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Keio University

Thesis Abstract

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Registration Number	■“KOU” “OTSU” No. *Office use only	Name	YAO NA

Thesis Title

Maternal circadian rhythms during pregnancy dictate metabolic plasticity in offspring
（母児概日リズム連関と代謝可塑性）

Thesis Summary

The circadian rhythm is a nearly 24-hour period of self-sustainable variation under constant conditions, a fundamental mechanism to maintain metabolic homeostasis by predicting changes in the environmental light-dark cycle. This is primarily driven by the transcriptional-translational negative feedback loop of the biological clock, which governs an extensive array of biological rhythms including metabolism. The central clock in the suprachiasmatic nucleus is reset by light, whilst the peripheral clock is entrained by feeding, exercise, hypoxia, among other cues. Emerging evidence showed that daily rhythms in a given tissue are subject to cyclic inputs from organismal behaviors and remote organs, such that tissue-intrinsic clocks integrate metabolic cycles to generate robust oscillations. Hence, the distal coordination of circadian rhythms is considered a fundamental aspect of metabolic homeostasis.

While inherent genetic variations are linked to adaptive capacity to the external environment and disease susceptibility, environment and nutrition during early life stages, including the gestational and postnatal periods, remarkably influence long-term health outcomes. Given the developmental origin of health and disease, maternal circadian rhythms during gestational period may play a fundamental role in dictating vulnerability to dietary habits in adulthood. Thus, recognizing the interactions underlying maternal-fetal circadian rhythms could provide crucial insights on the physiology and potential preventative approaches for metabolic diseases.

To define the long-term effects of maternal circadian rhythms on metabolism in the progeny, I employed animal models of circadian disruption, including chronic phase shifting of light-dark cycles and clock mutation during pregnancy. Despite reduced weight of the fetus and placenta of arrhythmic mothers, the offspring mice exhibited worsening of diet-induced obesity in adulthood. Decreased energy expenditure and arrhythmic eating behavior underlay such exacerbation of obesity and was associated with the central resistance to leptin in the offspring. The manners in which hepatic circadian rhythms are reprogrammed by high-fat diet were altered by maternal circadian desynchrony at the transcriptomic and metabolomic levels. Strikingly, chronic jetlag altered the circadian rhythms of the mother and fetus, such that they gave rise to changes in the lag of phase between the mother and fetus. Maternal circadian disruption caused a smaller placenta, although single-cell RNA-seq revealed the induction of genes encoding lineage development, differentiation, maintenance, and specificity in each cluster of cell types in such placenta, including syncytiotrophoblasts and decidual stroma. Furthermore, time-restricted feeding of the adult offspring failed to fully obliterate the additional weight gain elicited by maternal circadian misalignment in response to a high-fat diet, while the calorie-restricted food given every 24-hour at the beginning of the night prevented such exacerbation of obesity. Collectively, these findings highlight that maternal circadian rhythms pertain to fetal development, such that dissonant rhythms in utero contribute to unremitting metabolic vulnerability in the adult progeny.