EBioMedicine 10 (2016) 17–18

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Non-neoplastic Fallopian Tube Epithelium Carrying Gene Mutations of a Novel *SOX2* Repressor Region is Soil of High-grade Serous Ovarian Cancer

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ARTICLE INFO

Article history:
Received 8 July 2016
Accepted 8 July 2016
Available online 10 July 2016

High-grade serous ovarian cancer (HGSOC) has a high mortality rate because the disease is asymptomatic in early stages and is resistant to treatments. A novel modality for diagnosis in the early stages of carcinogenesis is needed. In this issue of *EBioMedicine*, Hellner et al. present novel genetic aspects of small lesions of HGSOC (Hellner et al., 2016). They performed screening by LFR WGS technology for small HGSOC lesions from a patient who underwent treatment and found 750 genomic mutations. Gene ontology analysis revealed that the gene mutations are related to stem cell differentiation, and the authors finally found 6 novel non-coding mutations (*BB1* - *BB6*) in proximity of *sex determining region Y-box2* (*SOX2*), a key driver of stem cell differentiation (Takahashi and Yamanaka, 2006). Deep genetic analysis revealed that the *BB5* region is commonly mutated in HGSOC tissues. A reporter assay and genome engineering using CRISPR/Cas9 system revealed that the *BB5* region is a novel repressor of the *SOX2* gene and that mutation in the *BB5* region induces protein expression of SOX2. Mutations in the *BB5* region were detected in non-neoplastic fallopian tube epithelium (FTE) of HGSOC cases and also in normal FTE of *BRCA1* or *BRCA2* mutation carriers who are at high risk for HGSOC. Surprisingly, immunohistochemical analysis of *BB5* mutation carriers revealed that SOX2 protein is broadly expressed in even normal FTEs, indicating that non-neoplastic FTEs with *BB5* mutation propagated clonally. SOX2 protein is expressed in earlier stages than TP53 protein expression indicating overexpression of SOX2 protein is earlier event than *TP53* gene mutation. Interestingly, SOX2 protein expression decreased after the establishment of an ovarian cancer lesion. These results suggest that mutation in the *SOX2 BB5* region is an early carcinogenesis driver mutation in HGSOCs and that detection of SOX2 protein is a promising biological marker for prediction of HGSOC.

In mouse models, stem cells in the ovary and tubal epithelia were identified as Lgr5-positive cells (Flesken-Nikitin et al., 2013; Ng et al., 2014), and Lgr5-positive epithelial stem cells are prone for genetically engineered ovarian cancer. Since Lgr5 is induced by Wnt/β-Catenin signaling, Wnt/β-Catenin signaling in epithelial stem cells seems to be activated (Barker et al., 2013). SOX2 is also induced by Wnt/β-Catenin signaling, indicating that epithelial stem cells that are sensitive for ovarian carcinogenesis are positive for SOX2. However, a recent study revealed that SOX2 protein is induced by mechanisms other than activation of Wnt/β-Catenin signaling (Hellner et al., 2016).

SOX2 protein expression was found to be decreased in HGSOC tissues in this study. On the other hand, SOX2 is overexpressed in ovarian cancer stem cells (CSCs) (Bareiss et al., 2013; Mariya et al., 2016), and SOX2 expression is essential for tumorigenicity of ovarian CSCs. Therefore, detection of SOX2 protein *in vivo* is important not only for early detection of high-risk FTEs but also for prediction of the outcome in advanced HGSOC cases. Finally, SOX2 protein might have two functional roles in the development of HGSOCs: (I) SOX2 protein is expressed in normal FTEs with *BB5* mutation and may have a role in clonal propagation *in situ*, and SOX2-positive FTEs are prone for HGSOCs and (II) after generation of an HGSOC lesion, SOX2 protein is expressed in a small subpopulation of HGSOC cancer stem cells. SOX2 is a transcription factor and further analysis of SOX2 target genes both in normal FTEs and cancer stem cells reveal the different functions of SOX2 protein in both cells.

Declaration of Financial Disclosure

The authors declare no competing interests.

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DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2016.06.048.

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http://dx.doi.org/10.1016/j.ebiom.2016.07.009

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