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MOUSE MODELS IDENTIFY A POTENTIAL OVARIAN CANCER CELL OF ORIGIN

Most cases of high-grade serous ovarian carcinoma (HGSC), the most common and lethal type of ovarian cancer, are not diagnosed until late stages of disease, making it difficult to determine early events in ovarian cancer development and discern the cell of origin. Increasing evidence suggests HGSC may arise not only from the ovarian surface epithelium but may also arise from dissemination of precursor lesions originating in the fallopian tube epithelium. To formally prove that HGSC can arise from the fallopian tube, Peters and colleagues developed a genetically engineered mouse model in which Trp53, Pten, and Brca1 or Brca2—genes that are often simultaneously altered in human HGSC—were deleted by Cre-mediated recombination specifically in cells expressing Pax8, a transcription factor gene required for development of the female genital tract that is expressed in the fallopian tubes (specifically in secretory epithelial cells) but not the ovaries. Deletion of Trp53, Pten, and Brca1/2 led to the transformation of fallopian tube secretory epithelial cells and the development of PAX8-positive invasive carcinomas that frequently metastasized to the ovary and peritoneum and were histologically and molecularly similar to human HGSC. HGSC could only be prevented in these mice by surgical removal of the fallopian tubes, but not removal of the ovaries or uterus, further indicating that HGSC can arise from the fallopian tube epithelium. In addition to establishing a faithful mouse model of human HGSC with the potential to provide insight into the early stages of ovarian cancer development and facilitate preclinical drug testing, these findings strongly suggest that early detection and prevention strategies for ovarian cancer should not only focus on the ovaries, but also on the fallopian tubes.


Lymphoma

CTLs SPECIFIC FOR EPSTEIN–BARR VIRUS ANTIGENS ARE EFFECTIVE IN LYMPHOMA

A large percentage of patients with Hodgkin and non-Hodgkin lymphoma express Epstein–Barr virus (EBV) type II latency antigens, including latent membrane protein 1 (LMP1) and LMP2, suggesting that these antigens may be effective immunotherapy targets. However, the frequency and activity of LMP-specific T cells in patients with these tumors is often low. To overcome these limitations, Bollard and colleagues expanded LMP-targeting cytotoxic T lymphocytes (CTL) from patients with EBV-associated Hodgkin or non-Hodgkin lymphoma ex vivo using antigen-presenting cells expressing LMP2 alone or both LMP1 and LMP2. This approach generated effector memory and central memory T cells that exhibited LMP-specific cytotoxic activity. Autologous LMP-CTLs were then administered to 50 patients with EBV-positive lymphoma, and event-free survival (EFS) was assessed. Among 29 patients in remission after multiple relapses or who were at high risk for relapse, adjuvant CTL therapy resulted in sustained remission and a 2-year EFS rate of 82%. In addition, infusion of LMP-CTLs induced 11 complete responses and 2 partial responses in 21 patients with active lymphoma who had experienced tumor relapse following conventional therapy. Antitumor responses following CTL therapy were associated with an increase in circulating LMP-specific T cells in responding patients. Furthermore, 4 of 7 responding patients analyzed exhibited a broader antitumor immune response characterized by activation of T cells specific for lymphoma-associated antigens, indicative of epitope spreading. No toxicities related to CTL infusion or deaths from lymphoma occurred; in contrast, several patients died of non-relapse-related complications resulting from prior chemoradiotherapy. These results show that administration of autologous LMP-specific CTLs results in durable clinical responses in heavily pretreated patients with EBV-positive lymphoma and suggest that this targeted immunotherapy may prevent relapse and limit off-target toxicities associated with conventional chemoradiotherapy.