Ketone body-mediated regulation of mitochondrial electron transport complexes via MALAT1 in human cardiomyocytes

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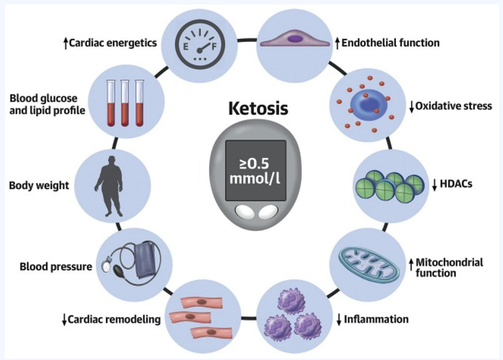
Background

- Heart failure is characterized by impaired mitochondrial oxidative phosphorylation and reduced metabolic flexibility, resulting in insufficient energy production for cardiac function.
- Ketone bodies, particularly β-hydroxybutyrate (BHB), have emerged as alternative energy substrates that may improve cardiac bioenergetics and mitochondrial function.



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- Long noncoding RNAs (lncRNAs) are important regulators of gene expression and cellular metabolism.
- Our previous studies demonstrated that BHB increases the expression of the lncRNA MALAT1 and upregulates genes involved in mitochondrial biogenesis and antioxidant defense.
- However, the role of MALAT1 in regulating mitochondrial electron transport chain (ETC) proteins remains unclear.

Objective

To determine the role of β-hydroxybutyrate and MALAT1 in regulating mitochondrial oxidative phosphorylation (OXPHOS) complex protein expression in human cardiomyocytes.

Methods

Cell Culture and Treatments

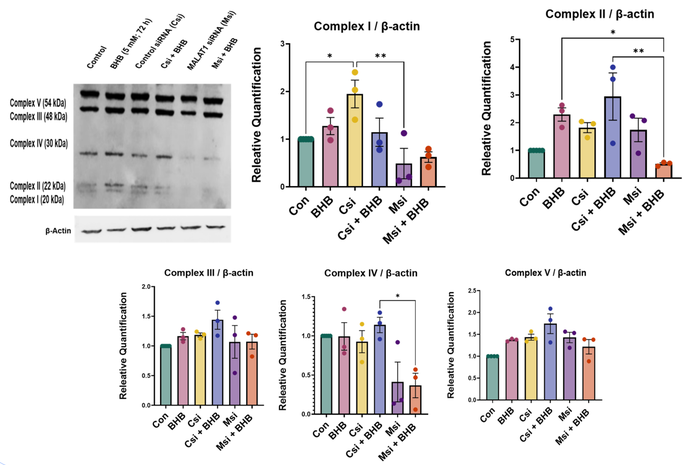
- Human AC16 ventricular cardiomyocytes were cultured under standard conditions.
- Cells were treated with β-hydroxybutyrate (BHB; 5 mM) for 72 hours.
- MALAT1 knockdown was achieved using MALAT1 siRNA (10 nM) for 72 hours.
- Control siRNA was used as a transfection control.

Western Blot Analysis

- OXPHOS protein expression was analyzed using a premixed antibody cocktail (Abcam; ab110411), targeting Complex I (NDUFB8), Complex II (30 kDa subunit), Complex III (Core 2), Complex IV (Subunit II), Complex V (ATP synthase α).
- β-actin was used as the loading control. Protein expressions were quantified by densitometry (LICOR Image Studio Software).
- Statistical analysis was performed using one-way ANOVA using Graphpad Prism.

Results

MALAT1 knockdown significantly decreases OXPHOS Complex I and IV proteins.



Key Findings

- BHB modestly enhances mitochondrial respiratory complex expression.
- MALAT1 knockdown significantly decreases OXPHOS Complex I, II, and IV proteins.
- BHB partially rescues mitochondrial protein expression following MALAT1 depletion.
- MALAT1 appears to be an important mediator of ketone body–induced mitochondrial adaptations in cardiomyocytes.

Conclusion

- β-Hydroxybutyrate modestly enhances mitochondrial electron transport chain protein expression, while MALAT1 is essential for maintaining OXPHOS complex abundance.
- These findings support a MALAT1-dependent mechanism linking ketone signalling to mitochondrial biogenesis and mitochondrial function in human cardiomyocytes.

Future Directions…

- Evaluate mitochondrial respiration using Seahorse metabolic analysis.
- Assess mitochondrial membrane potential, oxidative stress and antioxidant pathways regulated by MALAT1.
- Elucidate molecular mechanisms linking ketone signaling, MALAT1, and mitochondrial biogenesis.

Acknowledgements

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