EBioMedicine 2 (2015) 1268–1269

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

A Quest for Better Mouse Models of Breast and Ovarian Cancers

Blaine A. Harlan, Alexander Yu. Nikitin *

Department of Biomedical Sciences and Cornell Stem Cell Program, Cornell University, Ithaca, NY 14853, USA

ARTICLE INFO

Article history:
Received 11 September 2015
Accepted 11 September 2015
Available online 12 September 2015

Inherited mutations in the *BRCA1* (breast cancer 1, early onset) gene increase the risk of female breast and ovarian cancers. About 65% and 40% of females who inherit *BRCA1* mutations will develop breast and ovarian cancer, respectively (Antoniou et al., 2003). To address specific roles of *BRCA1* in the normal development and cancer pathogenesis, a number of genetically modified mouse models have been developed. It has been shown that mammary epithelium-specific inactivation of *Brca1* alone is insufficient for cancer induction. However, mammary carcinomas can be induced by concurrent inactivation of *Brca1* together with *p53* (aka *TP53*/*Trp53*) gene, another tumor suppressor gene commonly inactivated in familial breast carcinomas. Similar to human breast cancers mutant for *BRCA1*, mouse BRCA1/P53 deficient tumors are mainly basaloid and triple-negative (no expression of estrogen receptor, progesterone receptor and HER/ERBB2 protein) (Liu et al., 2007). Transplantation of the ovarian surface epithelium (OSE) cells null for *Brca1* and *p53* genes resulted in the formation of carcinomas, which closely resembled high-grade serous ovarian carcinomas (HGSOC), the most common type of ovarian carcinoma (Orsulic et al., 2002).

Albeit highly valuable, the models used in those studies were focused on genetic modification in target cells and did not allow for direct testing of the role of non-autonomous factors in the pathogenesis of cancers associated with BRCA1 deficiency. To address this problem, Liu et al., 2015 developed new mouse models allowing Cre-*loxP* mediated gene modifications in tissues expressing the Müllerian inhibiting substance receptor type 2 (Mis2r, aka anti-Müllerian hormone receptor type 2) and follicle stimulating hormone receptor (Fshr). The authors established patterns of expression directed by the *Mis2r* and truncated *Fshr* promoters, and inactivated floxed *Brca1* and *p53* via Cre recombinase driven by these promoters. Consistent with the detected expression of *Mis2r* and *Fshr* transgenes in the mammary gland, the authors observed the formation of *Brca1* and *p53* deficient tumors featuring preferentially basaloid triple negative phenotype. Interestingly, while transgene expression was observed in a number of other tissues, including the renal tubules, the cervix, the uterine horns, the uterine tubes (aka oviducts or fallopian tubes), and the ovaries, only few of these tissues have shown neoplastic lesions. This suggests that BRCA1 and P53 functions may be especially critical for tumor prevention in certain cells types.

Another interesting aspect of the paper is the observation of neoplastic lesions associated with endosalpingiosis, a condition in which the tubal epithelium is found outside of the uterine tube. Ovarian carcinoma's tissue of origin remains debatable. The original pathological observations suggested that EOC arises from the OSE and from cysts formed after OSE entrapment during ovulation (Auersperg et al., 2008; Flesken-Nikitin et al., 2014). This model has been supported by results from experimental transformation of rat, mouse, and human OSE cells, induction of ovarian carcinoma by OSE-targeted conditional genetic alterations in genetically modified mice and by genetic analysis of human ovarian cystic inclusions (Orsulic et al., 2002; Flesken-Nikitin et al., 2014; Auersperg, 2013). The broad variety of ovarian carcinoma phenotypes are usually attributed to the origin of the OSE from the coelomic epithelium. During embryonic development, this epithelium also gives rise to the Müllerian (paramesonephric) ducts, which, in turn, differentiate into the epithelia of the uterine tube, endometrium and endocervix (Flesken-Nikitin et al., 2014). Based on morphological similarities of HGSOC to the tubal epithelium, as well as findings of mutant P53 in atypical lesions of the uterine tube (serous tubal intraepithelial carcinomas, STICs), it was proposed that ovarian carcinoma may derive from that epithelium (Medeiros et al., 2006). Supporting this possibility, it has been shown that *p53*, *Brca1* and *Pten* inactivations in the PAX8-expressing secretory tubal epithelium cells lead to HGSOC in genetically modified mice (Perets et al., 2013). Previously, Dr. Louis Dubeau, the senior author of the current manuscript, has proposed that ovarian carcinoma may also arise from other components of the secondary Müllerian system such as endosalpingiosis (Dubeau, 2008). Although only very few endosalpingiosis-associated lesions have been observed in the current manuscript, their finding provides a proof of concept and justifies the need for a particular attention to the endosalpingiosis as a putative place of origin of some ovarian carcinomas.

