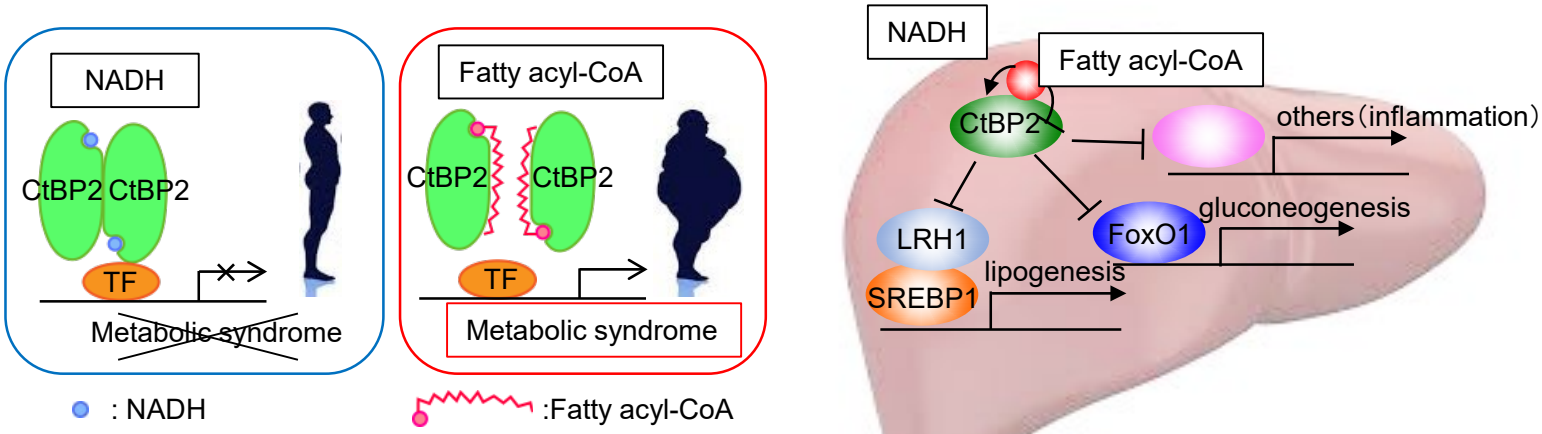
From Laboratory of Endocrinology and Metabolism

The transcriptional corepressor CtBP2 serves as a metabolite sensor orchestrating hepatic glucose and lipid homeostasis



The metabolic abnormalities associated with obesity, as represented here by diabetes, have been historically attempted to be treated by potentiating insulin signaling. However, insulin suppresses hepatic gluconeogenesis at the expense of aggravation of lipogenesis, indicating the existence of major therapeutic impasse.

To solve this problem, we identified a novel metabolic system where a transcriptional corepressor CtBP2 serves as a metabolite sensor. Accommodation of NADH activates CtBP2, that results in suppression of pathogenic genes responsible for metabolic syndrome while that of fatty acyl-CoA, increased in tissues in obesity, inactivates CtBP2, that causes metabolic disturbances. CtBP2 is markedly inactivated in obesity and activation of CtBP2 in obese liver ameliorates diabetes as well as hepatic steatosis.

This work lays the groundwork for understanding a key mechanism in metabolic diseases and highlights the potential of therapeutically targeting this system.

References: Sekiya M et al., Nature Communications. 2021; 12(1):6315

Contact: Motohiro Sekiya (msekiya@md.tsukuba.ac.jp)