

Orchestrated Signal Transduction Unites Mammalian Circadian Metabolism Across Tissues

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The circadian clock is known to play a critical role in maintaining metabolic homeostasis throughout the body, with clock dysfunction contributing to metabolic syndrome, obesity, and diabetes. How the clock regulates coordinated metabolic homeostasis across multiple organs is an important unanswered question in chronobiology. To address this issue our research team has created an atlas of circadian RNA expression in 12 mouse organs at a resolution of 2 hours every 48 hours using Affymetrix 1.0 ST Arrays. RNA transcript expression is profiled in the brain: hypothalamus, brainstem, and cerebellum, and peripheral metabolic tissues: adrenal gland, aorta, brown adipose, heart, kidney, liver, lung, skeletal muscle, and white adipose tissue. Our data show that over 7,000 genes have circadian expression in at least one organ. We furthermore find that transcripts cycling in multiple organs are highly enriched for all stages of signal transduction, proceeding from ligand and receptor expression and extending through down-stream second messenger signaling to gene regulation. For example, we find circadian expression of ligands POMC and adiponectin, as well as transcripts for their respective receptors MC4R and AdipoR2, which cycle in multiple organs. We also found rhythmic genes mediating down-stream signaling are also represented in the data, including MAPK, AKT, and MTOR as well as gene transcription pathways. This panoply of regulatory mechanisms now shown to be regulated by the clock at a systems level offers clues as to how the clock orchestrates diverse metabolic functions in multiple organs, including cholesterol, lipid, protein and carbohydrate metabolism, which we also found to be enriched across tissues. The richness of our high through-put data in many tissues allows us to uncover for the first time the intricate organization of clock coordination of activities in the brain and peripheral tissues.

