NewsLetter
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自治医科大学 地域医療オープン・ラボ

高タンパク食による肝臓の尿素回路の誘導メカニズムを発見

内科学講座内分泌代謝学部門の大学院生(特別研究学生) Samia Karkoutly 氏、矢作直也教授らは、肝臓でアンモニアから尿素を生成する尿素サイクル(オルニチン回路)が、高タンパク食負荷で誘導されるメカニズムを発見しました。その研究成果が Biochemical and Biophysical Research Communications (2024;739:150594) 誌に報告されましたので、Karkoutly 氏と矢作教授に研究の意義と経緯を伺いました。

Q1. What is the background of this study?

The urea cycle (ornithine cycle), which produces urea from ammonia in the liver, was discovered by Hans Krebs et al. in 1932, before the discovery of the TCA cycle, also by Krebs (1937), but its regulatory mechanism was poorly understood.

The urea cycle consists of five enzymes: CPS1 (carbamoyl-phosphate synthetase 1), OTC (ornithine transcarbamylase), ASS1 (argininosuccinate synthetase), ASL (argininosuccinate synthetase). However, only OTC was known to have a transcriptional regulatory mechanism. The regulatory mechanism of OTC by the transcription factor KLF15 was reported in 2012.

Q2. What is the role of FoxO in the control of the urea cycle in the liver?

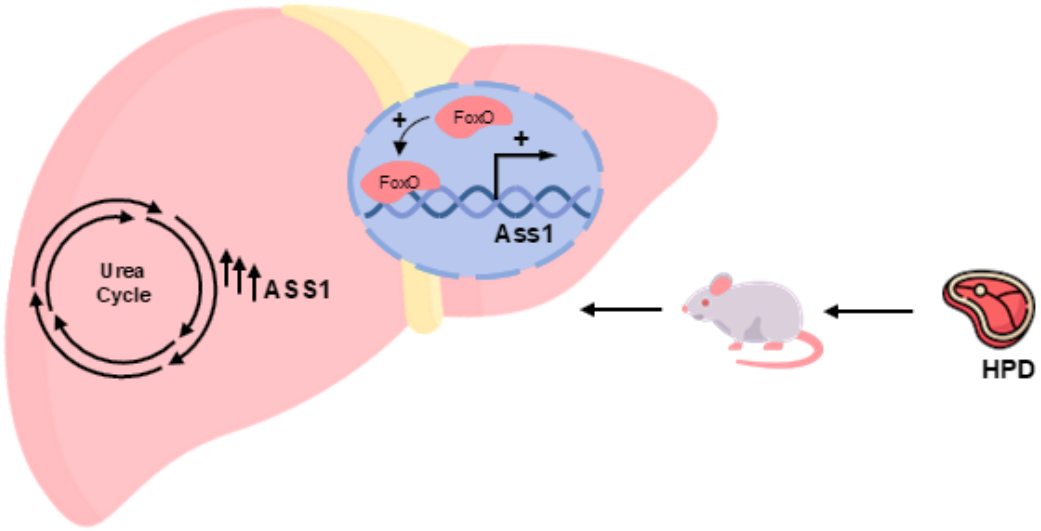
We identified the transcription factor FoxO1/3a as a transcriptional regulator of ASS1, one of the five enzymes of the urea cycle. Since we previously identified FoxO1/3a as a transcriptional regulator upstream of KLF15 (iScience. 2021), we investigated the involvement of FoxO1/3a in the regulation of the expression of each enzyme in the urea cycle and found that FoxO1/3a directly binds to an enhancer of the ASS1 gene without KLF15 to regulate its expression.

Q3. How did you elucidate the mechanism?

Specifically, metabolome analysis of metabolites in the livers of wild-type and KLF15 knockout mice with FoxO1/3a knockdown revealed a decrease in arginine and an increase in ornithine, from which the regulatory mechanism of ASS1 expression was successfully elucidated.

Q4. What are the future prospects for this research?

The identification of FoxO transcription factors as regulators of ureagenesis, adding them to the known array of amino acids metabolic regulators, can advance scientific efforts one step further towards uncovering hidden aspects of the mechanisms involved in amino acids-induced metabolic responses and revealing potential targets for therapeutic interventions aimed at optimizing metabolic health and managing metabolic disorders. This is particularly relevant given that high-protein diets are both affordable and beneficial, and believed to be effective tools for the prevention and treatment of various diseases.



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