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REVIEW

Ovarian cancer stem cells: ready for prime time?

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Abstract

Introduction The role of cancer stem cells (CSC) remains controversial and increasingly subject of investigation as a potential oncogenetic platform with promising therapeutic implications. Understanding the role of CSCs in a highly heterogeneous disease like epithelial ovarian cancer (EOC) may potentially lead to the better understanding of the oncogenetic and metastatic pathways of the disease, but also to develop novel strategies against its progression and platinum resistance.

Methods We have performed a review of all relevant literature that addresses the oncogenetic potential of stem cells in EOC, their mechanisms, and the associated therapeutic targets.

Results Cancer stem cells (CSCs) have been reported to be implicated not only in the development and pathways of intratumoral heterogeneity (ITH), but also potentially modulating the tumor microenvironment, leading to the selection of subclones resistant to chemotherapy. Furthermore, it appears that the enhanced DNA repair abilities of CSCs are connected with their endurance and resistance maintaining their genomic integrity during novel targeted treatments such as PARP inhibitors, allowing them to survive and causing disease relapse functioning as a tumor seeds.

Conclusions It appears that CSCs play a major role in the underlying mechanisms of oncogenesis and development of relapse in EOC. Part of promising future plans would be to not only use them as therapeutic targets, but also extent their value on a preventative level through engineering mechanisms and prevention of EOC in its origin.

Keywords Ovarian cancer · Stem cells · Very small embryonic-like stem cells · Epithelial–mesenchymal transition

Introduction

The role of CSCs has been increasingly investigated over the last years; however, a clear definition has not yet emerged for their value in carcinogenesis, progression, and tumor metastasis. Nevertheless, their potential in contributing to a better understanding of the behavior profile of malignant diseases, but also as therapeutic targets, is highly promising, with many cancer researchers worldwide turning their efforts in further exploring them as a promising "holy grail" in the field of oncology.

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CSCs have been described as being able to modulate core signaling pathways in epithelial ovarian cancer and are believed to be responsible for disease progression, relapse, and drug resistance development. Epithelial ovarian cancer has been shown to have a strong temporal and spatial intratumoral heterogeneity, which represents a challenge in the efficacy and success of any therapeutic attempts. Despite maximal effort cytoreductive surgery and platinum-based chemotherapy in combination with antiangiogenetic agents and immunomodulators, the majority of patients will eventually develop drug-resistant disease and die.

In this complex scenario, CSCs appear to have significant role in the development of intratumoral heterogeneity in epithelial ovarian cancer.

CSCs are isolated from cancer tissue and have the ability to self-regenerate, as a result of resistance to apoptosis, induced by loss of anchorage, and also the ability to undergo differentiation through asymmetric cell division; features also found in non-cancer stem cells. Still, the main difference and pathognomonic characteristic of CSCs or tumor-initiating cells is that once transplanted in an organism,

they are able to induce carcinogenesis on the basis of the same molecular characteristics of the original neoplasm from which they derive [1]. Hence, the CSCs appear to have a key role across all cancer stages: from the development of the disease and its initial treatment until the development of relapse and chemoresistance [2]. The plasticity that CSCs display as almost characteristic allows them to switch between different states (including non-stem states) [3], whereas by expressing molecular pumps that facilitate efflux of the various pharmacologic agents along with the presence of intracellular scavengers such as ALDH1, they significantly contribute to the development of resistance to systemic treatments [4].

A process that highlights this aspect is the so-called Epithelial-to-Mesenchymal Transition (EMT) in which stem cells not only acquire mesenchymal traits but also provide epithelial cells with staminal associated properties, conferring them with greater tumorigenic potential and chemoresistance [5, 6]. In tumor cells, the transition mechanism should not be understood in a static but rather a highly dynamic way, in which CSCs seem to be associated with a partial EMT phenotype [4, 7]. The various signal transduction pathways that govern cancer stemness include Wnt/β-catenin, NOTCH, IL6/JAK/STAT3, Hedgehog, NFκB, and PI3K/AKT [8] and specifically for ovarian cancer TLR2-MyD88-NFκB [9], HMGA1 [10], PKCι/Ect2/ERK [11], YAP/TEAD [12], and hypoxia/NOTCH1/SOX2, which play a central role as ovarian cancer stem cell markers.

