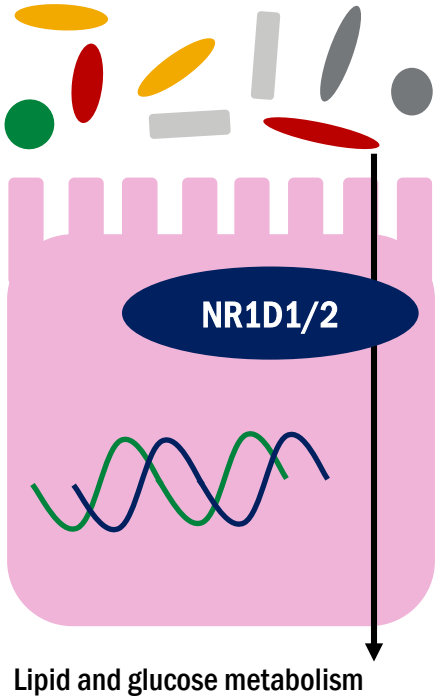
# The gut microbiota regulates host metabolism through circadian clock genes *Nr1d1* and *Nr1d2*

Samskrathi Sharma
Ph.D. student
Department of Biological Sciences

Advisor: Dr. Zheng Kuang




9th December 2023
6th International Conference on Microbiome Engineering
International House at UC Berkeley

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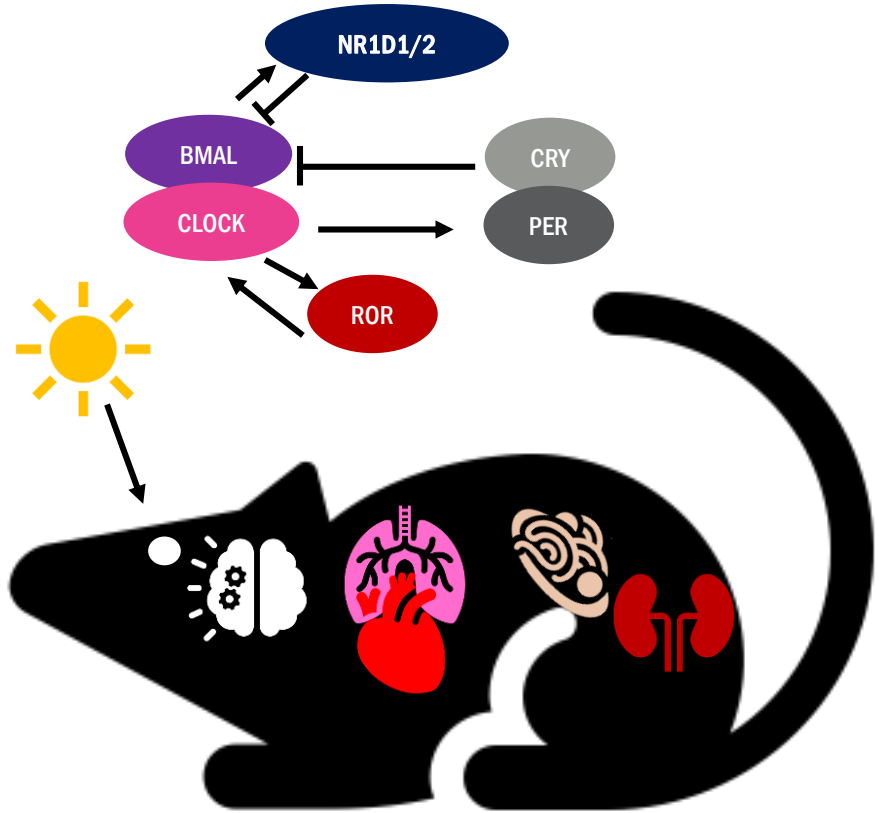
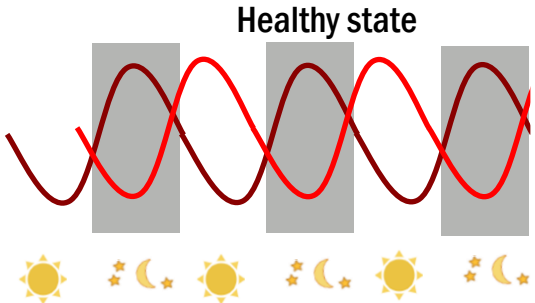
# Circadian rhythms are vital to health and are disrupted in disease




