Abstract

Disruptions within the circadian, metabolic, and immune systems contribute to the onset of metabolic illnesses, including type 2 diabetes. This doctoral thesis aimed to examine the mutual interactions between these three systems in relation to the development of metabolic disorders. The circadian system regulates a variety of mammalian physiological processes. On the molecular level, the circadian clock is in individual cells maintained by a complex of interconnected transcription-translation feedback loops. The circadian system is hierarchically organized, consisting of the central circadian clock residing within the suprachiasmatic nuclei (SCN) and of peripheral oscillators found in various organs and tissues, including the pancreas and compartments of the innate immune system such as macrophages and microglia. The central circadian clock synchronizes the peripheral oscillators via multiple pathways, including feeding-related metabolic changes to which some of the peripheral oscillators are highly sensitive.

Misaligned feeding can thus induce dyssynchrony between individual peripheral oscillators. Our results show that a reverse restricted feeding (rRF) regimen, when food is available only for a limited time during the resting period of the day, has distinct effects on the circadian clocks in the pancreatic exocrine and endocrine tissues. While the clock in the endocrine tissue synchronized with the time of food availability, the clock in the exocrine tissue became completely arrhythmic. This arrhythmicity was due to uncoupled and conflicting insulin and corticosterone signaling induced by the rRF.

Metabolic alterations also affect the circadian clock in macrophages. Both microglia and macrophages exhibit a wide range of functional phenotypes. The properties of their circadian clock change dynamically with changes in their polarization. In addition, the circadian clocks in the anti-inflammatory polarized macrophages are modulated by the activity of PPARγ and the process of fatty acid oxidation.

Microglia play an important role in homeostasis maintenance within the central nervous system. Depletion of microglia from organotypic SCN explants impairs the robustness and persistence of circadian rhythms generated by the central oscillator. Although the anti-inflammatory polarized microglia are not as susceptible to the PPARγ-mediated circadian clock regulation as macrophages, they positively affect the SCN clock function.

Keywords: circadian clock, pancreas, microglia, macrophage, reverse restricted feeding, polarization, suprachiasmatic nuclei.