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Elitsa Ivanova, Catherine Hue-Beauvais, Johan Castille, Johann Laubier, Sandrine Le Guillou, Christine Péchoux, Gilles Foucras, Madia Charlier, Fabienne Le Provost

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C57BL/6 mouse, The Jackson Laboratory

Characterization of the effects of a SOCS2 point mutation on mammary gland development and function

Ivanova E.[1], Hue-Beauvais C.[1], Castille J.[1], Laubier J.[1], Le Guillou S.[1], Péchoux C.[1], Foucras G.[2], Charlier M.[1], Le Provost F.[1]

Introduction

Mastitis is among the main reasons women cease breastfeeding, which leads to them supplementing breast milk with artificial formula. In farm animals, mastitis results in significant economic losses and the premature culling of some animals. Any factor that could regulate sensitivity to mastitis warrants further study. In 2015, Rupp et al reported a point mutation (R96C) in the SH2 domain of SOCS2 (suppressor of cytokine signaling 2) that leads to a loss of ligand recognition. Twenty-one percent of the Lacaune sheep studied were carriers of the mutation. Their size, weight, and milk production were significantly increased compared to controls; however, so was their sensitivity to mastitis. These findings suggest that SOCS2 is a potential regulator of mammary gland function and, thus, of milk production.

Methods

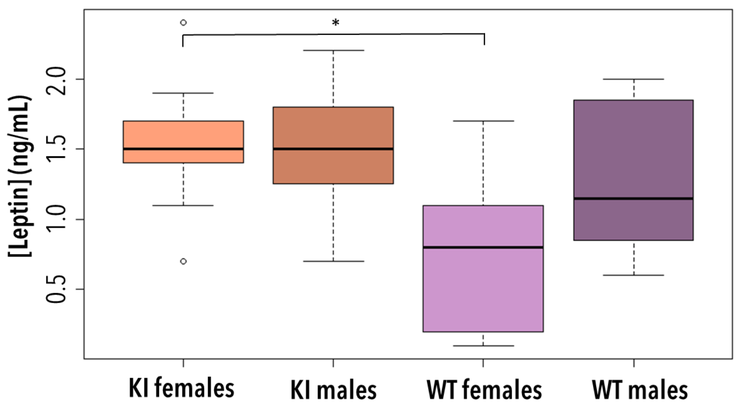
Proof of concept: **mouse knock-in** model, carrier of the R96C SOCS2 mutation

Blood serum samples from adult (12-15 weeks) male and female mice

Mammary gland samples from virgin (8-week old) mice, 18th day of pregnancy, and 7th day of lactation

- **Metabolic assay** (leptin)
- **Structural characterization** (WM, H&E, and TEM imaging)
- **Gene expression** via microarray (Agilent)

Leptin resistance in female KI mice

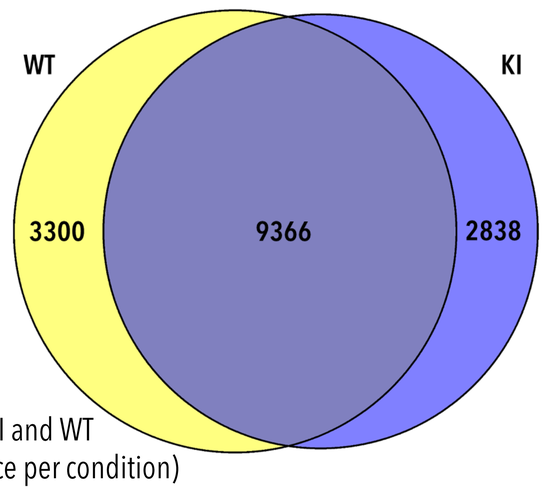


Female KI mice have **twice** as much **leptin** as **WT females.**

Leptin (ng/mL) assay of blood serum from adult mice (n=10 per condition)

Differences in virgin to pregnancy gene expression dynamic (KI *versus* WT)

15 504 differentially expressed genes in the mammary gland between **virgin** and **pregnant** mice → only **9 366 shared** between **KI** and **WT.** Enrichment analysis shows **KI specific genes** indicating **mitochondrial dysfunction**.