(eg. immune response, lipid metabolism, nutrient uptake)

(eg. carcinoma, obesity, diabetes & neurodegenerative disorders)

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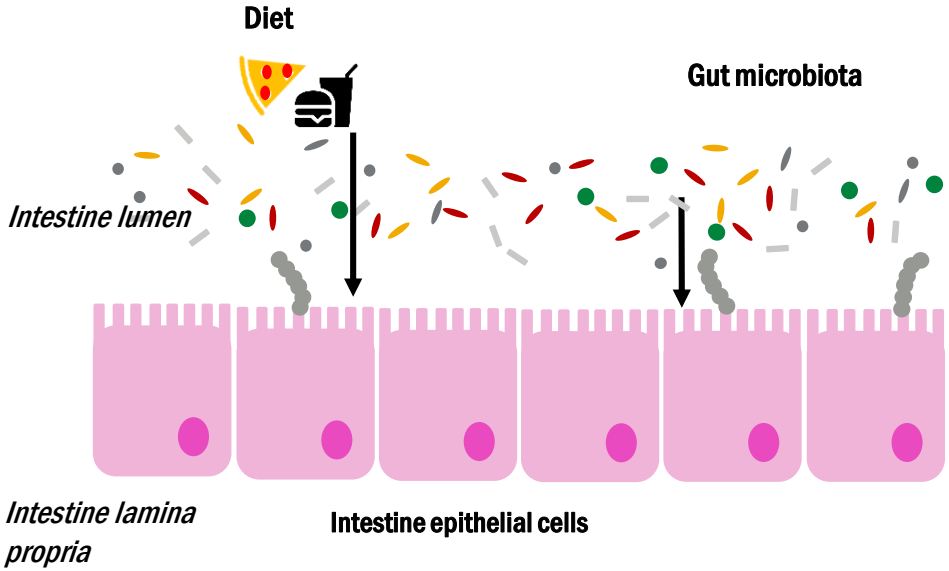
Xie et al. (2019), *Frontiers in Physiology,* Rijo-Ferreira and Takahashi (2019), *Genome Medicine*

# The intestine epithelial cells (IECs) are at the interface of host-gut microbiota interactions






IECs are important for

- **nutrient digestion and absorption**
- interacting with microbial components
- immunity

