THE TRANSCRIPTION FACTOR VOS-1 CONNECTS THE CIRCADIAN CLOCK TO RHYTHMIC GLYCOGEN METABOLISM IN NEUROSPORA CRASSA

Virgilio, S.¹; Ibarra, O.²; Bell-Pedersen, D.²; Bertolini, M.C.¹

¹Departamento de Bioquímica e Tecnologia Química, Instituto de Química, UNESP, Araraquara, SP, Brazil; ²Departament of Biology, Texas A&M University, College Station, TX, EUA.

The metabolism of glycogen is under control of the circadian clock in mammals, and defects in glucose metabolism and/or the circadian clock are associated with obesity, insulin resistance and diabetes. Glycogen is synthesized and degraded as a function of the organism’s metabolic status and the time of day. In Neurospora crassa, a eukaryotic model for circadian clock, the core component WCC directly regulates the VOS-1 transcription factor, which was previously identified as a regulator of glycogen metabolism. Our aim was to investigate the connection between circadian clock and glycogen metabolism, and to understand which proteins are associated to both processes. Glycogen accumulation, gene and protein expression, and ChIP-PCR assays were analyzed during the time course. Statistical analysis and mathematical predictions are carried out to confirm biological data. Glycogen accumulates rhythmically with a 26-h period in wild-type cells, peaking in the subjective night. The rhythm in glycogen accumulation was dependent on FRQ, a component of the N. crassa clock. Furthermore, transcripts from gsn and gpn, encoding glycogen synthase and glycogen phosphorylase, respectively, are clock-controlled in wild-type cells, peaking in the subjective morning. The rhythms in mRNA levels are dependent on VOS-1 and FRQ. Consistent with clock control of gsn and gpn through VOS-1, we demonstrated rhythmic binding of VOS-1 to the promoters of these genes. Our data suggest that VOS-1 confers positive circadian regulation of glycogenic genes. Glycogen accumulates during the night and is degraded during the day to supply the appropriate levels of energy to cells at the right time of the day, and this regulation is, in part, through the control of gsn and gpn expression by VOS-1. A model to dissect the molecular and biochemical pathways between the clock and metabolic activities is important to lead to new ideas for therapies to treat disorders.

Acknowledgements: FAPESP, CNPq, NIH

Key Words: circadian clock, gene regulation, glycogen