Inositol-requiring enzyme-1 (IRE1) blockade affects triple-negative breast cancer chemotherapy sensitivity and prevents chemotherapy-related cardiotoxicity

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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. TNBC patients are more likely to receive cytotoxic chemotherapy regimens since they have limited targeted options. This results in severe side effects resulting in chronic 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. Inositol-requiring enzyme-1 (IRE1) is an arm of the unfolded protein response (UPR) pathway that plays a crucial role in tumor development. 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 investigate the role of Obesity and IRE1 in targeting chemotherapy response and prevention of therapy-related cardiac toxicity, we obtained female BALB/c mice placed on control and western diets at 3-weeks of age 5 weeks. At 8-weeks of age, mice were injected with 4T1-luciferase breast cancer cells in the left inguinal fat pad. Primary tumor growth was monitored by IVIS and calipers weekly for 21 days. Primary tumors were then surgically resected, and one week after tumor resection, mice received 3.3 mg/kg doxorubicin (DOX) I.V. for 3 weeks. Cardiac function was measured by Vevo ultrasound. These studies demonstrated that the western diet stimulates primary breast tumor growth, decreases DOX responsiveness, and potentiates cardiac dysfunction compared with control diet-consuming mice. Also, the Western diet affected the development of DOX-induced cardiac dysfunction by increasing cardiac fibrosis in response to therapy. Also, we developed a syngeneic model of murine breast cancer by injecting female BALB/c mice consuming a control or western diet with 4T1-luc in the mammary gland. Once tumors developed, mice were treated with doxorubicin (DOX) with or without anti-sense morpholino to IRE1. We found that a combination of targeting IRE1 with DOX enhanced chemotherapy responsiveness in the 4T1 breast cancer model. Furthermore, we found that DOX alone reduces fractional shortening and ejection fraction, but this effect was prevented by targeting IRE1. Also, IRE1 blockade reduces interstitial fibrosis in combination with DOX and reduces vimentin, also known as intermediate fibroblast filament in combination with DOX. 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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