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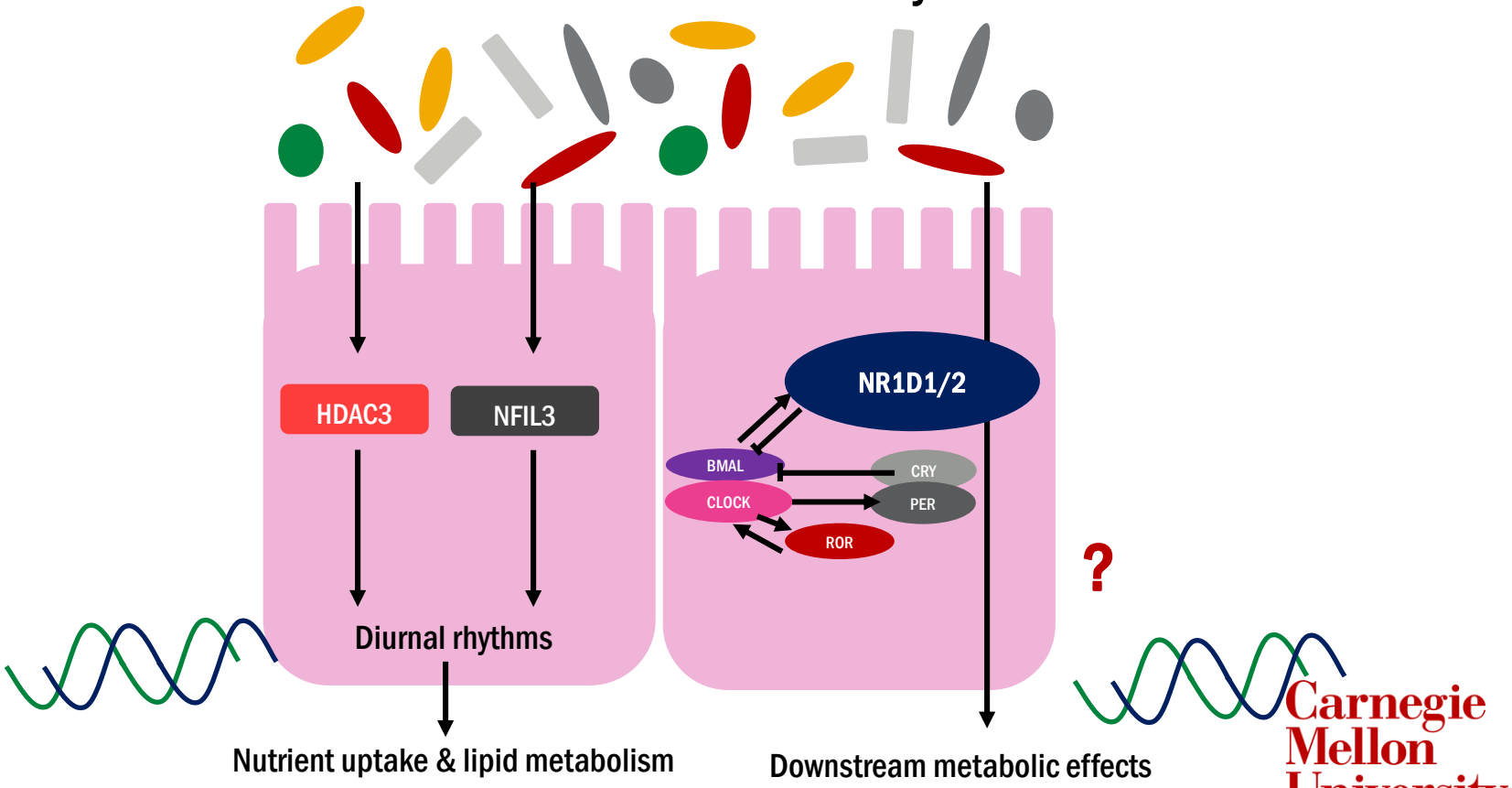
# How does the gut microbiota regulate host metabolism through core circadian clock machinery?



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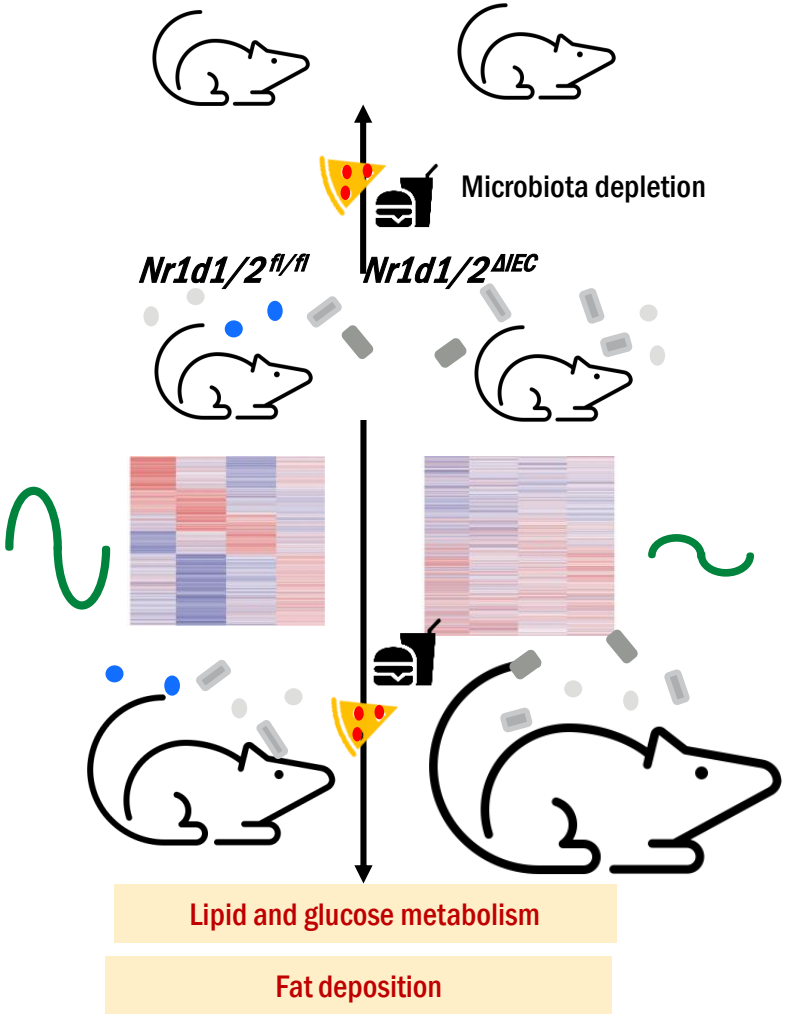
Kuang *et al.* (2019), *Science*, Wang *et al.* (2017), *Science*




