Chronic Elevation of Tumor Necrosis Factor-Alpha Suppresses Lactation via Downregulation Of Lipoprotein Lipase.

Freddie Schozer[1], Patrick Tso[1,2], Russell Hovey[3], Josephine Trott[3], Erin Wagner[4], Rebekah Karns[5], Sarah Riddle[5], Amy Thompson[1,6], Laura Ward[5], Laurie Nommsen-Rivers[4]

University of Cincinnati College of Medicine[1]; Department of Pathology and Laboratory Medicine, Metabolic Diseases Institute, University of Cincinnati[2]; University of California Davis[3]; Department of Animal Science, University of Cincinnati College of Allied Health Sciences[4]; Cincinnati Children's Hospital Medical Center[5]; Department of Obstetrics and Gynecology, University of Cincinnati[6]

Introduction: Lactation provides a critical source of nutrition for growing infants. Identification of factors that impede lactation is critical for developing interventions to support or restore adequate milk production, including the factors that regulate lipid synthesis and transport within the lactating mammary epithelial cells (MEC). Using transcriptome analysis, we examined the role of Tumor Necrosis Factor–Alpha (TNF-A), a potent regulator of lipid metabolism, in the suppression of lactation.

Hypothesis: We hypothesized that mothers with very low milk production, as compared to mothers with sufficient milk production, will have significantly elevated serum TNF-A and increased activity in MEC TNF-A signaling pathways.

Methods: Fresh breastmilk samples containing MEC RNA were collected from 5 mothers with low milk production [LMP] (0-177 mL/24h), and 8 mothers with sufficient milk production [SMP] (562-801 mL/24h). BMI, fasting serum triglycerides, and TNF-A were also assessed. Total RNA was isolated from the milk samples to construct an mRNA transcriptome. Differentially expressed genes were identified (FDR P-value <0.05) and interpreted using the PPAR and TNF-Alpha KEGG pathways.

Results: Mothers were 32(10.7) versus 47(19.2) days postpartum, respectively in LMP versus SMP groups (P>0.05). Fasting triglyceride, TNF-A, and BMI were significantly elevated in LMP versus SMP groups (P<0.05).

Transcriptome analysis revealed 1.7-fold down regulation of Lipoprotein Lipase (LPL) in LMP versus SMP groups. In addition, PPARA and RXRA, two regulatory factors upstream of LPL, were downregualted 1.8-fold.

Conclusions: Consistent with TNF-A's lipid regulatory function, we show that lactating mothers with insufficient milk production have elevated serum TNF-A and a corresponding reduction mRNA expression of lipid processing proteins downregulated by TNF-A, notably LPL which is necessary for the hydrolysis of triglycerides into free fatty acids and glycerol for transport into MECs. Since most of the lipids used in breastmilk production come from adipose tissue or diet, disruption in fatty acid transport deprives MECs of vital fuel and substrate towards the synthesis of breastmilk. Our findings shed light on TNF-A mediated lipid dysregulation and uncover a potential link between factors which cause elevated TNF-A, such as chronic obesity, and insufficient lactation.

Acknowledgements: This study was supported in part by NIH grants T35 DK 60444