Shared and specific differentially expressed genes in KI and WT mammary glands (n=7 virgin mice, n=5 pregnant mice per condition)

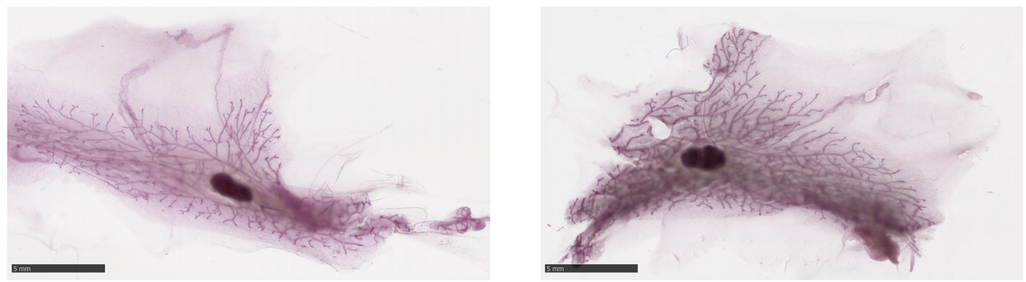
Conclusion

We found that the R96C mutation of SOCS2 causes **leptin resistance** in female mice. It affects mammary gland development as it **reduces ductal branching** in virgin glands and leads to **less mammary epithelial tissue development** in pregnancy and lactation. It influences **lipid droplet production** and **lowers milk fat globule secretion**. Furthermore, KI mice have a **different gene expression dynamic** (virgin to pregnant mice) compared to WT. Thus, SOCS2 is a **pleiotropic factor** essential in **mammary gland development** and **function**.

Structural characterization of the KI phenotype

Virgin 8-week old

KI | WT

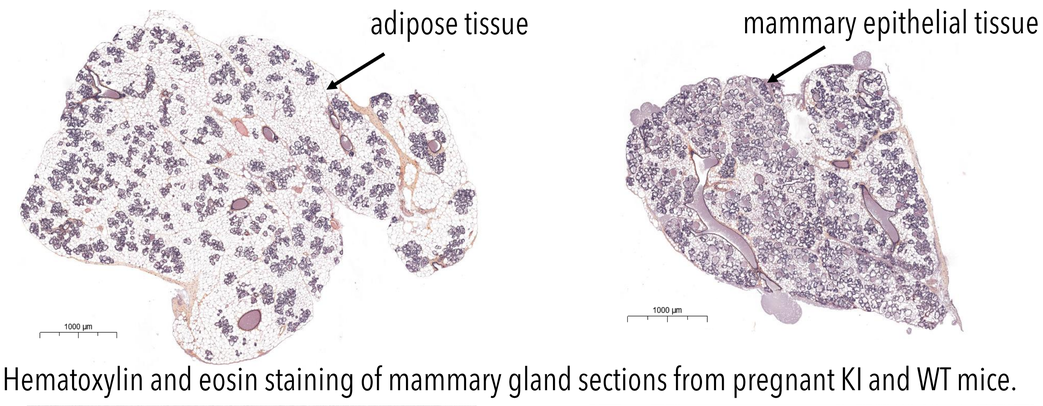


Whole mount (WM) mammary glands from 8-week old virgin KI and WT mice (Hamamatsu scanner).

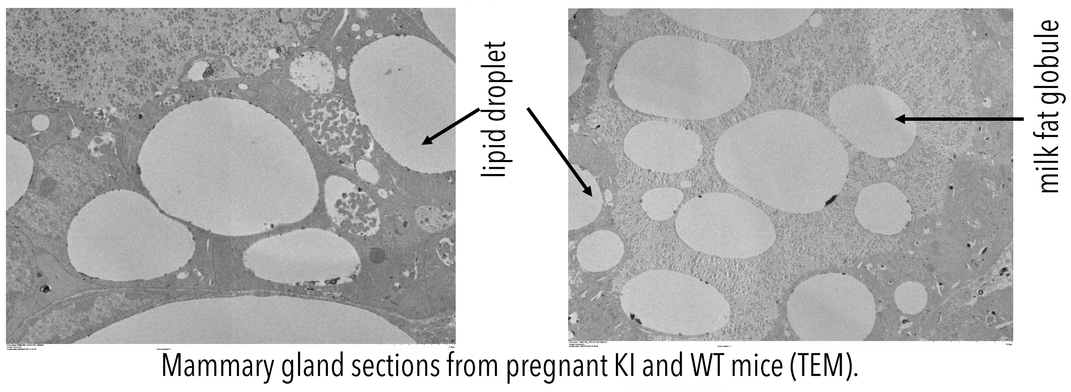
Mammary gland sections from 8-week old virgin KI and WT mice (TEM).