Experimental evidence for ovarian cancer stem cells

The exact pathophysiologic pathways of epithelial ovarian cancer carcinogenesis are still not well defined. From an embryogenic perspective, the most prevailing hypothesis is that very small embryonic-like stem cells (VSEL) play a central role in EOC stemness and carcinogenesis. The VSEL in human ovarian cancer cells express multiple genes connected with pluripotency and germinal lineage, especially primordial germ cells [13]. Klun et al. assessed the presence of VSEL in eight patients with borderline ovarian tumor comparing them with a similar population of small cells from the healthy ovaries of three women without cancer. Similar populations of small putative stem cells were found in the ovarian surface epithelium/ovarian cortex tissue of women with borderline ovarian cancer and in healthy women. However, only the small putative cancer stem cells from the "cancerous" ovaries intensely proliferated and spontaneously formed tumor-like structures in vivo, and in vitro in cell cultures after enzymatic digestion of ovarian cortex tissue [14]. Microarray analysis of the samples in this study showed that the gene expression profile of cancer stem cells appears to differ from healthy non-cancerous cells by 132 up-regulated and 97 downregulated genes, including some important SOX17, forkhead box (FOXQ1, FOXL2), and homeobox genes (HOXD9) known to regulate transcription, differentiation, cell growth, and embryogenesis [15].

The models for epithelial ovarian cancer stemness are rather scarce and not yet well standardized. Bapat et al. have attempted to develop such a model of disease progression based on EMT and CSCs from a single sample collection of malignant cells, isolated from the ascites of a stage IV EOC-patient [16]; the isolated cells in culture gave rise to 65 individual sublines of EOC cell clones, based on differentially morphology. Nineteen of the sixty-five spontaneously immortalized, while the remaining clones underwent senescence within 4–5 weeks of cloning. Semiquantitative reverse transcription (RT)-PCR was carried out to identify the nature of the isolated cells. Co-expression of cytokeratin 18 and vimentin, the growth factor receptors c-met and epidermal growth factor receptors and the surface adhesion molecule CD44 were evident in all of the clones. There was also an almost ubiquitous expression of E-cadherin; while Snail, a known mediator of EMT through transcriptional repression of E-cadherin, was also present in all examined cells. These identified expression patterns are a clear indicator of the mesothelial nature of the cells, which is in alignment with the current hypotheses of the EMT-based carcinogenesis processes in EOC. On the contrary, when assessing the growth of the 19 clones, only two clones (A2 and A4-T) were tumorigenic, and had the capacity for anchorage-independent growth and the ability to give rise to organized spheroids from one clone of cells. Nestin, Oct4, and Nanog, specific markers known to be associated with stem and/or progenitor cells, were expressed in both A2 and A4-T monolayers and absent or had lower expression in spheroids. The expression pattern of these three markers possibly indicates a potential multipotent nature of the A2 and A4-T clones. As a further step, the in vivo correlation of the in vitro clonogenic potential of the candidate tumor stem cells was assessed in nude mice: both clones were able to propagate a disease similar to that from the index patient, which led to the conclusion that the two transformed clones, A2 and A4-T, highly possibly represent CSCs [16]. Further studies point out the presence of adult stem cells within the human fallopian tube epithelium and their key role in the oncogenesis: the stem cells in the epithelial lining can give rise in vitro to a 3D organoid formed by ciliated and secretory cells. In addition, the organoid growth and differentiation process have been analyzed, revealing that both are under the Wnt and Notch paracrine signaling pathways control: through the inhibition of Notch route, there is a downregulation of stem cell-associated genes together with

decreased proliferation and increased numbers of ciliated cells [17]. Moreover, a 2019 preprint work by Hofmann et al. has showed the results of a study carried out on 15 organoid lines derived from high-grade serous ovarian cancer primary tumor: it was showed that the parental tumor almost shares the same mutational profile and phenotype with the organoids and that Wnt pathway activation leads to growth arrest of these cancer organoids [18].

The role of microenvironment is also crucial in its interaction with CSCs. Pro-tumorigenic properties of the microenvironment appear to carry a central value in the process of carcinogenesis, including EOC [19]. One hypothesis is that a pro-tumorigenic microenvironment in EOC, promotes processes like EMT and perhaps vice versa [20]; malignant ascites and also the omental cake are typical examples of such tumor-promoting platforms. Studies in EOC have shown that malignant ascites contains high level of Interleukin 6, which in turn promotes the JAK /STAT3 signaling pathway that has been shown to promote the ability of CSCs to develop and function [21–23]. At a similar level, the adipose tissue in the omentum, the most common site of metastasis in EOC, equally promotes cancer cell migration and dissemination, providing the required energy for tumor cells [24].

