Title: Modeling metastatic ER+ breast cancer in rats

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Link: https://www.abstractsonline.com/pp8/#!/20273/presentation/4119

Citation: AACR 2025 Annual Meeting

Funding: R01CA268183 to W.X. and T32 CA009135 to C. J.

Scientific Abstract:

Estrogen receptor-positive (ER+) breast cancer makes up over 70% of all breast cancer and is treated with frontline endocrine therapy. However, the five-year survival rate for metastatic patients is only 27%. At this stage, patients are treated with a combination of endocrine and CDK4/6 inhibitors (e.g., palbociclib), but the development of drug resistance often arises. Genetically engineered mouse models are largely ER-negative. We developed a first-in-class ER+ metastatic breast cancer rodent model to enable a mechanistic understanding of organotropism of metastasis and the development of new treatment regimens. Following estrogen implantation in the female August Copenhagen Irish (ACI) rats, the physiological levels of estrogen are sufficient to induce ER+ mammary tumors at an incidence of 100%. RNA-sequencing revealed that rat tumors recapitulate human luminal B tumors. We subsequently derived MG-1, an ER+ rat breast cancer cell line, from ACI rat tumors. The growth of MG-1 is estrogen-dependent and inhibited by fulvestrant and CDK4/6 inhibitors. However, MG-1 does not frequently metastasize following orthotopic injection. When MG-1 cells were tail-vein injected into female ACI rats, colonization to the lung, liver, lymph nodes, and bone, all the human-relevant metastatic organs, were observed. Cells were disassociated from these tissues, flow-sorted, and cultured. Although MG-1 metastatic sublines derived from different organs exhibit distinct gene expression profiles, they all display epithelial-to-mesenchymal (EMT) signatures and are more resistant to endocrine or CDK4/6 inhibitors. In clinical trials, fibroblast growth factor receptor (FGFR) amplification/overexpression is frequently associated with endocrine and CDK4/6 inhibitor resistance. Compared with parental MG-1, MG-1 metastatic liver sublines overexpress FGFR1, elicit enhanced migration and colony formation capabilities, and are resistant to fulvestrant and CDK4/6 inhibitors. Knockdown of FGFR1 partially restored CDK4/6 inhibitor sensitivity and decreased the metastatic phenotype. Since two pan-FGFR1 inhibitors are FDA-approved for the treatment of cancers with FGFR abnormality, our immunocompetent MG-1/ACI rat model is well-suited for testing different combinations of CDK4/6 inhibitors and pan-FGFR inhibitors in treating metastatic disease. The results will inform the treatment strategy for metastatic ER+ breast cancer patients harboring FGFR alterations.

Written Lay Abstract:

Most breast cancers are estrogen receptor positive (ER+). Metastatic cases are when cancer has spread through the body, and this is hard to treat. Scientists need animal models that can help them find new treatments for metastatic ER+ breast cancer. However, most mouse models are ER negative (ER-), not ER+.

In this study, the researchers wanted to make a rodent model of ER+ breast cancer. They used female August Copenhagen Irish (ACI) rats and gave them estrogen to grow ER+ breast tumors. The researchers took these breast cancer cells and created a cell line called MG-1, which can be grown and made into many copies of the ER+ breast cancer cells.

The researchers wanted to see where metastatic ER+ breast cancer cells spread to in the body. When they injected female ACI rats with the MG-1 cells, the cells spread to the rats' lung, liver, lymph nodes, and bone. These areas are also where metastatic ER+ breast cancer tends to spread in humans. The researchers also found that the MG-1 cells from these organs of the rats were resistant to (would not respond to) a type of cancer treatment drug called CDK4/6 inhibitors. However, the researchers were able to reverse this resistance by changing the cells so they do not make as much protein called FGFR1. A current drug also exists, called a pan-FGFR1 inhibitor, that can lower the amount of FGFR1 protein in humans.

Next the researchers will use the MG-1 ACI rat model to test CDK4/6 and pan-FGFR inhibitors to treat metastatic breast cancer.

Visual Lay Abstract: