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Hepatic lysosomal lipid remodeling in cold adaptation: Insights into TFEB-PLA2G15-BMP axis regulation

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When mammals are exposed to cold, their metabolism undergoes substantial changes. The liver plays a central role in maintaining energy homeostasis by shifting from glucose metabolism to lipid catabolism. A recent study by Davidson *et al*.[1], published in *Cell Metabolism*, highlights a novel mechanism involving lysosomal lipid remodeling during cold adaptation. Specifically, the study reveals that cold exposure elevates hepatic levels of Bis (Monoacylglycerol) Phosphate (BMP) lipids, which are regulated by Transcription Factor EB (TFEB) and Phospholipase A2 group XV (PLA2G15). These findings provide key insights into lysosomal lipid metabolism and its role in thermogenesis and energy balance, with implications for both metabolic diseases and lysosomal storage disorders.

1 The role of BMP lipids in cold adaptation

The study demonstrates that BMP lipids, especially those enriched in Polyunsaturated Fatty Acids (PUFAs), accumulate in hepatocytes following cold exposure[1]. This increase is associated with enhanced lysosomal lipid processing, suggesting that BMP facilitates the catabolism of stored lipids for heat production. Previous research has shown that BMPs influence lysosomal membrane fluidity and enzymatic activity[2], potentially explaining their role in lipid breakdown during thermal stress. The selective enrichment of BMP species further underscores their functional significance, as PUFAs are known to increase membrane flexibility and optimize enzyme activity[3].

2 TFEB as a central regulator of lysosomal lipid metabolism

Cold exposure activates TFEB, a master transcriptional regulator of lysosomal biogenesis, which then reprograms gene expression to favor lipid metabolism[1]. Notably, TFEB downregulates *Pla2g15* expression, thereby limiting BMP degradation and promoting its accumulation. This observation aligns with previous findings indicating that TFEB governs lysosomal and metabolic responses to nutrient stress[4]. However, the precise upstream signals linking cold sensing to TFEB activation remain unclear. Possible candidates include mTORC1 inhibition and AMP-activated Protein Kinase (AMPK) activation[5].

3 PLA2G15 as a key effector in BMP homeostasis

The identification of PLA2G15 as a BMP lipase represents a significant advancement in our understanding of lysosomal lipid regulation[1]. The study provides compelling evidence that TFEB-mediated suppression of PLA2G15 activity leads to BMP accumulation. This regulatory axis may have broader relevance, as BMP imbalance is a hallmark of certain lysosomal storage disorders[6]. Future research could explore the therapeutic modulation of PLA2G15 activity to ameliorate lipid accumulation in diseases like Niemann-Pick type C[7].

4 Implications for metabolic and lysosomal disorders

These findings open new avenues for targeting BMP metabolism in disease contexts. Given the importance of BMP in lysosomal function, modulating its levels through TFEB or PLA2G15 may benefit individuals with metabolic conditions such as metabolic Dysfunction-associated Steatotic Liver Disease (MASLD)[8]. Moreover, the study highlights the need to investigate sex-specific differences in BMP regulation, as lipid metabolism differs substantially between males and females[9].

5 Future directions

Future studies should focus on elucidating the upstream

signaling pathways that activate TFEB in response to cold. Potential mechanisms include: Inhibition of mTORC1, which facilitates TFEB nuclear translocation[4]; Activation of AMPK, potentially linking energy demand to lysosomal adaptation[10]; and Calcium signaling via TRPML1 channels, which has been implicated in TFEB activation[11]. Therapeutic interventions targeting the TFEB-PLA2G15-BMP axis may include: Small-molecule modulators of PLA2G15 to treat lysosomal storage diseases[5]; TFEB activators to promote lipid clearance in metabolic disorders[12]; and Exogenous BMP supplementation in Niemann-Pick type C disease models[13].

To bridge findings from murine models to humans, studies using iPSC-derived hepatocytes could validate the relevance of this pathway in human cells[5]. Clinical research should assess changes in circulating BMP levels during cold exposure or in metabolic syndromes[2]. Trials targeting this pathway could evaluate new pharmacologic strategies for treating metabolic disorders[3]. Advanced technologies such as single-cell lipidomics may elucidate hepatocyte-specific responses[8], while spatial omics could reveal BMP localization within hepatic lobules[14]. Structural studies using cryo-EM may clarify the molecular basis of BMP hydrolysis by PLA2G15[15].

The study by Davidson *et al*.[1] provides strong evidence that hepatic BMP lipids are critical for cold adaptation and are regulated by the TFEB-PLA2G15 axis. These results advance our understanding of lysosomal lipid remodeling and identify potential therapeutic targets for metabolic and lysosomal diseases. Future research should aim to unravel the detailed mechanisms, translational applicability, and sex-specific aspects of this regulatory pathway.

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Conflict of interest

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Data availability statement

Not applicable.

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