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Blocking IRE1 signaling pathway sensitizes triple-negative breast tumors to chemotherapy and prevents cardiac toxicities

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Triple-negative breast cancer (TNBC) is one of the most highly aggressive breast cancer types that predominately affect young and minority women. Triple-negative breast cancer is ER-negative, progesterone receptor (PR)-negative, and HER2 normal that accounts for 10-20% of all breast cancer cases. There are no targeted therapeutic options limiting TNBC patients to more severe toxic chemotherapy regimens associated with cardiac dysfunction. Another issue compounded in the risk of developing cancer and chemotherapy-related toxicities is Obesity. Obesity is associated with worse overall survival in women with TNBC. The unfolded protein response (UPR) is an endoplasmic reticulum (ER) stress pathway activated when unfolded or misfolded proteins accumulate within the lumen of the ER. Inositol-requiring enzyme-1 (IRE1) is an arm of the UPR pathway that plays a crucial role in tumor development. IRE1 signaling is the most evolutionary conserved branch of the UPR. It has been shown that IRE1/XBP1 protein levels are upregulated in TNBC. Preliminary work demonstrates that high-fat diets increased IRE1 levels in the DMBA tumor model. However, whether diet differentially stimulates IRE1 on TNBC is unknown.

To determine the role of Obesity and IRE1 targeting on chemotherapy response and prevention of therapy-related cardiac toxicity, we developed a syngeneic model of murine breast cancer by injecting female BALB/c mice consuming a control diet with 4T1-Luc in the mammary gland. Once tumors developed, mice were treated with the anthracycline doxorubicin with or without IRE1 blockade. Cardiac function was measured, and tumor or cardiac tissue was collected. We found that combination of targeting IRE1 with doxorubicin (DOX) enhanced chemotherapy responsiveness in the 4T1 breast cancer model. Furthermore, inhibiting IRE1 prevented DOX-mediated cardiac damage and preserved cardiac function. We found in vitro that human TNBC lines conditioned media differentially shift IRE1 signaling in H9C2 rat cardiac myoblast cells. Also, 4T1 TNBC cell line conditioned media significantly upregulated IRE1 protein levels and decreased p-JNK (54kDA) in H9C2 rat cardiac myoblast cells. Overall results suggested that systemic suppression of IRE1 protected cardiac tissue in mice treated with doxorubicin while enhancing anthracycline-mediated tumor killing.

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