Of mice and women

Transgenic mouse model faithfully reproduces human ovarian carcinoma and offers new opportunities for understanding the natural history of this frequently fatal disease.

Ovarian cancer is the most common cause of death from gynecological cancer in the western world, and despite advances in treatment, the prognosis remains poor for most women who develop the disease. The reason for this is mainly because in its early stages, it has few, rather minor, symptoms and by the time symptoms are persistent, the disease is often extensive, when treatment failure is the rule. The overall five-year survival from ovarian carcinoma in the United States in the years 1992–1997 was 52%, but once disease was present outside of the pelvis, the survival was only 29% (http://www.cancer.gov/cancer_information). Newer drugs, such as paclitaxel (that prolong progression-free survival) have provided some hope for women with late-stage disease (McGuire et al., 1996), but there have been no recent research breakthroughs in the basic understanding of the disease. Part of the reason for this may be that there are no valid animal models of this disease, and it is rarely seen in domestic animals. Guinea pigs and other rodents do spontaneously develop ovarian tumors, and adding male and female sex hormones to their feed can induce ovarian tumors that partly resemble human ovarian carcinoma (Silva et al., 1997). Nevertheless, these rodent models are not sufficiently faithful to the human disease to have been particularly useful in understanding the prevention, natural history, and treatment of ovarian carcinoma.

Given this preamble, the publication of the paper by Orsulic et al. (2002) in the inaugural issue of *Cancer Cell* is particularly welcome. In brief, the authors used their own technique to engineer mouse ovarian cells to express the avian retroviral receptor, TVA. On removing the ovaries from the mice, the team introduced marker genes and oncogenes via a retrovirus, RCAS (subgroup A). Tissue-specific expression was enabled by using β-actin and keratin promoters (importantly, in the keratin 5-TVA cell line, TVA receptor expression is limited to the surface epithelium of the ovary). The in vitro treated ovarian cells were replaced in the mice at various sites. Ovarian carcinomas resembling human disease resulted (Figure 1), thus providing a flexible model for studying early events, response to treatment, and possibly even ovarian cancer prevention.

What is particularly attractive about the model is this flexibility. For example, in this publication, the authors used c-*myc*, K-*ras*, and *Akt* constructs singly, or in combination, but as they point out, there are many other genes, including the members of the c-*erbB* family, that could be applied in this system to generate molecularly distinct models of ovarian carcinoma. Indeed, it is in some ways a bit surprising that the authors selected K-*ras*, since the common codon 12 mutation is seen much more frequently in human mucinous adenocarcinomas and tumors of low malignant potential than in the serous papillary tumors (Caduff et al., 1999) that the tumors occurring in the mice most closely resemble. As one might expect from previous studies, this model also differs from the human situation in a number of interesting ways. For example, in this model, infection with all three of the above oncogenes did not cause ovarian cancer at all unless the mice were already null for p53. Once $p53^{-/-}$ mice were crossed with the TVA mice, then any two oncogenes of the three used were sufficient to cause ovarian carcinoma. This is quite unlike the human situation, where heterozygosity for germline *TP53* mutations only very rarely results in ovarian carcinoma (Kleihues et al., 1997). The authors address this by arguing that p53 alterations are a necessary, but not initial, event in ovarian carcinogenesis: in the mouse model presented, such alterations appear to be necessary and initial events.

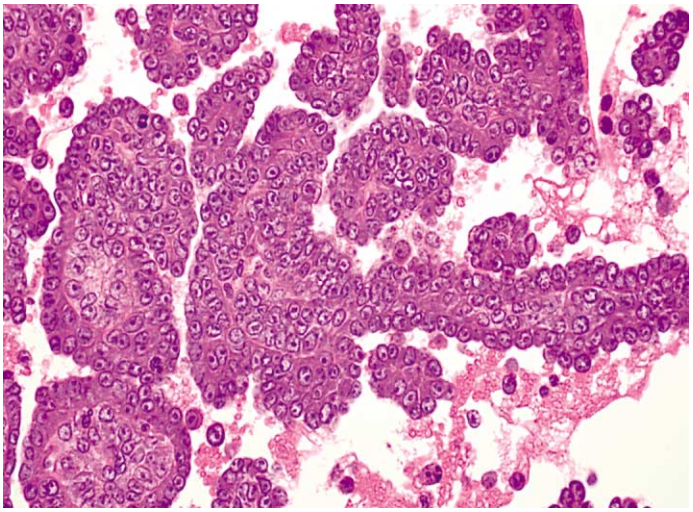

Figure 1. Ovarian carcinomas induced in a mouse model (figure courtesy of Orsulic et al., this issue).

