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Metastatic gastric cancer mouse models

Metastatic gastric carcinoma is a global health problem being that it is highly lethal and responds poorly to conventional and molecularly targeted therapies. Despite being valuable for evaluating potential cancer therapies, current genetically engineered mouse models (GEMMs) have limitations in representing all molecular subtypes of cancer and progressing to metastatic stages. A study in *Nature Cancer* shows the development of a method to introduce cancer-predisposing mutations or genes into murine gastric epithelium using electroporation for the generation of metastatic models of gastric cancer.

Using a somatic tissue engineering approach, with optimized surgical methods and electroporation conditions, the researchers engineered mice (EPO-GEMMs) with gastric tumors representing the three major non-viral cancer subtypes: chromosomal instability, genomic instability and microsatellite instability (MSI). The approach successfully recreated the histological and molecular features of the three tumor subtypes by introducing different mutations in tumor suppressor genes via gene editing and/or inserting oncogenes; the EPO-GEMM platform was also compatible with CRISPR base editing. The resultant models also exhibited transcriptomic profiles comparable to their human counterparts, allowing the identification of pathways that were either common or specific to each gastric cancer subtype. One of the main advantages of the EPO-GEMMs was their capability to metastasize, in contrast to other genetic mouse models. EPO-GEMMs showed metastases in the liver, lungs, peritoneum and adrenal glands, similar to human patients, with a subset of 10% of the animals showing rare ovarian metastases that are present in humans and that other models fail to replicate.

The researchers also studied the role of the immune system in gastric cancer metastasis by comparing a wild-type immunocompetent and a T, B and natural killer (NK) cell-deficient strain. Here, a greater incidence of liver metastasis was seen in the EPO-GEMMs mice from the immunocompromised strain when compared with EPO-GEMMs mice generated from wild-type mice. Next, by administering NK-cell targeting antibodies and further depleting $CD4^+$ and $CD8^+$ T cells in the EPO-GEMMs mice, the team discovered that in NK cell-depleted conditions, more metastases were present and $CD8^+$ T cells provided additional suppression of MSI tumors. These data reveal a surveillance mechanism for gastric cancer metastasis that relies on NK cells and $CD8^+$ T cells. Given the flexibility of the EPO-GEMMs and their similarities to human pathology, it is possible to study tumor–host interactions in a more straightforward way, which can help develop therapies for three major non-viral subtypes of the prevalent gastric cancer.

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