論文の内容の要旨

論文題目　Role of insulin signaling in the development of metabolic dysfunction-associated fatty liver disease
(代謝関連脂肪肝疾患形成におけるインスリンシグナルの役割)

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Metabolic dysfunction-associated fatty liver disease (MAFLD) has been proposed as a new nomenclature to encompass the full spectrum of fatty liver disease. This updated term is defined as the presence of hepatic steatosis combined with one of the following three conditions including overweight/obesity, type 2 diabetes, and metabolic derangements. Recently, the rapidly growing prevalence has made hepatic steatosis the most frequent chronic liver disease in many parts of the world. This raises the significance to gain more comprehension of the molecular basis underlying the pathogenesis of hepatic steatosis. Numbers of studies have revealed that hyperinsulinemia, insulin resistance and elevated PPARγ activity in the liver are the common findings of hepatic steatosis. However, the mechanistic relationship between those features towards the development of hepatic steatosis remains largely unidentified. Here we report that the hepatic cAMP levels were markedly raised in mice with fatty livers, which was caused by the insulin-induced suppression of the cAMP transporter, multidrug-resistance associated protein 4 (Mrp4). The overabundance of

cAMP augmented PPARγ expression through ER stress-induced FoxO6 upregulation, leading to the increase in triglyceride accumulation in the livers. On the other hand, ER stress inhibition or FoxO6 depletion greatly attenuated cAMP-induced PPARγ expression. In contrast to fatty liver mice, the mice lacking hepatic IRS1 and IRS2, which failed to develop high-fat diet-induced hepatic steatosis, displayed unaltered Mrp4-mediated cAMP efflux which resulted in minimal ER stress response, coupled with low FoxO6 and PPARγ expression levels. Collectively, our results indicate that the overaccumulation of hepatic cAMP due to the Mrp4 reduction under insulin-resistant state is, at least in part, contributable to the pathogenesis of hepatic steatosis. Thus, the approaches to improve Mrp4-mediated cAMP extrusion in the liver could serve as the potentially novel target for treatment of hepatic steatosis, which would eventually bring therapeutic benefits to MALFD.