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Impact Of The Microbiome On Therapeutic Response In Triple Negative Breast Cancer

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Triple negative breast cancer (TNBC) accounts for 15-20% of all breast cancer types, predominately affecting young and minority women. TNBC lacks estrogen receptor expression, progesterone receptor expression, and have normal levels of HER2. This type of breast cancer lacks targeted therapy options and treatment is limited to chemotherapy. TNBC is typically characterized by a high recurrence rate, with about 34% of TNBC patients relapsing around 2.6 years. Neoadjuvant chemotherapy is often used to shrink the tumor mass before surgery to improve outcomes. Previous studies demonstrated that breast tumors have their own microbiome population that differ from the surrounding normal breast tissue. Our group has demonstrated increased Pseudomonas abundance in breast cancer patients that received neoadjuvant chemotherapy. The purpose of our study was to determine whether chemotherapy modulates microbiome populations in preclinical models. We hypothesize that microbiota populations may be a predictive biomarker of chemotherapy response.

In this study, 8-week old female BALB/c mice were injected with 4T1-luc cells (TNBC cells) into their L4/5 mammary fat pad. Once tumors developed, mice were either untreated (control group), treated with 1 x weekly 2.5 mg/kg IV doxorubicin, or treated with doxorubicin+antibiotics (mixture of streptomycin, ampicillin, and colistin in the drinking water to ablate host bacterial populations) along 4 weeks. Fecal samples were collected at timepoint 0 weeks (before treatment) and timepoint 4 weeks (after treatment). Tumors, lungs, hearts and plasma were collected at the end of the study. 16S-bacterial sequencing analysis was performed to look at the microbiome content of the tumor and fecal samples. We subdivided the doxorubicin treated group into DOX-responders (tumors stopped growing or shrank) or DOX-nonresponders (tumors continued to grow on treatement). We demonstrate that at timepoint 0 weeks (before treatment), elevated fecal Ruminocoocus correlates with DOX-nonresponsiveness. Furthermore at timepoint 4 weeks (after treatment), we show increased fecal abundance of Oscillospira and Bacteroidales is associated with better therapeutic outcome. Also, we found a significant elevation of apoptosis marker (cleaved caspase-3 protein levels was measured in 4T1 tumors) from DOX-responders and DOX+antibiotic treated mice. Elevated CFTR protein levels were also observed in tumors from DOX-responding groups. Taken together these data suggest that fecal microbiota populations could be used as a biomarker of therapeutic response. Moreover, we plan on determining whether modulation of these gut microbiota populations may shift chemotherapy treatment outcomes.

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