Title: CTR9 controls the mammary luminal lineage and susceptibility to carcinogen/hormone-induced breast tumors

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Scientific Abstract:

CTR9 encodes a key component of the human RNA polymerase II (RNAPII)-associated factor complex (hPAFc). CTR9 loss-of-function variants are predisposed to rare myeloid malignancies and Wilms tumors. Although CTR9 promotes the growth of estrogen receptor (ER)-positive breast cancer cells and controls the expression of 90% of ER-target genes, the roles of CTR9 in mammary gland development and breast cancer etiology in vivo remain unknown. About 0.1 % of breast cancer patients were found to harbor loss of function CTR9 mutations based on TCGA data. Analyzing normal mouse mammary gland scRNA-seq data reveals that CTR9 is highly expressed in luminal cells, which is confirmed by immunofluorescence staining in human breast tumors. To study the effects of the loss-of-function of CTR9 on mammary gland development, we generated a mammary gland-specific CTR9 knockout (KO) mouse using MMTV-Cre and CTR9 loxP system. CTR9 depletion from mammary epithelial cells was validated using qPCR, Western blot, and IHC. Loss of CTR9 in C57B/6 female mice led to increased duct branching and elongation during puberty and increased alveologenesis during pregnancy. This observation coincides with the detection of expanded mammary stem cells by flow cytometry in the 6-week-old mouse mammary glands. When treated with DMBA and progestin (MPA) to induce mammary tumors, both wild-type (WT) and CTR9 null mice began to develop tumors 6 weeks after the last DMBA treatment, but CTR9 null mice exhibited a markedly enhanced susceptibility to carcinogen/hormone-induced mammary tumors as compared with the WT counterparts. To detect changes during the early stage of tumorigenesis, we profiled the stem and luminal progenitor cell populations in the mammary gland 4-week after the last DMBA treatment. Remarkably, CTR9 depletion enhanced the stem cell and luminal progenitor populations while decreasing the mature luminal cells. CTR9 KO mammary gland had elevated Ki67 levels, decreased ER and PR, decreased mature luminal cells, and increased expression of KRT15, a luminal progenitor marker. The CTR9 null mammary gland expressed lower levels of KDM5A and higher levels of H3K4me3 as compared to the wild-type mice. Taken together, our findings establish that CTR9 depletion blocks the terminal differentiation of luminal cell lineage possibly through epigenetic regulation of histone methylation, and renders the mammary glands more susceptible to carcinogen/hormone-induced tumors.

Written Lay Abstract:

Breast cancer can sometimes happen in a part of the mammary gland called the mammary ducts and alveoli, which make and release milk. Cells in these parts of the breast all come from the mammary luminal lineage, which are a type of stem cell.

A protein called CTR9 normally helps cells use DNA to make other proteins, so when CTR9 stops working, the cell can no longer work normally. About 1 in 1000 patients with breast cancer have a DNA mutation that causes CTR9 to stop working.

CTR9 increases growth of estrogen receptor positive (ER+) breast cancer, but researchers do not know how CTR9 is involved in mammary gland development and breast cancer. To better understand how CTR9 may be involved in breast cancer, researchers studied mouse breast cancer tumors and cells.

The researchers found that there is a lot of CTR9 in mammary luminal cells. In mice without working CTR9, the mammary ducts and alveoli had more growth than normal. These mice had more mammary stem cells than normal. Researchers also gave mice carcinogens (something that can cause cancer). Mice without CTR9 given carcinogens had more tumors than the mice with normally working CTR9. The mice without CTR9 had fewer mature (fully grown) luminal cells and more stem cells compared to mice with normal CTR9. The mice without CTR9 also had higher levels of an enzyme (KDM5A) linked to protein changes (H3KRme3) and cancer growth.

These findings tell us that when CTR9 is not working normally, mammary gland cells are more likely to be affected by carcinogens and grow breast cancer.

Visual Lay Abstract: