Glucocorticoid regulation of milk production and α-lactalbumin gene expression

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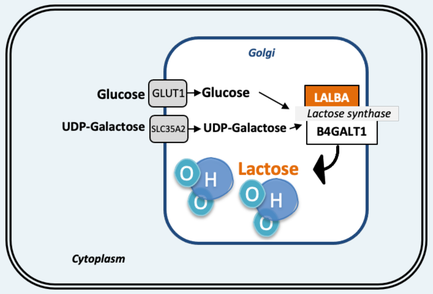
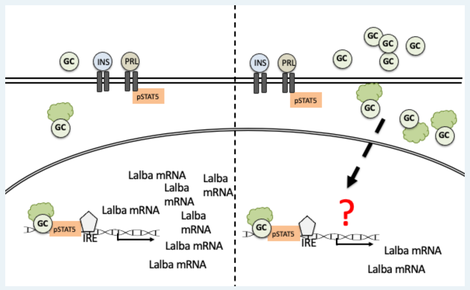
Background

- Perceived or real low milk production is a primary reason for undesired breastfeeding cessation.
- Stress involving cortisol dysregulation decreases milk production. Synthetic glucocorticoids administered during lactation transiently suppress milk production.
- α-lactalbumin is a protein required for lactose synthesis.



- Glucocorticoids biphasically regulate α-lactalbumin gene expression in culture.



- The mechanism by which endogenous or exogenous glucocorticoids affect milk production is not defined.

Objectives

- Define the effect of a single dexamethasone administration on milk volume and composition and mammary gene expression in lactating dairy cows
- Define the concentration-dependent effect of glucocorticoids over time on the expression of LALBA and GR mRNA and protein using mammary explants in culture from mid-pregnant mice

Methods

Lactating dairy cows received a single administration of dexamethasone (40 mg, IM) and milk volume, composition, and tissue biopsies were collected. RNA was extracted from tissue and subjected to RNAsequencing. Differential gene expression at 0, 12, 24, and 72 hours post-treatment was determined using a pairwise comparison. Differentially expressed genes at 12 and 24 hours relative to time 0 were further evaluated in DAVID, Reactome, and Enrichr platforms.

Single, high dose administration of dexamethasone to dairy cows results in a transient suppression of *LALBA* expression, lactose synthesis, and milk production.

