CANCER

A new mouse model of ovarian cancer metastasis

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High-grade serous ovarian cancer, also known as high-grade serous carcinoma (HGSC) accounts for >80% of advanced-stage ovarian cancers. Most HGSC cases are diagnosed in advanced stages, when tumors have already spread to the pelvic and peritoneal cavities, which portends poor prognosis. Mouse models of HGSC are available but they do not fully recapitulate the metastatic nature and/or genomic features of the disease. A study in *PLoS Genetics* describes a new genetically engineered mouse model that develops HGSC with 100% metastatic penetrance and recapitulates human metastatic HGSC; this model might be valuable to elucidate the mechanisms driving metastatic dissemination in HGSCs and evaluate potential therapies.

The triple mutant mice (TKO) were generated via introduction of a *p53* mutation into a previously described *Dicer1-Pten* double-knock-out (DKO) mouse model of HGSC. Analysis of DKO and TKO mice revealed that both models formed tumors in the fallopian tube, which subsequently

spread to the ovary and formed metastases into the pelvic and abdominal cavities, leading to ascites and ultimately death. Median survival was reduced in TKO mice compared to DKO mice (6.6 months versus 9.1 months of age; $P < 0.0001$), primary tumors emerged earlier (2 months versus 3 months of age) and metastasis was accelerated. The findings suggest that *p53* mutation—a molecular feature observed in 96% of HGSC—can accelerate tumor development and progression by increasing cell proliferation and migratory capacity. Previous studies have shown that genetic mutations of the *p53* gene alone are not sufficient to cause HGSC; this new study suggests that *p53* collaborates with other genetic alterations to increase tumor aggressiveness in HGSC.

HGSC tissues from DKO and TKO mice were cultured to establish cell lines. Spectral karyotyping analysis showed that, compared to DKO cells, TKO cells displayed a higher number of chromosomal

alterations, a characteristic of genomic instability and a hallmark of HGSC. HGSC TKO cells intraperitoneally inoculated into control immunocompetent mice produced peritoneal HGSCs with ascites similar to those observed in TKO mice, but with varying tumor-forming abilities. TKO cell lines that reliably produce HGSC in vivo should be selected to establish a syngeneic line model for HGSC.

“In summary, robustly modeling the clinical metastases of human HGSC with genomic and molecular similarities, TKO and DKO mice can offer unique opportunities to elucidate the pathogenic mechanisms underlying metastatic HGSC, including tumor initiation, development, progression, and metastatic dissemination,” conclude the investigators in their report.

Alexandra Le Bras

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