Yuki Sasahara et al., J Proteomics Bioinform 2018, Volume 11
DOI: 10.4172/0974-276X-C1-113

Mathematical exploration of selective pressures that shaped the metabolic zonation of liver nitrogen metabolism

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As ammonia which is one of the simplest nitrogen compounds is toxic for the central nervous system, its blood concentration should be maintained at low level. Human excrete most of nitrogen as urea in urine and urea synthesis exclusively occurs in liver. Ammonia is an inescapable metabolic intermediate during urea synthesis from various nitrogen compounds in hepatocytes. Most of ammonia is produced in hepatocytes and many of it is converted into urea and the rest is converted into reusable glutamine. The human liver is super-parallel metabolic filter with approximately 500,000 hepatic lobules that consist of approximately 500,000 hepatocytes. Blood flows into a hepatic lobule from fine branches of hepatic artery and portal vein and goes out from central vein. While upstream (periportal, PP) blood abundantly contains external molecules absorbed in the gastrointestinal tract, downstream (perivenous, PV) blood carries almost adjusted substances. Therefore, metabolic heterogeneity inevitably arises between PP and PV. Moreover, it is known that many enzymes heterogeneously express between PP and PV. Such heterogeneity is called metabolic zonation. For nitrogen metabolism, activity of urea cycle is dominant in PP and Glutamine Synthase (GS) activity is confined in PV. Recently, it is shown that hepatic GS deficient transgenic mice exhibit hyperammonemia and some organs other than liver affect its pathophysiology. In this study, we made the nitrogen homeostasis model of the whole body which incorporated metabolic zonation and tried to represent the systematic condition of nitrogen metabolism found in the GS deficient mice.

Biography

Yuki Sasahara is a undergraduate student of department of environment and information studies of Keio University. She is expected to earn B.A.(Environment and Information Studies) in Mar.2019. She graduated Ferris Girls' Senior High School and entered Keio University in 2015. She has joined the E-Cell project and majors in computational biology at the institute for advanced biosciences of Keio University.

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