another study suggests that CD 44+CD 24 resembles a set of cancer stem cells, e.g., ovarian adeno CA cell lines. These cancer cells differentiate to CD 44 + CD 24 + cells and are resistant to chemotherapy, e.g., carboplatin and paclitaxel.

ALDH

Landen et al. and Deng et al. studied and found a new prognostic marker in ovarian malignancy known as ALDH. They found that increasing levels of ALDH1 expression co-relate with poor prognosis in an ovarian malignancy [12].

Side Population Cells as OCSC

In flow cytometry-based cell sorting mechanism, few cells were isolated. These cells were known as side population (SP). These cells seemed to have characteristics like stem cells. The SP cells have capacity to renew themselves in ovarian malignancy [13].

The OCSC have a property of lying quiet [14]. These OCSC become active during cancer recurrence [15].

Enrichment of OCSC in situ and Tumor Recurrence

For the management of the malignancy of ovary, the recognition of the OCSC among the primary malignancy of ovary is important. This knowledge will help in understanding malignant cell metastasis and the response to treatment. According to OCSC theory, even if a few stem cells of ovarian cancer remain in situ after the primary treatment, then there are chances that the disease may recur [15]. Besides, if the OCSC are totally eliminated there is lesser chance of the recurrence of the disease. Because the ovarian cancer stem cells

1. are resistant to apoptosis,
2. express drug transporters which actively extrude the toxic components out of the cells,
3. make tumor markers dormant and become quiet,
4. cause enrichment and progress of the malignancy.

Future Research

The cause of ovarian cancer metastasis and its recurrence can be multifactorial. But the proposition of the epithelial ovarian cancer as a disease caused and influenced by stem cells can alter the approach to management of ovarian cancer. Ovarian cancer stem cells develop resistance to therapy because of intrinsic mechanism of resistance and epigenetic plasticity of cells [16]. This signifies that even a single ovarian cancer stem cell is capable of causing tumor recurrence [17]. So, therapies are designed to target at molecular level rather than conventional therapeutic agents [4]. The ovarian cancer stem cells and other factors within tumor microenvironment are major causes of metastasis and are prognostic markers [18]. In the past, isolation of these stem cells was difficult. In recent times, a variety of possibilities have been developed for derivation of the OCSC cells from ovarian

tumors. Maybe, it will be the first step for developing newer strategies which will be effective in controlling this highly aggressive and lethal malignancy, that is difficult to treat. Hence, the newer generation cancer treatment modalities are being developed targeting specific OCSC. It is a known fact that the normal ovarian stem cells differ from OCSC. The OCSC are not regulated by cell division signals and hence cause metastasis and recurrence. By research, if specific gene regulatory mechanisms in progression of ovarian cancer are also identified, then a correlation will be established between chromatin modifications and gene expression patterns. In the future, this area, i.e., the ovarian cancer, may also be targeted by gene therapy. By targeted gene therapy, those cancer cells may be eliminated which are responsible for chemo-resistance.

The attempts to isolate ovarian cancer stem cells are on. There is also a desire to isolate and identify ovarian cancer stem cells-associated genes as biomarkers. These researches may define a very specific prognostic and predictive approach to biomarkers. To conclude, there is an urgent requirement to establish an association of OCSC to their origin and mechanism of survival.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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