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The role of small heterodimer partner in hepatic lipid homeostasis

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Article commented:

Lee SM, Zhang Y, Tsuchiya H, Smalling R, Jetten AM, Wang L. Small heterodimer partner/neuronal PAS domain protein 2 axis regulates the oscillation of liver lipid metabolism. *Hepatology* 2015; 6: 497-505.

Comment:

Small heterodimer partner (SHP, NR0B2) interacts with orphan members of the nuclear receptor superfamily, including the constitutive androstane receptor, retinoid receptors, thyroid hormone receptor, and orphan receptor MB67.[1] The SHP ability to bind directly to a variety of nuclear receptors is crucial for its physiological function as a transcriptional inhibitor of gene expression. SHP binds to the ligand-dependent transactivation domain AF-2 through two functional LXXLL-related motifs which are located in the putative N-terminal helix 1 of the ligand-binding domain LBD and in the helix of the C-terminal region.[2] SHP gene is expressed and detected in a variety of tissues in mice and human.[3,4] For example, in some strain of mice (12931/SvJ and C57/BL6) as well as in humans SHP is predominantly expressed in the gallbladder and liver.[3,4]

Interestingly, it has been reported that a variety of nuclear receptors and transcription factors target the SHP promoter and regulate *SHP* gene expression, including those involved in the lipid metabolism and the core circadian component CLOCK-BMAL1.[5]

In the present study Lee, *et al*. explored the potential role of SHP to coordinate the metabolism and circadian rhythms. The investigators studied S*hp*$^{+/+}$ and S*hp*$^{-/-}$ mice on a C57BL/6 background (n = 3-5/group) which were fed a standard chow diet and water *ad libitum*. Serum and livers were collected at Zeitgeber time 2, 6, 10, 14, 18 and 22. *In vivo* and *in vitro* assays included RNA sequencing, quantitative polymerase chain reaction, very-low density lipoprotein production, adenovirus overexpression and small interfering RNA knockdown, serum parameters, circadian locomotor activity, Oil Red O staining, transient transfection, luciferase reporter assay, chromatin immunoprecipitation assay, gelshift assay, coimmunoprecipitation, and western blottings. The researchers observed that S*hp* deficiency had a robust global impact on major liver metabolic genes. Several components of the liver clock, including peroxisome proliferator-activated receptor-γ, coactivator 1 (Pgc-1α), neuronal PAS domain-containing protein 2 (Npas2), and retinoic acid-related orphan receptor (Ror)α/γ were sharply induced in S*hp*$^{-/-}$ liver. At the molecular level, SHP inhibited Npas2 gene transcription and promoter activity through interaction with Rorγ to repress Rorγ transactivation and by interacting with Rev-erb to enhance its inhibition of Rorα activity. Conversely, Npas2 controlled the circadian rhythm of S*hp* expression by binding rhythmically to the S*hp* promoter, which was enhanced by nicotinamide adenine dinucleotide, but not nicotinamide adenine dinucleotide phosphate. Phenotypically, Npas2 deficiency induced severe steatosis in S*hp*$^{-/-}$ mice, which was attributed to the dysregulation of lipoprotein metabolism. The investigators concluded that S*hp* and Npas2 crosstalk is essential to maintain hepatic lipid homeostasis.

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What is the importance of Lee' study? Firstly, numerous independent *in vitro* studies have identified a number of interaction partners for SHP, indicating the potential for SHP to regulate a wide array of genes in various biological pathways. Secondly, the existence of an internal circadian clock has long been recognized as natural daily fluctuations have been observed in blood concentrations of glucose, glycolysis, insulin levels and insulin sensitivity.[6] Fatty acid and triglyceride levels, as well as lipid metabolising enzymes, display circadian fluctuations.[7] Taken these observations together. We can speculate that changes in our lifestyle might affect our circadian rhythms and may also have metabolic and cardiovascular consequences.

The results of the commented study suggest that the metabolic genes analyzed exhibited an oscillatory pattern of expression, consistent with the notion that circadian rhythms and cellular metabolism are intimately linked. Also, as the authors of this study point out. The overall gene expression profile altered by S*hp* in turn suggesting that SHP mainly serves as a modulator of metabolic homeostasis by interfacing with some pathways to modulate the regulation and function of Npas2.

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