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### **Investigating lactate isoforms as a potential mechanism to reduce obesity –mediated breast cancer risk**

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The production of lactate is often associated with cellular stress and as a metabolic waste product. Under normal, non-stressful conditions, the metabolism of glucose via glycolysis results in an overarching production of pyruvate, which can then be used in the mitochondria in the tricarboxylic acid cycle (TCA) to generate adenosine triphosphate (ATP) for cellular processes and function. In a stressful environment, like that lacking oxygen and/or uncontrolled proliferation, there is a shift in the glycolytic pathway to produce more lactate from pyruvate thereby resulting in less mitochondrial utilization to produce ATP. Lactate can also be used as an alternative energy source by being converted back into pyruvate or can also be shuttled out of the cell by the monocarboxylic transporters (MCT) 1 and MCT4 to promote immunosuppression within the microenvironment. Obesity is a prevalent health condition in the United States and is a modifiable risk factor for breast cancer development in postmenopausal women. As poor diet is a major contributing factor for the development of obesity and subsequent breast cancer, it is essential to maintain a healthy dietary lifestyle as a way to prevent breast cancer development. Balanced diets can also maintain essential intestinal and gut health by maintaining the symbiotic relationships between the microbes found there, but may also play a role on microbes found in distal organs and tissues, like the breast. Using a nonhuman primate (NHP) model, our lab performed metabolomics on mammary glands from *M. fascicularis* NHP fed a Western or Mediterranean diet for 2.5 years. With the animals separated in groups based on body fat composition, we were able to look at the impact of adiposity within dietary patterns on mammary gland (MG) metabolism. Comparing metabolites identified from these MGs, NHP with the highest body fat composition displayed decreased lactate concentrations when compared with lean NHP breast tissue levels. In addition to the increased levels of lactate found in these MGs independent of diet, elevated proportional abundance of lactate-producing bacteria were present in lean NHP breast tissue, suggesting a potential role of the microbiome in the regulation of gland-specific lactate. C57BL/6 mice demonstrate susceptibility to dietary induced obesity. When analyzing gene expression and protein levels of lactate dehydrogenase (LDH) enzyme isoforms responsible for converting pyruvate to lactate, LDHA (L-lactate isoform specific) and LDHD (D-lactate isoform specific), LDHA and LDHD were higher in MG tissue of low-fat control diet-fed mice compared to Western diet-fed mice. These data suggest the regulation of lactate metabolism by obesity within the mammary gland compartment may be mediated through repression of enzyme activity. Future goals of the study include to investigate the impact of L-lactate and D-lactate isoforms on obesity-mediated breast cancer risk, breast metabolic pathways, and localized gland inflammation. Moreover, we plan to explore the effect of the breast microbiome on regulating localized lactate levels within the MG to potentially modify breast cancer risk.