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Journal of Stem Cell Research & Therapeutics

Mini Review

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# Stem cells in epithelial ovarian cancer

**Keywords:** epithelial ovarian cancer-cancer stem cells- ovarian surface epithelium-targeted therapy

Volume 5 Issue 1 - 2019

Noha Ehssan Mohamed[1,2]

[1]European cancer stem cell research institute, Cardiff University, UK

[2]Hormones Evaluation Department, National Organization for Drug Control and Research, Egypt

**Correspondence:** Noha Ehssan Mohamed, European cancer stem cell research institute, Cardiff University, Hadyn Ellis building, Maindy road, Cathays, Cardiff, UK CF24 4HQ, 6 Abu Hazem street, El-Haram road, Giza, Egypt, Email mohmedna@cardiff.ac.uk, noha.ehsan@gmail.com

**Received:** July 11, 2017 | **Published:** February 28, 2019

## Introduction

Ovarian cancer (OC) is the most lethal gynaecological malignancy accounting for 4128 deaths in UK in 2014, equivalent to 56% of cases diagnosed in that year.[1] Approximately 90% of OC are epithelial, and the rest are stromal tumours and germ cell tumours.[2] Epithelial ovarian cancer (EOC) includes many histologic subtypes, which differ in their origin, pathogenesis and molecular alterations.

## Roles of stem cells in EOC initiation

The cell of origin of epithelial ovarian cancer (EOC) has been debated for a long time, and many theories were postulated based on clinical evidence or mouse models, with the dualistic model for ovarian carcinogenesis (intra-ovarian and extra-ovarian origins) being proposed and accepted during the last decade.[3] Historically, it was believed that EOC originates from the ovarian surface epithelium (OSE), being the only epithelial cells in the ovary. This theory has been questioned because of the differences in histology and embryonic origin between OSE (single layer of squamous to cuboidal mesothelial cells) and EOC (resembles müllerian-duct derived epithelium). Although, no clinical data supported this hypothesis, results from genetically-engineered mouse models proved it could be accepted. EOC models driven by recombination of floxed genes exclusively in the OSE of the mouse ovary were developed and represented 4 main histotypes of EOC (serous, endometrioid, mucinous and clear cell).[4–7]

According to the theory, epithelial cells at the site of continuous rupture and repair are highly susceptible for mutations. When these cells are trapped inside the ovary during ovulation, they form inclusion cysts. These epithelial cells in the cyst, supported by paracrine signals coming from the surrounding niche (inflammatory mediators and steroidal hormones) as well as autocrine signals from inside the cells, accumulate mutations and undergo metaplastic transformation into müllerian epithelium, a pre-requisite for neoplasia. According to the type of mutations happening in the cells, as well as factors present in the surrounding niche, differentiation into different histotypes of EOC happens.[8,9]

With the recent isolation and characterization of stem cells from the OSE,[10,11] this theory could gain more acceptance and be refined. Ng and colleagues showed that, in addition to the hilum,[10] stem cells are present at cleft regions between growing follicles or corpora lutea and are abundant at the ovulatory rupture sites.[11] If SCs are trapped inside the ovaries during ovulation, interacting with the surrounding niche might initiate tumourigenesis and different histologic types arising could be explained in terms of the differentiating capacities of stem cells.[12]

## Targeting ovarian cancer stem cells: The way forward

Cancer stem cells (CSCs) represent a very small subgroup of tumour cells characterized by their capacity of self-renewal, differentiation and tumour initiation.[13] Unlike rapidly dividing cancerous cells, CSCs are quiescent, thus escaping the effects of current cytotoxic therapies designed to destroy rapidly dividing cells. CSCs can originate by critical mutations of normal SCs,[14] or by dedifferentiation of tumour cells.[15] CSCs have upregulated DNA repair capacity, are resistant to apoptosis and over-express ATP-binding cassette (ABC) drug efflux transporters. They are thus believed to play a crucial role in tumour development, chemo-resistance and relapse after initial treatment.[16]

CSCs from OC were first isolated from malignant ascites,[17] and thereafter from primary human ovarian tumours and OC cell lines.[18,19] Ovarian CSCs are regulated by variety of genes, micro RNAs and the surrounding tumour microenvironment (termed 'CSC niche'). Developmental signalling pathways, including Notch, Wnt, Hedgehog and TGF-β have been implicated in the regulation of CSCs including ovarian CSCs.[20]

Targeting CSCs appears attractive and several approaches are currently being developed. One approach is to target regulatory signalling pathways of CSCs e.g. Wnt signalling. A new Wnt antagonist, OMP-54F28, was recently developed and tested. Preclinical studies showed reduced tumour growth and decreased CSC frequency when OMP-54F28 was used as a single agent or in combination with other chemotherapeutic agents. A phase 1B trial is ongoing to study OMP-54F28 in combination with paclitaxel and carboplatin in ovarian cancer.[21]

Another approach is to use immunologic therapy, with antibodies to CSC-surface markers. Hyaluronic acid-cisplatin and hyaluronic acid-paclitaxel conjugates were both tested to target CD44-positive cancer cells in a xenograft EOC model.[22,23] Both interventions reduced tumour growth when compared to free unconjugated cytotoxic treatment. A third approach is to target the metabolic interaction between CSCs and their microenvironment. Modulating energy metabolism in ovarian CSCs using metformin was shown to restrict the growth and proliferation of ovarian cancer stem cells *in vitro* and *in vivo*.[24]

All the previous studies described in this mini-review point to possible roles of SC in EOC pathogenesis. Targeting CSCs should be considered in combination treatment for EOC patients in the future to kill cancer cells and prevent tumour relapse.