# What did we find?

*Nr1d1/2*$^{\Delta IEC}$ mice have disrupted circadian rhythms of expression

*Nr1d1/2*$^{\Delta IEC}$ mice are more obese on a high-fat diet

The gut microbiota is important for *Nr1d1/2*$^{\Delta IEC}$'s higher obesity

Microbial components LPS and flagellin modulate *Nr1d1/2*

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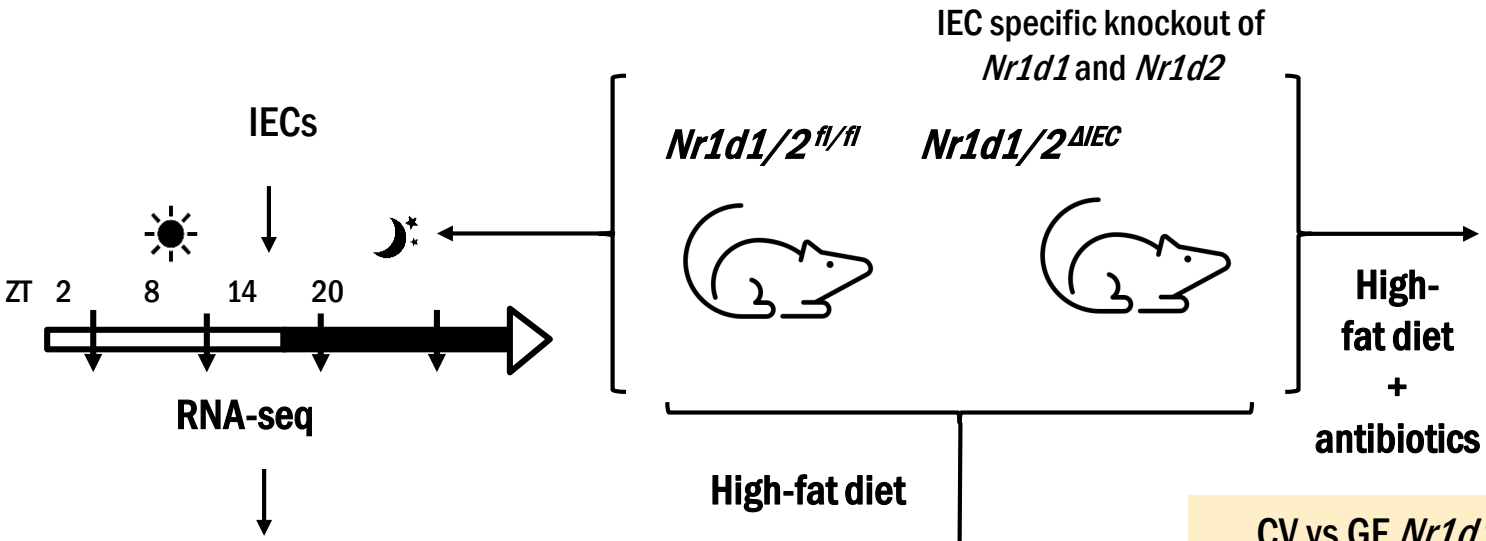
# What did we do?