It is not surprising that there are some differences in the molecular basis of experimental ovarian carcinoma in mice and the all-too-real ovarian carcinoma in women. It will be particularly interesting to see whether the permissive effect of initial loss of tumor suppressor gene function is restricted to p53, or whether other genes implicated in ovarian carcinoma susceptibility in humans, such as *PTEN* and *MSH2*, could also be important first steps in ovarian carcinogenesis. The authors refer to some unpublished data implicating INK4A/ARF, but again, this is rather dissimilar to the human situation, where germline heterozygous mutations in *CDKN2A* result in increased susceptibility to cutaneous malignant melanoma, pancreatic cancer, and possibly breast and oral cancer, but not to ovarian carcinoma. These observations raise the question of specificity: Orsulic and her colleagues have elegantly shown us that combined overexpression of selected oncogenes can cause murine ovarian carcinoma that closely resembles the human disease histopathologically, but it remains to be seen whether this effect is specific to the choice of oncogenes. The fact that "any two from three" will do, rather suggests

that the effects are not specific to these three oncogenes, but further experiments will be required to clarify the molecular requirements for development of the disease in this system.

One of the important questions that this paper has tried to answer is that of the cell of origin of human ovarian carcinoma. This may seem an unnecessary question: as an *ovarian* carcinoma mustn't it, by definition, arise from an *ovarian* epithelial cell? The immediate answer is yes, but on further examination, it is not quite so simple. Unlike almost all other epithelial tumors, which occur commonly, ovarian carcinoma in situ is extremely rare, and the benign-to-malignant transformation of ovarian epithelium is surprisingly infrequent. This curiosity along with other observations regarding the histopathology of the female genital tract, has led some to question whether in fact the carcinoma might arise from proximal peritoneal epithelium rather than the ovary itself (Dubeau, 1999). The peritoneal epithelium is physically and ontologically contiguous with the ovarian surface epithelium, making the distinction reliant on physical contact of the latter with the ovarian stroma. Here, Orsulic and colleagues argue persuasively for an ovarian surface epithelial origin for ovarian carcinoma, not only because they used transplanted ovaries, but also because the use of keratin- and β-actin-specific promoters allowed the authors to show unequivocally that the cancers arose from the ovarian surface epithelium. One could argue that some, but not necessarily all, ovarian carcinomas have been shown to arise from this surface, but the ball is back in the court of the naysayers.

The incidence of ovarian carcinoma is disproportionately high relative to carcinomas of the peritoneum, and peritoneal carcinomas, when they do occur, are found almost exclusively in women, originate in the pelvic region, and are often histologically indistinguishable from ovarian carcinomas. Clearly there must be something special about the interactions between ovarian stroma and peritoneal epithelium that promote the neoplastic growth of the latter cell-type. The greatest risk for both ovarian carcinoma and this type of peritoneal cancer is borne by women who carry germline *BRCA1* or *BRCA2* mutations. In a recent North American study of 208 Ashkenazi Jewish women with ovarian carcinoma, over 40% carried a *BRCA1* or *BRCA2* mutation (Moslehi et al., 2000). The ovarian carcinomas that develop in *BRCA1/2* mutation carriers closely resemble those reported here in the murine model. In a mouse model of human *BRCA1*-related breast cancer developed by Deng and colleagues who conditionally disrupted *Brca1* in mammary epithelial cells (Xu et al., 1999), the incidence of breast tumors was low unless the mice were crossed into a $p53^{+/-}$ background. Within a year, 90% of the doubly mutant mice developed breast cancer that was accompanied by loss of the wild-type p53 allele. It will be interesting to see if alterations in *Brca1* or *Brca2* will influence the phenotype reported by Orsulic et al.

The existence of a model may also help with evaluating new treatments, as the last really clear advance was the prolongation of survival provided by paclitaxel, mentioned previously. Ovarian carcinoma occurring in *BRCA1/2* mutation carriers appears to respond very well to platinum-based therapies (Boyd et al., 2000). A conditional knockout model of *Brca1*-related ovarian cancer with the ability to introduce specific oncogenic alterations could be a very useful tool in the further understanding of the basis of the observed response.

The authors have described a flexible, if technically challenging, murine model that offers new opportunities for research into the causes and treatment of human ovarian carcinoma. It will be interesting to see how such models contribute to the understanding of this disease when compared with easier and more generally available techniques such as expression microarray analysis (Tonin et al., 2001).

William D. Foulkes

Program in Cancer Genetics
Departments of Oncology
and Human Genetics
McGill University, Montreal, QC
Canada H3G 1A4
E-mail: william.foulkes@mcgill.ca

Selected reading

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