Mesenchymal stem cells and macrophages are fundamental components of the stem cell niche and function in a coordinated fashion to regulate stem cell renewal and mobilization [25]. Hence, extracellular vesicles play a key role not only in the development of pre-metastatic niche and metastatic colonization, but also in intercellular signaling and transportation of genetic messages: by transporting different lipids, proteins, double-stranded DNAs, RNAs, non-transcribed RNAs, and microRNAs, they can coordinate the communication between cancerous cells, stromal cells, and the extracellular matrix. The upregulation of matrix metalloproteinase 9 is a central factor in this process providing the cancer cells with the required energy for nesting and invasion [26]. Several groups have identified surface biomarkers that are used to characterize CSCs in ovarian cancer and can be studied to develop novel target therapies. Common CSC surface markers are CD24, CD44, CD 133, EpCAM, and ROR1; CD 133 is associated with tumor formation, disease progression, chemoresistance, and poor prognosis [27–31]. CD24 and CD44 are linked with tumor formation, metastasis, poor prognosis, chemoresistance, and recurrence of disease [32–36]. The expression of the enzyme aldehyde dehydrogenase ALDH1 alone or in combination with cell surface stem cell markers is an accepted method for CSC identification in ovarian cancer. Evidence suggests that ALDH can be used as expression of cell proliferation, migration promotion, poor survival, and chemoresistance [37–39], and in animal models, its inhibition reversed resistance of the tumors to treatment [40]. Moreover, a recent meta-analysis highlight that high-expression levels of ALDH1 significantly correlated with poor 5-year overall survival and progression-free survival rate in ovarian cancer patients. No further links between ALDH1 expression profile and clinico-pathological features such as FIGO Stage, tumor grading, lymph nodal status, and patients' age at diagnosis were emerged [41].

Ovarian cancer stem cells: therapeutic target options

Understanding the biological mechanisms inducing the development of chemoresistance in EOC similarly to other epithelial cancers remains a challenge. Evidence has shown a key role played by CSCs in progressing relapse following systemic chemotherapy. While chemotherapy and radiotherapy target actively proliferating cells, CSCs are characterized by a rather slow cycling rate which makes them resistant to standard cytotoxic treatments [42, 43]. Prevailing hypotheses suggest that the high frequency of EOC relapse might be originating from a subpopulation of quiescent EOC stem cells that, by remaining in the G0 phase of the cell cycle, are not sensitive to cytotoxic treatments. However, once they return to an active reproduction phase, they have the ability to become the potential driving force of the cancer relapse. Various studies have highlighted the direct correlation between emerging chemoresistance at EOC relapse and CSC abundance: tissue sample analyses from primary, metastatic, and recurrent EOC patients have demonstrated increased expression of CD44 in the less favorable patients with metastatic and relapsed tumors [44, 45]. Furthermore, CD44 was found to be overexpressed in drug-resistant EOC cell lines and up-regulated in mouse models with tumor recurrence after chemotherapeutic treatment [46]. Different studies highlight this hypothesis: ovarian cancer cells with stem-like traits ($CD44^+/CD24^-$) showed higher relapse rate as well as shorter progression-free survival [30] compared to those without abundant stem cell-like features. Similar results were observed analyzing other ovarian cancer stem cell-related markers such as CD133, which are connected with a poor response to chemotherapy and, hence, a less favorable survival [47]. It is evident that several biological pathways involving CSCs promote chemoresistance, and, therefore, developing therapies that will inhibit those pathways may alter the development of chemoresistance. A potential design of such an inhibiting agent should ideally target mainly CSCs to minimize toxicity, even though one would need to be cautious of potential toxicity issues attributed to the fact that CSCs may share epitopes with normal stem cells [48]

Recently, the emerging value of PARP inhibitors in ovarian cancer has become increasingly evident and

multiple PARPi have been approved for use in patients with recurrent ovarian cancer; however, their interaction with CSCs is not well described [49, 50]. Despite the highly encouraging response rates of PARP inhibitors in both BRCA1/2 mutant and non-BRCA1/2 mutant patients, most will develop eventually resistance. The molecular process underlying this event has not yet been fully elucidated. A potential hypothesis as formulated by Bellio et al. is that the antitumor activity of PARPi is rather due to their focused targeting of non-CSC population of cells; suggesting that PARPi treatment result in the induction of an enrichment of cell populations expressing antigens linked to stem phenotype in ovarian cancer including CD133, CD117, and ALDH [51]. Another important aspect is the fact that ovarian CSCs and non-CSCs respond in different way to DNA damage, and that CSCs may feature more efficient DNA repair mechanisms due to the activation of embryonic repair mechanisms that can confer a survival advantage, contributing in turn to treatment resistance and recurrence [52]. It appears that the enhanced DNA repair abilities of CSCs are connected with their endurance and resistance maintaining their genomic integrity during PARPi treatment, allowing them to survive and causing disease relapse functioning as a tumor seeds.

Conclusion

Decoding the underlying mechanisms of the interaction between CSCs and EOC may significantly contribute in developing effective strategies to overcome chemotherapy resistance in a challenging disease. As a future, even ambitious aim, it could even be used as a preventative platform by engineering at a stem cell level. The first important step would probably be the determination of the progenitor stem population involved in the development, progression, and metastasis of EOC, to be able to target the disease at its origin.

Author contributions CS: project development and manuscript writing. FS: project development and manuscript writing. PC: manuscript editing. CF: project development and manuscript writing.

Compliance with ethical standard

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

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