## Acknowledgments

None.

## Conflicts of interest

Author declares that there is none of the conflicts.

## References

1. Cancer Research UK. Ovarian cancer statistics. 2017.
2. Bidus MA, Elkas JC, Rose GS, et al. *Germ cell, stromal, and other ovarian tumors*. Clinical gynecologic oncology. 8th ed. Elsevier. 2012. 720 p.
3. Kurman RJ, Shih IM. The Dualistic Model of Ovarian Carcinogenesis: Revisited, Revised, and Expanded. *The American Journal of Pathology*. 2016;186(4):733–747.
4. Wu R, Hendrix–Lucas N, Kuick R, et al. Mouse Model of Human Ovarian Endometrioid Adenocarcinoma Based on Somatic Defects in the Wnt/β–Catenin and PI3K/Pten Signaling Pathways. *Cancer Cell*. 2007;11(4):321–333.
5. Chandler RL, Damrauer JS, Raab JR, et al. Coexistent ARID1A–PIK3CA mutations promote ovarian clear–cell tumorigenesis through pro–tumorigenic inflammatory cytokine signalling. *Nature communications*. 2015;6:6118.
6. Szabova L, Yin C, Bupp S, et al. Perturbation of Rb, p53, and Brca1 or Brca2 cooperate in inducing metastatic serous epithelial ovarian cancer. *Cancer Res*. 2012;72(16):4141–53.
7. Ren YA, Mullany LK, Liu Z, et al. Mutant p53 Promotes Epithelial Ovarian Cancer by Regulating Tumor Differentiation, Metastasis, and Responsiveness to Steroid Hormones. *Cancer Res*. 2016;76(8):2206–2218.
8. Dubeau L. The cell of origin of ovarian epithelial tumours. *Lancet Oncol*. 2008;9(12):1191–1197.
9. Kurman RJ, Shih Ie M. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. *Am J Surg Pathol*. 2010;34(3):433–443.
10. Flesken–Nikitin A, Hwang CI, Cheng CY, et al. Ovarian surface epithelium at the junction area contains a cancer–prone stem cell niche. *Nature*. 2013;495(7440):241–245.
11. Ng A, Tan S, Singh G, et al. Lgr5 marks stem/progenitor cells in ovary and tubal epithelia. *Nature cell biology*. 2014;16(8):745–757.
12. Ng A, Barker N. Ovary and fimbrial stem cells: biology, niche and cancer origins. *Nat Rev Mol Cell Biol*. 2015;16(10):625–638.
13. Wicha MS, Liu S, Dontu G. Cancer stem cells: an old idea–a paradigm shift. *Cancer research*. 2006;66(4):1883–1890.
14. Bu Y, Cao D. The origin of cancer stem cells. *Frontiers in bioscience (Scholar edition)*. 2012;4:819–830.
15. Friedmann–Morvinski D, Verma IM. Dedifferentiation and reprogramming: origins of cancer stem cells. *EMBO reports*. 2014;15(3):244–253.
16. Tomao F, Papa A, Strudel M, Rossi L, et al. Investigating molecular profiles of ovarian cancer: an update on cancer stem cells. *J Cancer*. 2014;5(5):301–310.
17. Bapat SA, Mali AM, Koppikar CB, et al. Stem and progenitor–like cells contribute to the aggressive behavior of human epithelial ovarian cancer. *Cancer Res*. 2005;65(8):3025–3029.
18. Lin S, Long HX, Xiang T, et al. Isolation and identification of cancer stem cells from primary human ovarian cancer tissues. *Zhonghua Zhong Liu Za Zhi*. 2011;33(12):896–899.
19. Wang L, Mezencev R, Bowen NJ, et al. Isolation and characterization of stem–like cells from a human ovarian cancer cell line. *Mol Cell Biochem*. 2012;363(1–2):257–268.
20. Kwon MJ, Shin YK. Regulation of ovarian cancer stem cells or tumor–initiating cells. *Int J Mol Sci*. 2013;14(4):6624–6648.
21. Le PN, Mcdermott JD, Jimeno A. Targeting the Wnt pathway in human cancers: Therapeutic targeting with a focus on OMP–54F28. *Pharmacology & therapeutics*. 2015;146:1–11.
22. Li SD, Howell SB. CD44–targeted microparticles for delivery of cisplatin to peritoneal metastases. *Mol Pharm*. 2010;7(1):280–290.
23. Lee SJ, Ghosh SC, Han HD, et al. Metronomic activity of CD44–targeted hyaluronic acid–paclitaxel in ovarian carcinoma. *Clin Cancer Res*. 2012;18(15):4114–41121.
24. Kim TH, Suh DH, Kim MK, et al. Metformin against cancer stem cells through the modulation of energy metabolism: special considerations on ovarian cancer. *BioMed research international*. 2014. Article ID. 132702.