Circadian regulation of liver energy metabolism: translational studies in diabetes

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Project outline

Background
Circadian clocks are an essential adaptive feature allowing our physiology and behaviour to predict day/night transitions. In mammals, the circadian timing mechanism is present in most cell types and establishes local cycles of gene expression and metabolic activity. These distributed tissue clocks are synchronised by the hypothalamic suprachiasmatic nucleus.

The circadian clock is an influential regulator of energy metabolism allowing key pathways to be tuned across the 24hr cycle as metabolic requirements vary. Some core clock components (CRY, REVERB) also play essential roles in energy metabolism, and inflammation. Our studies reveal that these proteins regulate glucocorticoid receptor (GR) function, a major drug target and crucial regulator of liver energy metabolism. Strikingly, two recent studies reveal that shiftwork, which disrupts liver circadian rhythmicity, predisposes to type II diabetes, a highly prevalent human metabolic disease.

Hypothesis
Circadian control mechanisms in the liver are essential for energy homeostasis. Their disruption results in hepatosteatosis, inflammation and cancer.

Plan
This project capitalises on recent innovations which permit human liver organoids to be used as a translational model for diabetes and metabolic dysfunction. The microlivers will be challenged with lipogenic, high-energy culture medium, to drive lipid accumulation within the hepatocytes. The impact of this challenge, the mechanism underlying human hepatosteatosis, on the core circadian clock will be assessed by tracking the PER2-luc output, and by measuring gene expression profiles through the optimised circadian time-series model described above.

The deep phenotyping of these microlivers with high throughput ‘omics technology platforms, cell based assays and systems microscopy allows entirely novel biology to be revealed in this important human disease with new insights, high-impact publications, and potential therapeutic advances. We build on unique strengths coupling circadian biology and metabolic science, and will use CRISPR, and genetic engineering approaches to investigate novel pathways regulating liver phenotype, and
metabolic flux. We can couple this genetic approach to chemical biology interventions, such as those we have recently pioneered to target circadian clock components (5).

**Outputs**

There is an expectation that the candidate will publish in high-impact journals, present at international meetings, drive project progression, and capitalise on the joint academic/pharma stakeholders. There is considerable scope to pursue exciting new biological pathways emerging from the discovery platforms.

**Supervisor’s recent relevant publications:**

https://orcid.org/0000-0002-4739-6773; h index 53


