



Commentary

A Quest for Better Mouse Models of Breast and Ovarian Cancers



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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

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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

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