Mammary glands from **virgin KI mice** have **deficient branching of the ductal network** compared to WT. TEM shows **aberrant plasma membranes** in KI mice.

Pregnancy Day 18

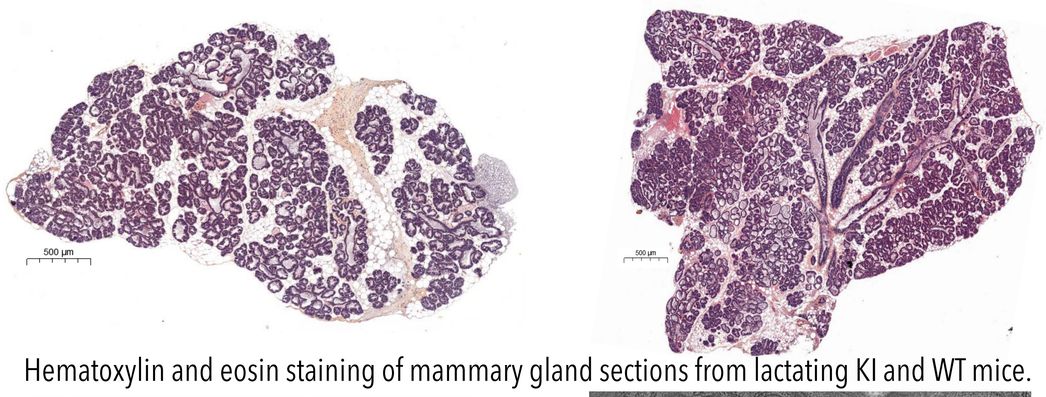


Hematoxylin and eosin staining of mammary gland sections from pregnant KI and WT mice.

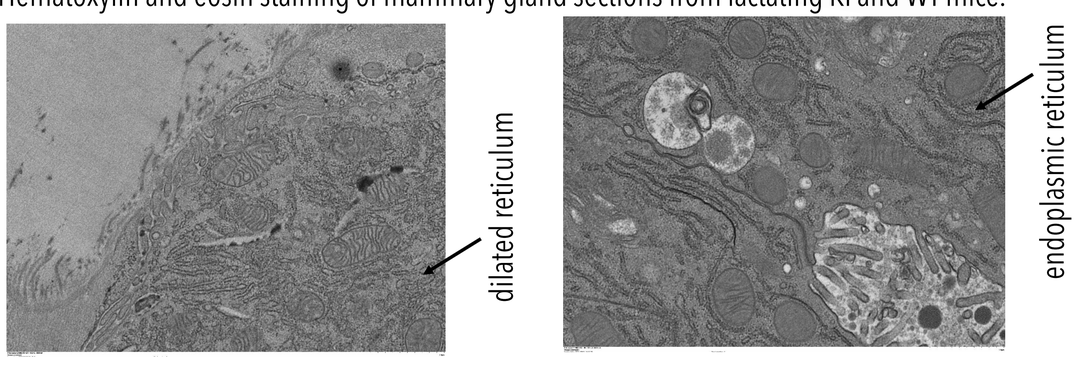


Mammary gland sections from pregnant KI and WT mice (TEM).

Lactation Day 7



Hematoxylin and eosin staining of mammary gland sections from lactating KI and WT mice.



Mammary gland sections from lactating KI and WT mice (TEM).

Mammary glands from **pregnant** and **lactating KI mice** have **a higher ratio of adipose to mammary tissue** compared to WT. TEM shows **lipid droplet retention** in **pregnant KI mice** and **dilated endoplasmic reticulum** in **lactating KI mice**.

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[1] Université Paris-Saclay, INRAE, AgroParisTech, GABI, 78350, Jouy-en-Josas, France
[2] IHAP, Université de Toulouse, INRAE, ENVT, 31076, Toulouse, France

Centre Ile-de-France - Jouy-en-Josas
GABI Unit - UMR 1313
GaLac - Mammary Gland and Lactation Team
elitsa.ivanova@inrae.fr