The Microbiome Mediates Carcinogenic Alterations of the Mammary Gland in the Context of Obesity

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Obesity increases the relative risk for breast cancer incidence. Several obesity-linked molecular mechanisms are demonstrated to drive breast cancer progression, however, if and how obesity contributes to breast cancer initiation is poorly understood. Obesity alters adipose tissue structure and signaling, immune cell activity, and shifts the microbiome in ways that could potentially increase breast cancer risk. Our preliminary experiments with a mouse mammary carcinogenesis model indicate that diet-induced obesity alters the microbiome in the gut and the mammary gland that leads to decreased tumor-free survival, reduced tumor latency, and increased tumor multiplicity. Microbial-associated molecular pattern (MAMP)-proteins and metabolites such as lipopolysaccharide (LPS), a toll-like receptor 4 (TLR4)-agonist, could directly affect breast epithelial cell signaling. LPS was found to be elevated in the plasma and mammary glands of obese mice. Experiments in a 3D culture model of breast glandular units (acini) show that LPS disrupts the tight junctions (TJs) that maintain apical polarity. The loss of apical polarity is a known functional biomarker of breast cancer risk. Other biomarkers of risk include DNA damage and oxidative stress which were shown to be elevated by LPS treatment. Preliminary data show that LPS activates the nuclear factor-kappa B (NFκB) pathway by binding to the TLR4 receptor leading to an increased expression of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α). The outcomes of our study underscore the importance this under-appreciated component of the tumor microenvironment, the microbiome, in the prevention of breast cancer. In conclusion, we show that obesity-modulated gut microbiome increases breast cancer risk, at least partly, through the involvement of microbiome metabolites such as LPS.

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