Intermittent Fasting Enhances CISD2 to Improve Glucose Homeostasis and Fatty Liver in Western Diet-induced Obese Mice

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The pro-longevity gene CISD2 mediates healthy lifespan in mammals. CISD2 protein is located in the mitochondria outer membrane and endoplasmic reticulum membrane; it is involved in modulating Ca^{2+} homeostasis, redox status, and mitochondrial integrity. Previously we demonstrated that a persistent high level of CISD2 expression extends healthspan and delays aging in Cisd2 transgenic mice. However, molecular mechanism underlying the regulation of CISD2 expression remains elusive. Recent studies indicate that intermittent fasting (InF), which is a type of dietary restriction that cycles between periods of eating and fasting, has several health benefits, including promoting healthy longevity and improving western diet (WD)-induced metabolic disorders. Interestingly, our findings reveal that fasting enhances CISD2 expression, which suggests that the beneficial effects of InF may be associated with CISD2. In this study, we investigate the role of CISD2 during InF using a mouse model of WD-induced obesity and metabolic disorders. Several preliminary findings can be highlighted. **Firstly**, InF enhances CISD2 expression and improves WD-induced metabolic disorders and metabolic associated fatty liver disease (MAFLD) in wild-type mice. **Secondly**, the beneficial effects of InF on WD-induced glucose dyshomeostasis and MAFLD are attenuated in hepatocyte-specific CISD2 knockout (CISD2hKO) mice. **Finally**, we have identified several InF-associated transcriptional factors that potentially serve as upstream regulators of CISD2 gene expression. In summary, our findings reveal that CISD2 plays a critical role in mediating the beneficial effects of InF on glucose homeostasis and MAFLD, and highlight enhancing CISD2 by InF as a potential therapeutic strategy for metabolic syndromes and promoting healthy lifespan.

Keywords: CISD2, Intermittent fasting, MAFLD, Glucose homeostasis