（様式３号）

学 位 論 文 の 要 旨

氏名 Zou Meng

〔題名〕

Thioredoxin-interacting protein is a pivotal factor for brown adipose tissue function and adaptive thermogenic property to acute cold stress

（Thioredoxin-interacting protein は褐色脂肪組織の機能および急性寒冷ストレスへの適応的熱産生特性における重要な因子である）

〔要旨〕

Background: Mammals adaptively regulate energy metabolism in response to environmental changes such as starvation and cold circumstances. Thioredoxin-interacting protein (Txnip), known as a redox regulator, serves as a nutrient sensor regulating energy homeostasis. Txnip is essential for mice to adapt to starvation, but its role in cold-induced thermogenesis remains unclear.

Methods: Non-shivering thermogenesis and adaptive property in Txnip-deficient ($Txnip^{-/-}$) mice were assessed under acute cold stress using indirect calorimetry, biochemical, histological, transcriptomic, and metabolomic analyses in vivo or in dissected brown adipose tissue (BAT).

Results: Txnip protein levels in BAT were upregulated by the acute cold exposure. $Txnip^{-/-}$ mice acclimated to thermoneutrality (30°C) exhibited significant BAT enlargement and triglyceride accumulation with downregulation of BAT signature and metabolic gene expression. Upon acute cold exposure (5°C), $Txnip^{-/-}$ mice showed a rapid decline in BAT surface temperatures with the failure of increasing metabolic respiration, developing lethal hypothermia. The BAT dysfunction and cold susceptibility in $Txnip^{-/-}$ mice were corrected by acclimation to 16°C, protecting the mice from life-threatening hypothermia. Transcriptomic and metabolomic analysis on BAT revealed that despite preserving glycolysis, the BAT of $Txnip^{-/-}$ mice failed to activate the catabolism of branched-chain amino acids and fatty acids in response to acute cold stress.

Conclusion: These results revealed that Txnip is required for maintaining basal BAT function and ensuring cold-induced thermogenesis. By advancing the understanding of the physiological basis in response to acute cold stress, this study provides valuable insights into mammalian biology and offers insights into potential therapeutic approaches for metabolic conditions.

作成要領

１．要旨は、８００字以内で、１枚でまとめること。

２．題名は、和訳を括弧書きで記載すること。

(様式９号)

学位論文審査の結果の要旨

令和 7 年 2 月 12 日

報告番号	医博甲第 1718 号	氏　名	Zou Meng

論文審査担当者	
	主査教授　朝霧成孝
	副査教授　(有末誠
	副査教授　太田康晴

学位論文題目名（題目名が英文の場合、行を変えて和訳を括弧書きで記載する。）

Thioredoxin-interacting protein is a pivotal factor for brown adipose tissue function and adaptive thermogenic property to acute cold stress

(Thioredoxin-interacting protein は褐色脂肪組織の機能および急性寒冷ストレスへの適応的熱産生特性における重要な因子である)

学位論文の関連論文題目名（題目名が英文の場合、行を変えて和訳を括弧書きで記載する。）

Txnip deficiency causes a susceptibility to acute cold stress with brown fat dysfunction in mice

(Txnip 欠損マウスでは褐色脂肪細胞機能障害とともに急性寒冷ストレス誘導性熱産生が障害される)

掲載雑誌名 Journal of Biological Chemistry （令和６年 11 月　アクセプト済み）

著者（全員を記載）

Meng Zou, Katsuya Tanabe, Kikuko Amo-Shiinoki, Daisuke Kohno, Syota Kagawa, Hideki Shirasawa, Kenji Ikeda, Akihiko Taguchi, Yasuharu Ohta, Shigeru Okuya, Tetsuya Yamada, Tadahiro Kitamura, Hiroshi Masutani, Yukio Tanizawa

（論文審査の要旨）

Thioredoxin-interacting protein (Txnip) plays a critical role in enabling mice to adapt to physiological stresses by regulating energy metabolism. However, its role in adapting to cold stress remains unclear. This study investigated the effect of Txnip on cold tolerance and brown adipose tissue (BAT) function using whole-body Txnip knockout mice (Txnip-/-) and dissected BAT, highlighting the pivotal role of Txnip in maintaining BAT function and supporting cold-induced thermogenesis.

Under thermoneutral and room temperature conditions, Txnip-/- exhibited abnormal BAT morphology along with downregulation of BAT signature and metabolic gene expression. When exposed to acute cold stress, Txnip-/- mice demonstrated severe cold susceptibility together with a defect in BAT thermogenesis. Transcriptomic and metabolomic analyses revealed that BAT in Txnip-/- mice failed to activate the catabolic pathways of branched-chain amino acids and fatty acids in response to acute cold stress. These findings underscore the essential role of Txnip in preserving BAT function and adaptive thermogenic property to acute cold stress.

This study contributes significantly to the understanding of the physiological mechanisms underlying mammalian responses to environmental stress and offers valuable insights into mammalian biology. It is recognized as a valuable dissertation.

備考　審査の要旨は８００字以内とすること。