Disruption of paternal circadian rhythm affects metabolic health in male offspring via nongerm cell factors

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INTRODUCTION

– Circadian rhythm controls physiology, and disruption of normal circadian rhythm alters whole body homeostasis and predisposes to several complex conditions, including metabolic, oncological, and neurological disorders. Glucocorticoids (**GC**) are a potent internal *Zeitgeber*. Their endogenous secretion in mice and humans is characterized by a prominent and robust circadian oscillation with peak anticipatory of the active phase. Partial or complete loss of this rhythm is associated to profound circadian disruption. GCs are also essential for fetal development and likely involved in fetal entrainment to the environment through placental-fetal communication. Exposure to high levels of GCs during pregnancy predisposes offspring to metabolic and neurological diseases later in life most likely through impaired placental function and induction of Fetal Growth Restriction (**FGR**). Parental health at conception or maternal health during pregnancy are important determinants of offspring development and adult health. Among a series of environmental challenges affecting intergenerational health, recent reports have highlighted the relevance of maternal circadian rhythm for pregnancy success and offspring health in humans and model organisms. So far, instead, nothing is known about the relevance of paternal circadian rhythm.

METHODS

– Founder male mice were circadian disrupted by 30 days of night-restricted feeding (**RF** - food available from 6 a.m. to 6 p.m.) and mated to age-matched and unexposed females. Offspring (from four independent cohorts) were followed for 10 months with regular monitoring of body weight, glycaemia, and cage-based food intake. At 10 months of age, 12 randomly selected mice were housed in metabolic cages and analyzed by Indirect Calorimetry to monitor individual food intake, energy homeostasis, and physical activity in real time.

IVF and embryo transfer were performed in accordance with the INFRAFRONTIER Standard Operating Procedures. Placentas (E18.5) were sampled for macroscopic, morphometric, and expression analyses.

For RNA-Seq analysis, we used the *NOISeq* package for differential expression, JTK_CYCLE for the identification of oscillatory transcripts. For annotation to glucocorticoid receptor (**GR**) target genes, we used publicly available data. Functional annotation of differentially expressed genes was performed by using the MGI database for gene/phenotype association.

CONCLUSIONS

- Paternal circadian health at conception is important for offspring metabolism
- The effects of paternal circadian disruption are transmitted via corticosterone in the seminal plasma
- Corticosterone in the seminal plasma is a sensor of paternal stress
- Corticosterone in the seminal plasma is an important mediator of parental communication at conception

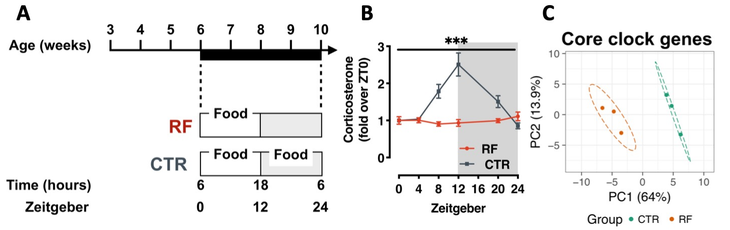

Figure 1 – 30 days of RF (**A**) disrupt circadian rhythm as measured by circulating GC (**B**) and expression of core clock genes in liver at ZT0 (**C**).

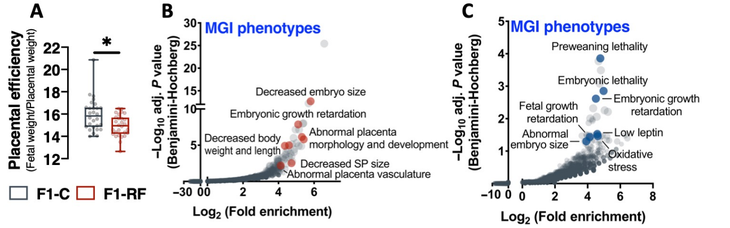

Figure 3 – RF placentas are significantly less efficient (**A**) and placenta RNA-seq highlights a signature of FGR (**B**) mainly at differentially expressed GR target genes (**C**).

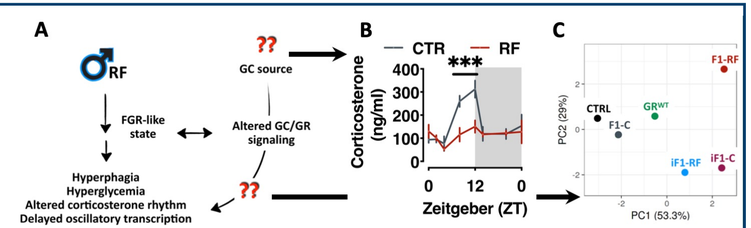

Figure 4 – Mechanistically, paternal RF leads to offspring phenotypes via FGR (**A**) induced by altered corticosterone rhythm in seminal fluid (**B**). Both IVF and maternal loss of GR phenocopy, at least partly, paternal RF (**C**).

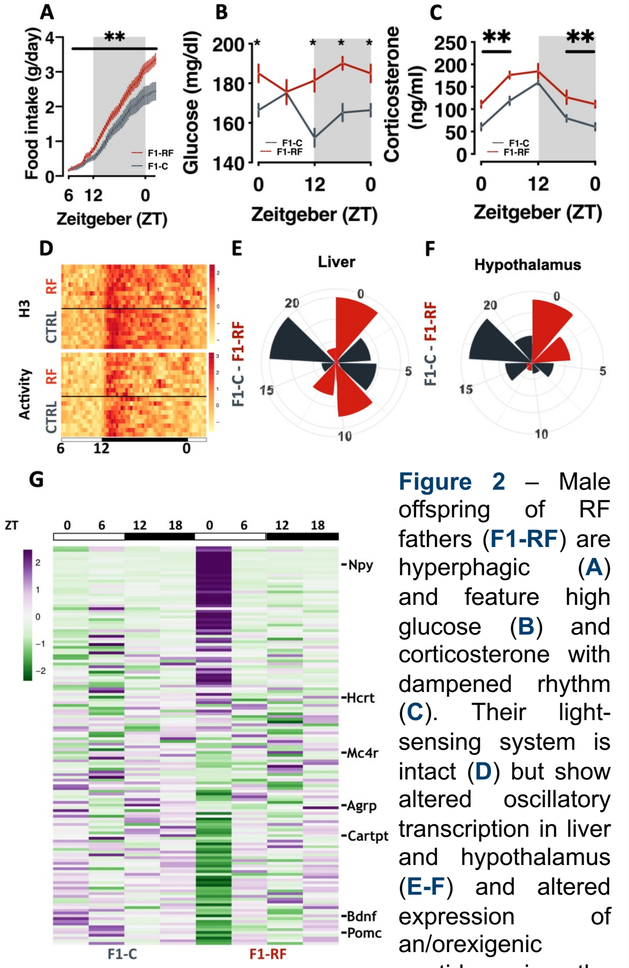

Figure 2 – Male offspring of RF fathers (**F1-RF**) are hyperphagic (**A**) and feature high glucose (**B**) and corticosterone with dampened rhythm (**C**). Their light-sensing system is intact (**D**) but show altered oscillatory transcription in liver and hypothalamus (**E-F**) and altered expression of an/orexigenic peptides in the hypothalamus at the night-day transition (**G**).

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