Circadian regulation of liver energy metabolism: translational studies in diabetes

Oxford supervisor: Professor David Ray[1]

Novo Nordisk supervisors: Dr Nicola Beer[2] and Dr Fang Zhang[2]

Departments: 1. OCDEM, Radcliffe Department of Medicine
2. Novo Nordisk Research Centre Oxford (NNRCO)

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

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4. Pariollaud M, Gibbs J, Hopwood T, Begley N, Vonslow R, Poolman T, Guo B, Saer B, Heulyn Jones D, Tellam JP, Bresciani S, Tomkinson NCO, Wojno-Picon J, Cooper AWJ, Daniels DA, Trump RP, Grant D, Zuercher W, Willson TM, Bolognese B, Podolin PL, Sanchez Y, Loudon ASI, **Ray DW**. Circadian clock component REV-ERBα controls homeostatic regulation of pulmonary inflammation. *J Clin Invest* 2018; 128:2281-2296 .
5. Caratti G, Iqbal M, Hunter L, Kim D, Wang P, Vonslow RM, Begley N, Tetley AJ, Woodburn JL, Pariollaud M, Maidstone R, Donaldson IJ, Zhang Z, Ince LM, Kitchen G, Baxter M, Poolman TM, Daniels DA, Stirling DR, Brocker C, Gonzalez F, Loudon AS, Bechtold DA, Rattray M, Matthews LC, **Ray DW**. REVERBa couples the circadian clock to hepatic glucocorticoid action. *J Clin Invest* 2018 Sep 4. pii: 96138. doi: 10.1172/JCI96138. [Epub ahead of print]