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Review

Ovarian cancer stem cells: Molecular concepts and relevance as therapeutic targets

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ABSTRACT

In spite of recent progress in cancer therapeutics and increased knowledge about the cellular and molecular biology of cancer, ovarian cancer still remains a clinical challenge. Chemoresistance followed by tumor recurrence are major causes of poor survival rates of ovarian cancer patients. In recent years, ovarian cancer has been described as a stem cell disease. In this scenario, a small percentage of ovarian tumor cells with cancer stem cell-like properties should survive therapeutic treatments by activating the self-renewal and differentiating pathways resulting in tumor progression and clinical recurrence. The mere concept that a small subset of cells in the tumor population drives tumor formation and recurrence after therapies has major implications for therapeutic development. This review focuses on the current understanding of normal and malignant ovarian stem cells in an attempt to contribute to our understanding the mechanisms responsible for tumor development as well as recurrence after chemotherapy. We also discuss recent findings on the cancer stem cell niche and how tumor and associated cells in the niche may respond to chemotherapeutic stress by activating autocrine and paracrine programs which may opt as survival mechanisms for residual cells in response to frontline chemotherapy. Using mouse ovarian cancer models we highlight the role of cancer stem cells in response to chemotherapy, and relate how cancer stem cells may impact on recurrence. Understanding the distinct mechanisms that facilitate cancer stem cell survival and propagation are likely to reveal opportunities for improving the treatment outcomes for ovarian cancer patients.

Contents

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1. Introduction

Ovarian cancer is the most lethal of all gynaecological malignancies and the fifth leading cause of cancer death among women worldwide (Aletti et al., 2007; Jemal et al., 2009). In the majority of the cases, it presents as an advanced metastatic disease where the clinical condition of the patients is compromised by wide spread of cancer to the surrounding abdominal organs (colon, intestine, liver, pancreas, lungs) and accumulation of ascites (tumor fluid) in the peritoneal cavity (Lengyel, 2010; Kipps et al., 2013). Ascites contain single and aggregated clusters of tumor cells as well as a heterogenous population of stromal, red blood and different subsets of immune cells (Latifi et al., 2012). Advanced-stage ovarian cancer patients are treated with primary debulking surgery followed by platinum and taxane-based chemotherapy resulting in a median progression-free survival period of 16–22 months but a subsequent 5-year survival rate of only 27% (Kipps et al., 2013). The latest clinical trials of targeted therapies (bezicumab, imatinib, etc.) as well as the use of combination drugs have failed to improve the outcome of ovarian cancer patients significantly (Matei et al., 2008; Ozols, 2006; Schilder et al., 2008). This is mainly due to a lack of understanding the biology of heterogeneous chemoresistant and recurrent ovarian tumors, thus compromising the efforts to develop treatment modalities for this lethal disease.

Ovarian cancer represents a diverse group of tumors displaying a wide range of morphological features, and genetic-epigenetic alterations each with distinct tumor behaviour (Auersperg et al., 2001; Conic et al., 2011). The heterogeneous nature of ovarian tumors has led to efforts to elucidate the genomic and epigenomic nature of epithelial ovarian cancer (EOC) in particular (Vaughan et al., 2011; Tothill et al., 2008). Of late, the Cancer Genome Atlas (TCGA), using high throughput technologies such as mRNA and microRNA analyses, promoter methylation, DNA copy number changes, and DNA exon sequencing on 489 high-grade serous carcinomas (HGS) published an integrated analyses which provided a comprehensive understanding of the genomic and epigenomic alterations that can affect the clinical outcome of HGS patients (2011). However, the data from the TCGA was derived from primary HGS and does not provide information on the chemoresistant and recurrent EOC. As such, the mechanisms underlying the chemoresistant and recurrent phenotype of ovarian cancer remain relatively unknown resulting in a major hindrance in the development of improved treatments of advanced-stage EOC patients who currently do not have effective treatment options.

One of the emerging concepts in tumor biology is that of 'cancer stem cell (CSC)' (Medema, 2013). The CSC theory dictates that the progression and recurrence of cancers are governed by a small subpopulation of CSCs within a tumor which drive tumor progression and relapse due to a recurrent disease (Vermeulen et al., 2008; Vermeulen et al., 2012). Ovarian cancer has been postulated to imitate the CSC model (Aguilar-Gallardo et al., 2012; Curley et al., 2011; Ahmed et al., 2013). The concept that ovarian cancer progression and recurrence is driven by the proliferative and regenerative capacity of CSC has tremendous implications for therapy of ovarian cancer.

This review summarizes the current literature on the existence of normal and cancerous ovarian stem cells and also addresses the cancer stem cell concept in relation to ovarian cancer. We also describe recent data on ovarian CSCs and their interaction with tumor microenvironment in response to therapeutic stress. Considering that the CSC phenotype is influenced by the therapeutic stress-induced 'CSC niche' understanding the crosstalk between chemotherapy-treated residual ovarian tumors and their associated microenvironment may help in the development of pre-emptive strategies designed to disrupting the specific 'pro-stemness' support required for recurrence. We also provide proof of concept of the 'ovarian CSC recurrence model'. This supports the 'Ovarian CSC concept' and demonstrates that the CSC signature endowed by tumor cells in response to chemotherapy treatment is preserved at relapse in recurrent tumors, emphasising again on the need for the development of CSC-based therapeutic strategies for better management of ovarian cancer patients.

2. Adult stem cells of the ovaries

Normal tissues constantly undergo turnover as a result of cell death due to age, injury or shedding, and are replaced by new healthy cells. Homeostasis in adult tissues is maintained by a subpopulation of potent tissue-specific stem cells (Berardi et al., 1995; Barker et al., 2007). Despite the fact that the female reproductive tract constantly undergoes tissue remodelling during the reproductive years of a woman (Auersperg et al., 2001), adult stem cells in the ovaries have been understudied. The development of the somatic gonads starts at day 10 in mice (4 weeks gestation in humans) as a thickening of the coelomic epithelium, commonly known as the gonadal ridge on the mesoderm, (Conic et al., 2011; Auersperg et al., 2001). The Mullerian duct develops from the urogonadal ridges (Auersperg et al., 2001; Oktem and Oktay, 2008; Loffler and Koopman,