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

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Several mechanisms have been shown to drive breast cancer progression in obesity, however, if and how obesity contributes to breast cancer initiation is poorly understood. Obesity alters adipose tissues, the immune environment, and 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 and leads to decreased tumor-free survival and tumor latency, and increased tumor weights and multiplicity. Microbiome metabolites such as the toll-like receptor-agonist, lipopolysaccharide (LPS), could directly affect breast epithelial cells. These metabolites were shown to be elevated in the plasma of obese mice. Experiments in a 3D culture model of breast glandular units (acini) show that LPS disrupts tight junctions (TJ), which strictly define apical polarity. The loss of apical polarity is a known functional biomarker of breast cancer risk. Other biomarkers of risk include DNA damage and reactive oxygen species (ROS) generation. Our preliminary data also indicate elevated ROS and DNA damage in breast acini treated with LPS. A recent finding by our lab hinted to the importance of redox balance in polarity maintenance, and hence, ROS generation by LPS could provide a mechanism for polarity loss. The outcomes of our study underscores the importance of this almost-forgotten organ, the microbiome, and the need to consider in prevention and treatment strategies in the future. 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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