Seminar abstract

Mouse Models of Ovarian Cancer: Fallopian tube and ovarian origins

Jaeyeon Kim, Ph.D.

Department of Biochemistry and Molecular Biology, Melvin & Bren Simon Cancer Center, Indiana University School of Medicine, Indianapolis, Indiana, U.S.A.

Though named "ovarian cancer," it has been unclear whether the cancer actually originates in the ovary, especially for high-grade serous ovarian cancer, also known as high-grade serous carcinoma (HGSC), the most common and deadliest ovarian cancer. To understand the tissue origin of HGSC, we have made a genetically engineered mouse model by inactivating two genes, *Pten* and *Dicer*, in the reproductive tract. These tissue-specific *Dicer-Pten* double-knockout (DKO) mice develop metastatic HGSC arising from the fallopian tube. After enveloping seemingly normal ovaries, this fallopian tube-originated HGSC aggressively metastasizes, most notably, to the omentum — the most common site of metastasis in women with ovarian cancer. In addition, this cancer also causes widespread metastases across the peritoneal cavity, including the diaphragm, mesentery, and peritoneal membrane. The extensive metastases invariably induce massive ascites and inevitably kill the mice (100%). Moreover, not only does this mouse HGSC duplicate the clinical metastatic diseases of human HGSC, but this mouse cancer also resembles human HGSC histologically and at the molecular level.

The tumor suppressor p53 is the most frequently mutated gene in HGSC, as p53 mutation is found in 96-97% of human HGSC cases. To make a mouse model even more genetically relevant to human HGSC, we have thus bred a p53 mutation (R172H) into DKO mice, generating a triple-mutant (TKO) mouse model. Like DKO mice, these *p53* $^{R172H/+}$*-Dicer-Pten* TKO mice develop metastatic HGSC arising from the fallopian tube — a phenocopy of DKO HGSC. Moreover, intriguingly, when fallopian tubes are surgically removed from TKO mice, about 30% of these fallopian tube-deficient TKO mice develop metastatic HGSC originating in the ovary. To confirm this ovarian origin of HGSC, we have generated p53^{R172H}*-Pten* double-mutant (DMu) mice, one of the genetic control lines for TKO mice. Like fallopian tube-deficient TKO mice, 30% of these DMu mice also develop metastatic HGSCs from the ovary. Our study therefore shows that the fallopian tube is the primary origin, but the ovary can also be an alternative tissue of origin, for high-grade serous ovarian cancer, which reflects the current prevailing notion on the origins of human HGSC.

High-grade serous ovarian cancer is rarely detected at an early stage, which makes this cancer deadly. Most cases (>95%) are diagnosed, with metastases, in stage III or IV. Predictably, these advanced-stage diagnoses result in a poor five-year survival (28.8%). To cut ovarian cancer deaths, therefore, our long-term effort should aim at three fronts: (1) timely early detection and intervention, (2) effective treatment of advanced cancer, and (3) primary prevention (such as prophylactically removing ovaries or fallopian tubes or both). Achieving these goals will all require better understanding of the underlying mechanisms of ovarian cancer, in particular for HGSC. Applying these DKO and TKO mice — animal models faithfully reproducing human ovarian cancer — will help understand the molecular blueprint detailing the initiation and early as well as advanced tumor progression of HGSC. This knowledge will offer vital translational insights on identifying novel biomarkers for early detection, elucidating key driver mutations crucial to effective treatment for advanced cancer, and designing a beneficial prevention strategy for ovarian cancer.