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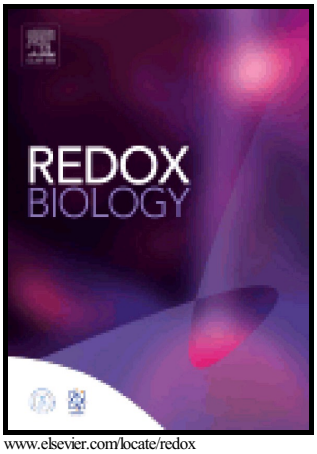

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Fasting exacerbates hepatic growth differentiation factor 15 to promote fatty acid β-oxidation and ketogenesis via activating XBP1 signaling in liver

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Abstract

Liver coordinates a series of metabolic adaptations to maintain systemic energy balance and provide adequate nutrients for critical organs, tissues and cells during starvation. However, the mediator(s) implicated in orchestrating these fasting-induced adaptive responses and the underlying molecular mechanisms are still obscure. Here we show that hepatic growth differentiation factor 15 (GDF15) is regulated by IRE1α-XBP1s branch and promotes hepatic fatty acids β-oxidation and ketogenesis upon fasting. GDF15 expression was exacerbated in liver of mice subjected to long-term fasted or ketogenic diet feeding. Abrogation of hepatic *Gdf15* dramatically attenuated hepatic β-oxidation and ketogenesis in fasted mice or mice with STZ-initiated type I diabetes. Further study revealed that XBP1s activated *Gdf15* transcription via binding to its promoter. Elevated GDF15 in liver reduced lipid accumulation and impaired NALFD development in obese mice through enhancing fatty acids oxidation in liver. Therefore, our results demonstrate a novel and critical role of hepatic GDF15 activated by IRE1α-XBP1s branch in regulating adaptive responses of liver upon starvation stress.

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