Role of gut microbiota in *Nr1d1/2* mediated lipid metabolism?

Role of *Nr1d1/2* in gene expression diurnal rhythms?

Role of *Nr1d1/2* in lipid metabolism ?

CV vs GF *Nr1d1/2* expression & microbial component exposure assays

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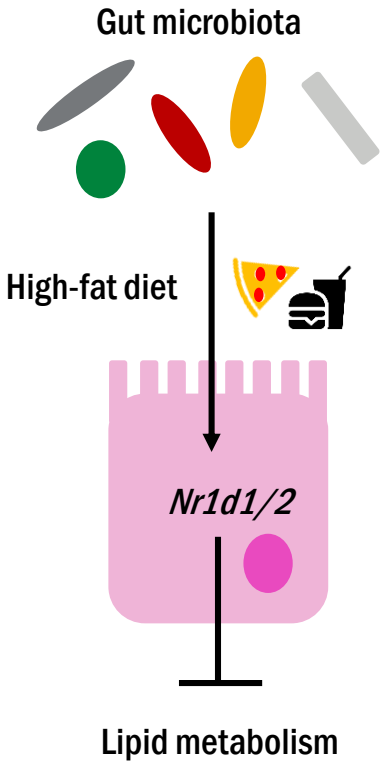
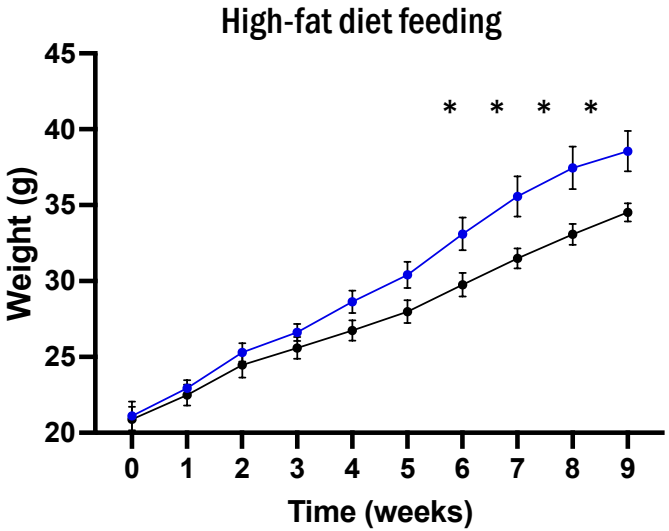
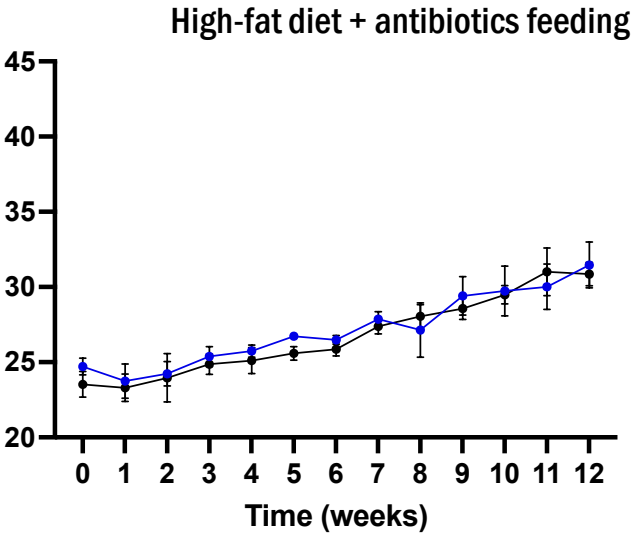
# The gut microbiota is important for the higher obesity of *Nr1d1/2*$^{\Delta IEC}$ mice on a high-fat diet






