Hormone sensitive gene signatures in the lactating mammary epithelial cells (MEC) of women with persistent low milk production.

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Introduction: Exclusive breastfeeding is recommended for the first 6 months of life. Unfortunately, some mothers struggle to produce enough milk supply to meet this breastfeeding goal. There is growing evidence that rising rates of maternal obesity and diabetes are fueling an increase in mothers who are physiologically unable to produce sufficient breast milk. Understanding the molecular mechanism of low milk production may offer avenues on which to begin treating this condition.

Objective: Using a pre-established database of the transcriptome of extracellular mammary epithelial cells (MEC) of mothers with low vs sufficient milk production, our objective was to examine differential expression of genes involved in insulin-sensitive and prolactin-sensitive signaling.

Methods: Insulin signaling and prolactin signaling KEGG pathways and a broad literature search were used to establish a candidate gene list . Differential expression of these candidate genes in the MEC transcriptomes of 8 sufficient milk producing mothers (Sufficient-vol) and 5 low milk producing mothers (Low-Vol) were then compared and analyzed.

Results: All Low-Vol samples analyzed in this study came from mothers who were obese and had significantly high markers of insulin resistance. We observed a significant decrease in insulin-sensitive signaling, including a 2.3-fold decrease in insulin receptor substrate 2 (IRS2) in Low-Vol versus Sufficient-Vol. There was no differential expression seen in genes involved in prolactin signaling, such as the prolactin receptor or JAK2.The synthesis of milk proteins such as casein 2 (CSN2) showed a 2.1-fold decrease in expression in Low-Vol versus Sufficient-Vol. There was also a 2.7-fold decrease in expression of UDP-glucose pyrophosphorylase 2 (UGP2) in low milk producing mothers, thus elucidating a decrease in production of lactose, a driver of milk volume.

Conclusion: In sum, the downregulation of milk production in obese, low-milk producing mothers seems to be driven more so by down regulation of insulin-signaling genes rather than by prolactin-signaling genes. The significant overlap of genes involved in insulin and prolactin signaling pathways yields a mechanism by which both pathways are affected by the downregulation of insulin-signaling genes. Many genes involved in hormone-sensitive regulation did not show the expected change in expression, thus emphasizing the need for further studies.

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