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Journal Club

Keep Hypoxia-Inducible Factor α and Stay Cool

Adipocyte HIFα regulates thermogenic execution.

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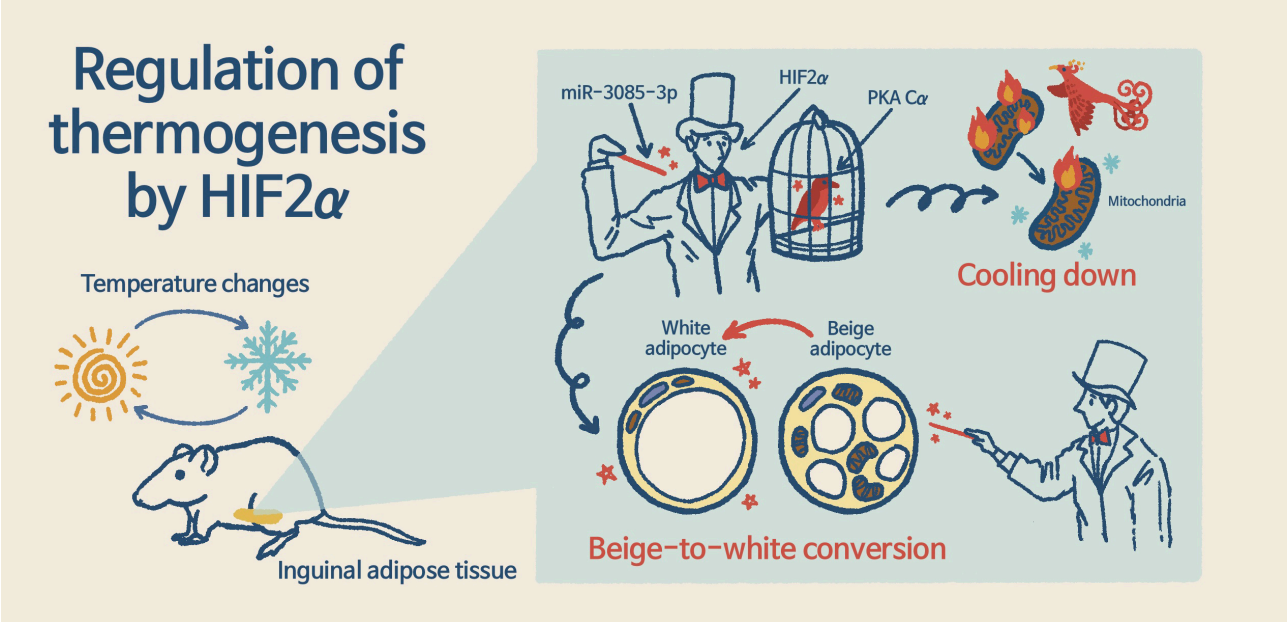

Hypoxia-inducible factor 2α (HIF2α)-dependent thermogenic regulation upon temperature changes. Upon cold exposure, HIF2α is stabilized and fine-tunes thermogenic activity via PKA Cα (protein kinase A catalytic subunit α) regulation. HIF2α also coordinates beige adipocyte plasticity to actively respond to temperature shift.

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Given that most aerobic organisms heavily depend on oxygen, which is essential for various metabolic processes, they have evolved to develop defense mechanisms against oxygen deficiency. The hypoxia-inducible factor α (HIFα), a molecular oxygen sensor and responder, has been identified as a crucial player in modulating glucose and lipid metabolism in response to oxygen deficiency (Lee et al., 2020). Under the hypoxic condition, HIFα inhibits mitochondria, where catabolic processes primarily occur by consuming a large amount of oxygen, for metabolic rewiring.

Adipose tissue suffers from hypoxic stress in obesity due to limited vasculature formation and altered metabolism (Seo et al., 2019; Trayhurn et al., 2008). In obesity, hypoxia is closely associated with adipose tissue remodeling, accompanied by adipose-derived protein secretion and immune cell recruitment (Choe et al., 2016; Moon et al., 2020). Adipocytes control their lipid metabolism via HIFα-dependent pathways to adapt to hypoxic stress (Mylonis et al., 2019). In particular, HIFα alters lipid catabolism from the initial step of lipid breakdown, known as lipolysis. To prevent futile lipolysis and lipotoxicity during hypoxia, HIFα downregulates adipose triglyceride lipase, a major enzyme responsible for hydrolyzing triacylglycerol to diacylglycerol and fatty acid (Han et al., 2019).