*Nr1d1/2*$^{fl/fl}$

*Nr1d1/2*$^{\Delta IEC}$

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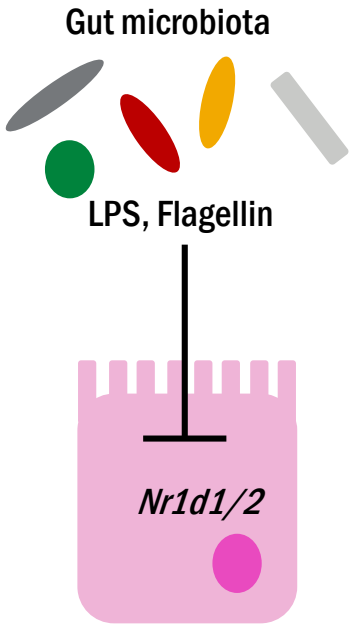
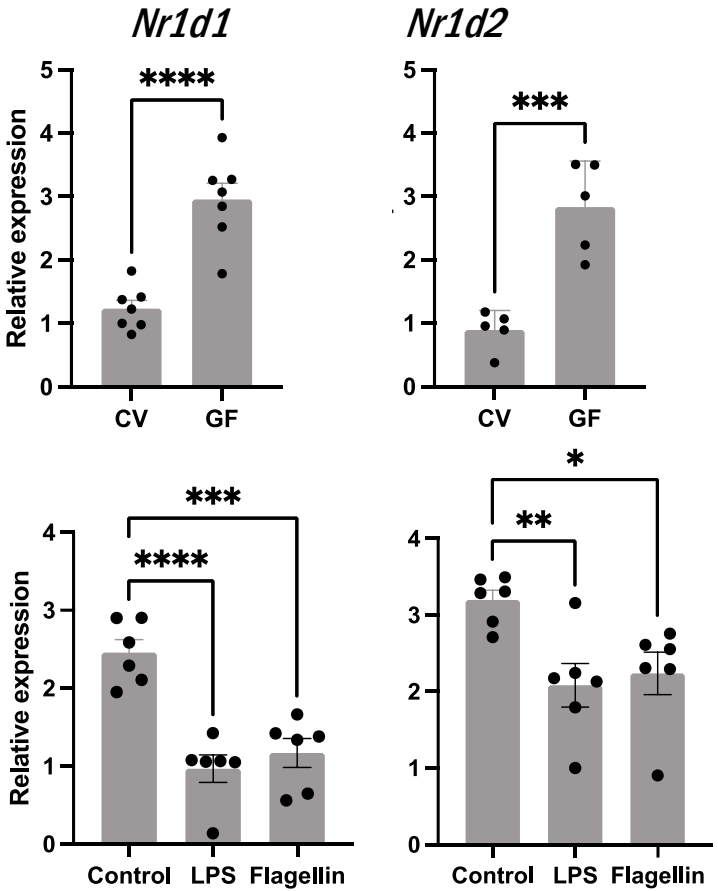
n=8 per group, Data is plotted as Mean±SEM

# The gut microbiota represses *Nr1d1/2*




CV: Conventional mice
GF: Germ-free mice
LPS: Lipopolysaccharides

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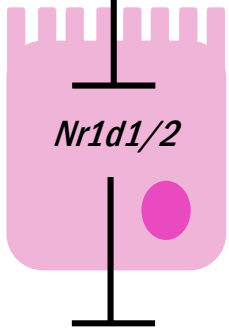
n=5-7 per group, Data is plotted as Mean±SEM, assayed at ZT8 (timepoint of highest *Nr1d1/2* expression)

# The gut microbiota regulates host metabolism through circadian clock genes *Nr1d1* and *Nr1d2*

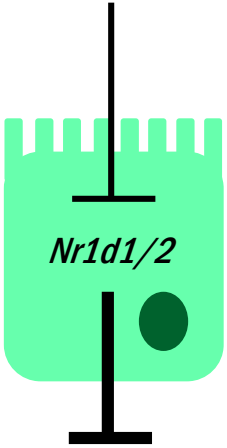



*Directly/ indirectly*




Lipid & glucose metabolism (not significant at homeostasis)