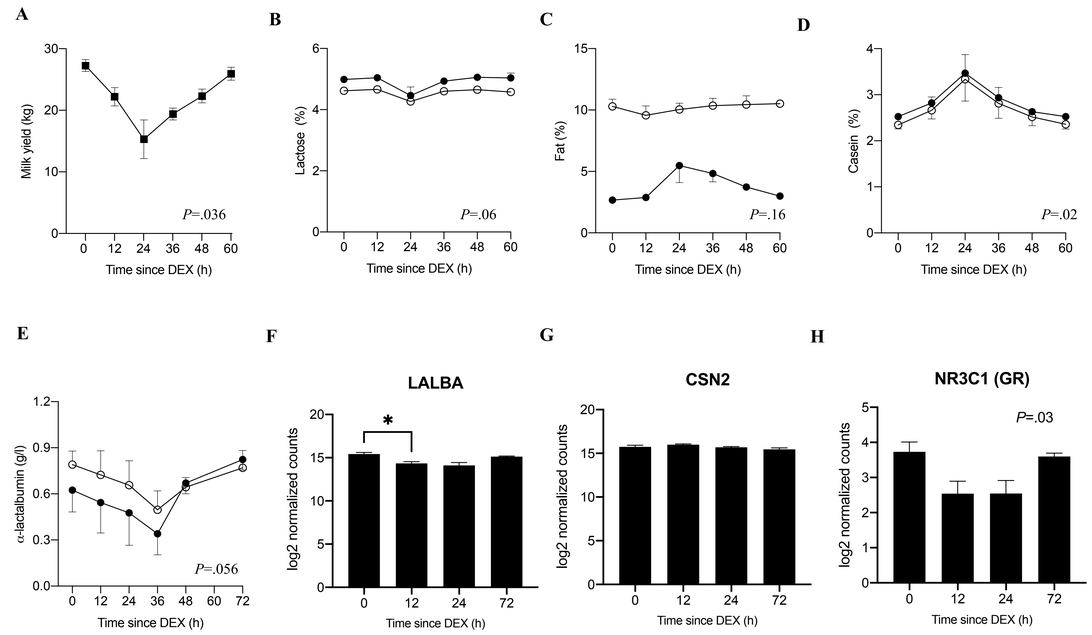
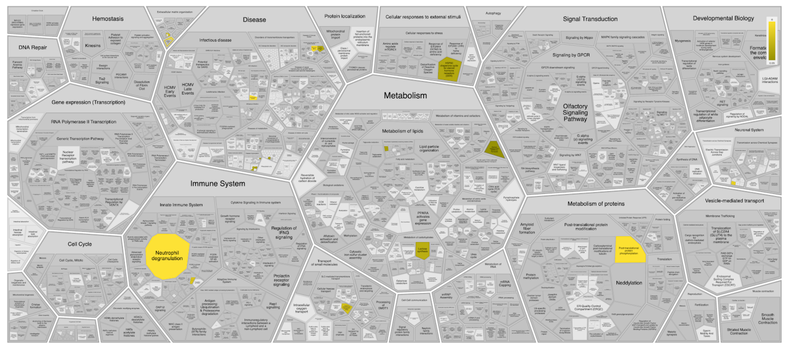
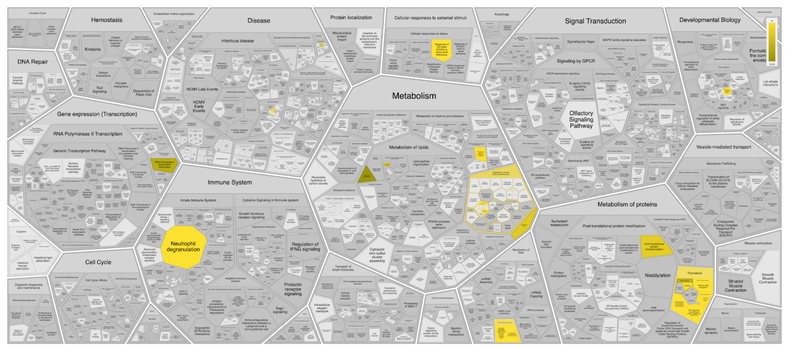


Figure 1. In response to a single dexamethasone administration (40 mg, IM), raw milk volume (A), milk lactose content (B), and milk α-lactalbumin (LALBA) content (E) decreased. Milk fat (C)and β-casein (CSN2, D) concentration increased. The expression of the *LALBA* (F) and glucocorticoid receptor (*NR3C1, H)* genes were decreased at 12 h while the expression of CSN2 (G) was unchanged. Data are presented for three cows. Filled circles are foremilk, open circles are hindmilk. *, P<.05.



12 hours after dexamethasone

Figure 2. Expression of genes responsible for inflammation and lactose synthesis is down regulated



24 hours after dexamethasone

Figure 3. Expression of genes responsible for mRNA translation are upregulated

Mammary explants from mice as the *ex vivo* system

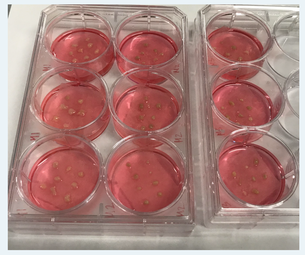


Figure 4. Mammary tissue from mice is removed, chopped up, placed on siliconized lens paper, and floated in a culture (right). Tissue is removed and RNA is extracted.

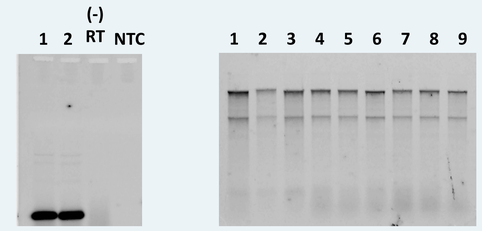


Figure 5. Fresh, non-explanted tissue from a lactating mouse (DNA gel, left) has high levels of *Lalba* expression. RNA after DNase treatment (RNA gel, right) isolated from mammary explants maintained in a non-supplemented culture medium for five days from Figure 4.

Next steps

Define the concentration-dependent effect of glucocorticoids over time on the expression of LALBA and GR mRNA and protein using mammary explants in culture from mid-pregnant mice.

Determine when and where the GR binds the *Lalba* promoter in response to stimulatory and inhibitory concentrations of glucocorticoids.

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