In addition to obesity, adipose tissues undergo hypoxia during cold acclimation (Xue et al., 2009). Recently, it has been demonstrated that HIF2α is a key regulator for thermostasis in brown and beige adipocytes (Han et al., 2022). Cold stress increases uncoupling protein 1 (UCP1) expression in brown and beige adipocytes for heat generation. Due to elevated oxygen demands, thermogenic adipose tissue exhibits hypoxia, thereby stabilizing HIF1α and HIF2α proteins. We created adipocyte-specific HIF1α, HIF2α, and HIF1/2α double knockout (HIF1α AKO, HIF2α AKO, and HIF1/2α DKO, respectively) mice to examine the thermoregulatory functions of HIF in adipocytes. Compared to wild-type mice, adipocyte HIFα deficient mice promote thermogenic activities with increased body temperature upon cold exposure. Moreover, brown adipocyte-specific HIF1α and HIF2α KO (HIF1α BKO and HIF2α BKO, respectively) mice are cold-resistant, indicating that adipocyte HIFα plays a suppressive role in thermogenesis regulation.

Transcriptome analysis using bioinformatic approaches was used to investigate the underlying mechanism(s) by which HIF exerts antithermogenic roles in brown and beige adipocytes. Intriguingly, in HIF2α AKO mice, the expression of protein kinase A catalytic subunit α (PKA Cα), a key signaling component of adrenergic-stimulated thermogenesis, was significantly increased. Furthermore, we revealed that HIF2α suppresses PKA Cα via miR-3085-3p which targets 3'UTR of *Prkaca*. Given that HIF2α-dependent miR-3085-3p expression suppresses PKA Cα, we examined PKA signaling pathways and thermogenic gene expression. PKA plays pleiotropic roles in the activation of thermogenesis in adipocytes in response to adrenergic stimuli. PKA stimulates lipolysis to provide fatty acids as fuel in mitochondria. Moreover, the PKA signaling pathway is critical for the expression of thermogenic genes such as *Ucp1*, *Ppargc1a*, and *Dio2*. In HIF2α deficient beige adipocytes, upregulated hyper-thermogenic phenotypes are downregulated by miR-3085-3p. In addition, administration of miR-3085-3p mimic suppresses the formation of beige adipocytes, proposing that the "HIF2α-miR-3085-3p-PKA Cα axis" could coordinate thermogenic activity for tight regulation of body temperature. When cold stimuli dwindle, beige adipocytes lose their features and return to white adipocytes (Shao et al., 2019). In the process of beige-to-white transition, thermogenic machinery including UCP1 and mitochondrial oxidative phosphorylation complex is downregulated, and small and multilocular lipid droplets are enlarged and unified. Collectively, we found that HIF2α facilitates beige-to-white transition by turning down PKA Cα. As the administration of miR-3085-3p mimic expedites the whitening of beige adipocytes in HIF2α AKO during rewarming, miR-3085-3p could be a novel mediator regulating beige adipocyte plasticity.

This study newly proposes that HIF2α-mediated PKA Cα regulation is crucial for adjusting thermogenic function in brown and beige adipocytes. Although we show that HIF2α-miR-3085-3p-PKA Cα is a key axis to control thermogenic execution, other HIF2α-dependent pathways may potentially play a role in the regulation of thermogenesis. In addition, it is still possible that HIF1α-dependent thermoregulatory function might exist independent of PKA Cα control. As HIF1/2α DKO mice did not exhibit additive effects on body temperature or thermogenic execution upon cold exposure, we set aside the influence of HIF1α in this study. Of course, HIF1α may contribute less to thermoregulation than HIF2α or the HIF1α-dependent thermoregulatory mechanism may already be a part of the HIF2α-dependent pathway. Further studies including comparative analyses are required to delineate the distinct molecular roles and regulatory mechanisms of HIF1α and HIF2α in thermogenesis. Nonetheless, this study provides compelling evidence that HIF2α-dependent thermoregulation prevents overheating and futile energy consumption in thermogenic adipocytes.

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CONFLICT OF INTEREST

The author has no potential conflicts of interest to disclose.

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