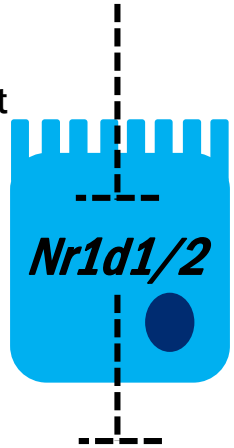
*Nr1d1/2*$^{\Delta IEC}$




Lipid & glucose metabolism

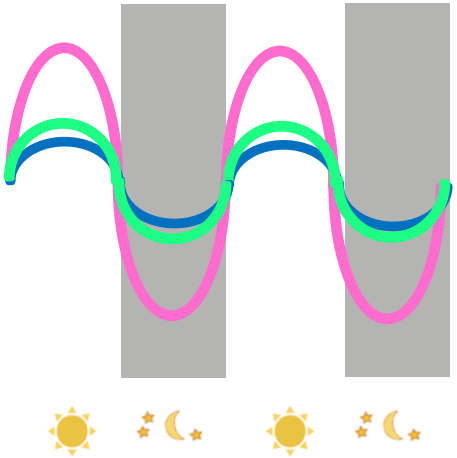
Absence of gut microbiota

High-fat diet




Lipid & glucose metabolism (effects dampened)

Diurnal rhythms of gene expression (e.g., lipid and glucose metabolism)



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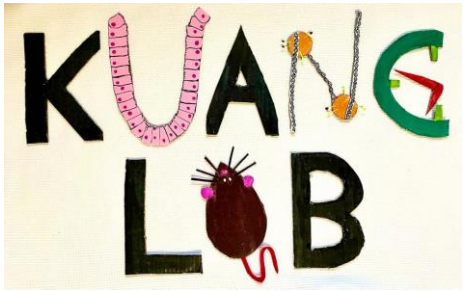



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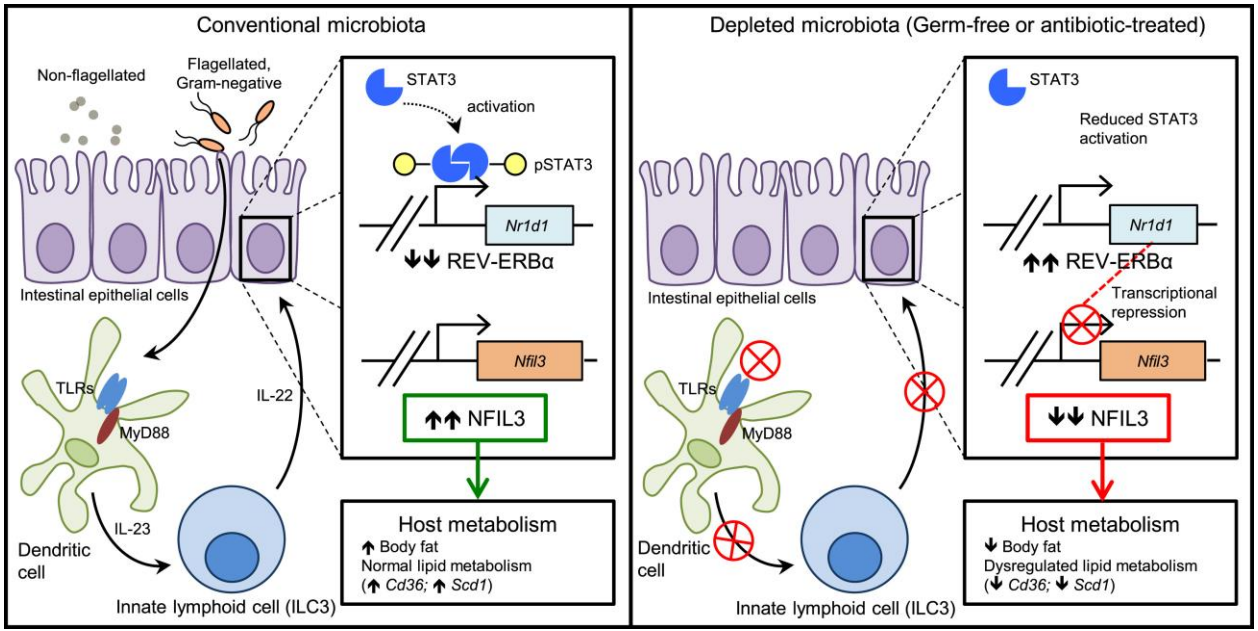
## Pronovost & Hsiao (2017)

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