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Role of hepatic Src homology phosphatase 2 in regulating adiposity and energy balance

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The Src homology 2 domain-containing protein-tyrosine phosphatase Src homology phosphatase 2 (Shp2) is a negative regulator of hepatic insulin action in mice fed regular chow. To investigate the role of hepatic Shp2 in lipid metabolism and energy balance, we determined the metabolic effects of its deletion in mice challenged with a high-fat diet (HFD). We analyzed body mass, lipid metabolism, insulin sensitivity, and glucose tolerance in liver-specific Shp2-deficient mice (LSHKO) and control mice fed HFD. Hepatic Shp2 protein expression is regulated by nutritional status, increasing in mice fed HFD and decreasing during fasting. LSHKO mice gained less weight and exhibited increased energy expenditure compared with control mice. In addition, hepatic Shp2 deficiency led to decreased liver steatosis, enhanced insulin-induced suppression of hepatic glucose production, and impeded the development of insulin resistance after high-fat feeding. At the molecular level, LSHKO exhibited decreased hepatic endoplasmic reticulum stress and inflammation compared with control mice. In addition, tyrosine and serine phosphorylation of total and mitochondrial signal transducer and activator of transcription 3 were enhanced in LSHKO compared with control mice. In line with this observation and the increased energy expenditure of LSHKO, oxygen consumption rate was higher in liver mitochondria of LSHKO compared with controls. Collectively, these studies identify hepatic Shp2 as a novel regulator of systemic energy balance under conditions of high-fat feeding.

Biography

Haj completed his D.Phil. studies at the University of Oxford and did postdoctoral research at Harvard Medical School and European Molecular Biology Organization. Currently, he is Associate Professor in Department of Nutrition and Department of Internal Medicine at University of California Davis, and serves a Co-Director of Endocrinology & Metabolism core at National Mouse Metabolic Phenotyping Center at UCD.

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