As stated by the authors, in the current configuration, the models are not suitable for the discrimination between cell autonomous and non-autonomous mechanisms of cancer formation; however, the value of these models is in their applicability to transplantation assays. It will be very interesting to determine if transplantations of non-mutant mammary epithelium and/or Müllerian derivatives into mice carrying

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2015.08.034.
* Corresponding author.
E-mail address: an58@cornell.edu (A.Y. Nikitin).

http://dx.doi.org/10.1016/j.ebiom.2015.09.017

Brca1 and *p53* mutations in tissues expressing *Mis2r* and/or *Fshr* genes will result in carcinogenesis. Such studies may provide essential new insights into the pathogenesis of familial cancers associated with *BRCA1* mutations and facilitate the development of new therapeutic approaches.

Disclosure

This paper is supported by the funding from the National Institute of Health/National Cancer Institute (CA182413), the New York Stem Cell Science (NYSTEM, C028125) and Ovarian Cancer Research Fund (327516).

References

Antoniou, A., Pharoah, P.D.P., Narod, S., et al., 2003. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am. J. Hum. Genet. 72, 1117–1130.

Auersperg, N., 2013. Ovarian surface epithelium as a source of ovarian cancers: unwarranted speculation or evidence-based hypothesis? Gynecol. Oncol. 130, 246–251.

Auersperg, N., Woo, M.M., Gilks, C.B., 2008. The origin of ovarian carcinomas: a developmental view. Gynecol. Oncol. 110, 452–454.

Dubeau, L., 2008. The cell of origin of ovarian epithelial tumours. Lancet Oncol. 9, 1191–1197.

Flesken-Nikitin, A., Odai-Afotey, A.A., Nikitin, A.Y., 2014. Role of the stem cell niche in the pathogenesis of epithelial ovarian cancers. Mol. Cell Oncol. 1, e963435.

Liu, X., Holstege, H., van der Gulden, H., et al., 2007. Somatic loss of BRCA1 and p53 in mice induces mammary tumors with features of human BRCA1-mutated basal-like breast cancer. Proc. Natl. Acad. Sci. U. S. A. 104, 12111–12116.

Liu, Y., Yen, H.-Y., Austria, T., et al., 2015. A mouse model that reproduces the developmental pathways and site specificity of the cancers associated with the human brca1 mutation carrier state. EBioMedicine 2, 1318–1330.

Medeiros, F., Muto, M.G., Lee, Y., et al., 2006. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. Am. J. Surg. Pathol. 30, 230–236.

Orsulic, S., Li, Y., Soslow, R.A., et al., 2002. Induction of ovarian cancer by defined multiple genetic changes in a mouse model system. Cancer Cell 1, 53–62.

Perets, R., Wyant, G.A., Muto, K.W., et al., 2013. Transformation of the fallopian tube secretory epithelium leads to high-grade serous ovarian cancer in Brca;Tp53;Pten Models. Cancer Cell 24, 751–765.