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FAM210A: Implications in mitochondrial dynamics and metabolic health

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Brown adipose tissue (BAT), crucial for mammalian thermoregulation and energy metabolism, boasts a dense concentration of mitochondria. As a vital cellular organelle, mitochondria undergo substantial remodeling in cold environments, playing a pivotal role in maintaining body temperature and energy balance[1]. Mitochondrial dynamics, particularly mitochondrial cristae remodeling, are key processes governing BAT functionality. A recent study by Qiu *et al.* unveils groundbreaking insights, highlighting the significance of FAM210A (family with sequence similarity 210 member A) in orchestrating cold-induced mitochondrial remodeling in brown adipocytes. This research sheds light on the molecular mechanisms underpinning mitochondrial adaptability in cold environments[2]. Central to these discoveries is the protein FAM210A, recognized as a critical regulator of mitochondrial cristae remodeling in BAT. This revelation introduces new perspectives on metabolic regulation and thermogenic adaptation. This editorial aims to dissect these findings, extrapolating their broader implications for understanding metabolic health. Additionally, it explores potential therapeutic targets and discusses future directions in mitochondrial research.

1 Mitochondrial Dynamics: driving energy metabolism and cellular adaptability

Mitochondria have long been known as the epicenter of cellular energy metabolism, garnering considerable attention for their dynamic transformations, a key focus in biological research. Conventionally recognized for ATP generation *via* oxidative phosphorylation within their inner membrane protrusions known as cristae, mitochondria have recently surged in interest not only for their role in energy metabolism, but also because of their adaptive structural changes in response to cellular stress[3,4]. The exploration of the intricate relationship between the structure and function of mitochondrial cristae has birthed a burgeoning field of research. These cristae, beyond mere energy production sites, wield direct influence over mitochondrial function, thereby shaping cellular metabolic states and adaptability[5-6].

Studies on BAT have elucidated the pivotal role of mitochondrial cristae remodeling in maintaining and regulating thermogenic functions[7]. Cold s exposure sparks a surge in mitochondrial numbers and structural alterations within BAT, particularly in the density and morphology of mitochondrial cristae[1]. These changes are crucial for enhancing oxidative metabolism and bolstering thermogenic efficiency.

2 Role of FAM210A in mitochondrial remodeling and BAT function

The study of Qiu *et al.* shows the dynamic remodeling of mitochondrial cristae in BAT, unveiling a complex regulation orchestrated by multiple proteins. This new understanding of mitochondrial dynamics offers new insights into leveraging these mechanisms to finely modulate cellular functions. Among the identified proteins, FAM210A emerges as a key mitochondrial protein significantly upregulated in BAT upon exposure to cold stimuli. Its pivotal role in orchestrating mitochondrial cristae remodeling in BAT becomes evident. Experiments involving the targeted suppression of FAM210A in adipocytes showcase a disruption in mitochondrial cristae structure, resulting in a substantial reduction in BAT's thermogenic capacity. This underscores the indispensable nature of FAM210A in preserving both the structure and function of mitochondria. FAM210A knockout mice exhibit whitening of BAT, impaired thermogenesis,

diminished mitochondrial functionality, and heightened the risk of lethal hypothermia upon acute cold exposure. These findings underscore the criticality of FAM210A in preserving BAT function and overall energy metabolism. Mechanistically, FAM210A interacts with the mitochondrial protease YME1L and regulates its cleavage activity towards OPA1, which in turn influences the structure and function of mitochondrial cristae. OPA1 is an important mitochondrial inner membrane protein and its cleavage and balance are critical for maintaining the integrity of mitochondrial cristae[8].

3 FAM210A: broader perspectives and future directions

At present, managing metabolic disorders like obesity and type 2 diabetes stands as a formidable challenge. Enhancing BAT functionality emerges as a promising avenue to elevate energy expenditure, holding potential in treating these conditions. Uncovering the role of FAM210A in BAT's mitochondrial dynamics opens up fresh possibilities for addressing metabolic diseases. Precise modulation of BAT's mitochondrial dynamics and thermogenic functions *via* FAM210A regulation could be instrumental in therapeutic strategies. Beyond its impact on Beyond its impact on BAT, FAM210A's influence might extend to other metabolically active tissues like the liver, skeletal muscle, crucial for overall metabolic health. Initial investigations hint at its relevance in liver metabolism[9], while also playing a pivotal role in regulating muscle cell differentiation and degradation, closely intertwined with insulin dynamics[10]. Given its enhancement of BAT's thermogenic function and potential influence on liver metabolism, FAM210A's role in muscle cell differentiation and degradation could set the stage for a FAM210A-insulin-FAM210A positive feedback loop. Moreover, FAM210A may influence osteoporosis through signaling pathways related to muscle[11], promising insights into potential treatments for osteoporosis and sarcopenia.

The health of the cardiovascular system hinges significantly on mitochondria function, particularly in cardiac muscle cells under the conditions with high energy demands. With heart disease frequently linked to mitochondrial dysfunction, if FAM210A can regulate mitochondrial structure and function in cardiomyocytes, it might play a crucial role in maintaining myocardial energy metabolism, preventing myocardial damage, and aiding cardiac repair processes. Evidence suggests a cardioprotective role for FAM210A in heart failure, which is mediated by microRNA-574[12]. Its diminished expression in ischemic heart failure samples from humans and mice contrasts with its overexpression, protecting the heart from myocardial infarction-induced heart failure, underscoring its potential in sustaining mitochondrial homeostasis and normal cardiomyocyte contractile function[13]. In addition, decline in mitochondrial function is a prominent indicator of aging. Its diminished expression in ischemic heart failure samples contrasts with its overexpression protecting the heart from myocardial infarction-induced heart failure[13], underscoring its potential in sustaining mitochondrial homeostasis and normal cardiomyocyte function. Furthermore, as declining mitochondrial function signals aging-related diseases, FAM210A's association with age-related conditions gains prominence. This protein holds promise for clinical applications, potentially steering research toward treating metabolic disorders, osteoporosis, sarcopenia, aging-related illnesses, and cardiovascular diseases.

An important note emerges regarding FAM210A's absence in serum, suggesting limitations in potential dosage forms for clinical applications[11]. This constraint could impact the scope of FAM210A-related therapies.

4 Conclusion

In essence, the study conducted by Qiu *et al.* marks a significant leap forward in comprehending BAT's response to cold stimuli, spotlighting the indispensable role of FAM210A in mitochondrial biology. This newfound understanding not only enriches our insights into metabolic health but also paves the way for pioneering research avenues and potential therapeutic interventions in managing metabolic diseases and their associated pathologies. Delving deeper into mitochondrial dynamics, particularly the functions of pivotal proteins like FAM210A, stands as a cornerstone for unlocking novel frontiers in medical science. Such revelations hold immense promise for crafting treatments addressing a spectrum of diseases stemming from mitochondrial dysfunction.

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Author contributions

Lou H drafted the manuscript. Xu H H revised the manuscript. Zhang Y edited and reviewed the manuscript.

Conflicts of interests

Zhang Y is an Editorial Board Member of Frigid Zone Medicine. The article was subject to the journal's standard procedures, with peer review handled independently of these Members and their research groups.

Data availability statement

No additional data.

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