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“ATPAF2 Maintains Proper Cardiac Function and Mitochondrial Quality Control”

BACKGROUND: The heart exhibits a high, constant energy demand that increases further under physiological stress, underscoring the importance of proper ATP synthase bioassembly in energy production. Yeast studies have shown that ATP12 is essential for assembling the α subunit into the F1 ATP synthase complex; however, the specific role of ATP assembly factor 2 (ATPAF2), the mammalian homolog of ATP12, in cardiac ATP synthase and its potential to meet heightened energy demands remain unexplored.

METHODS: Homozygous male and female *Atpaf2*-floxed (8-10 weeks old; n=10-12 mice/sex/group) mice were injected with adeno-associated containing cardiac troponin-driven Cre recombinase or Control Vector (AAV9-cTnT-Cre/GFP; 10^{12} genomic copies/kg) to generate cardiomyocyte-specific ATPAF2 gene knockout (cATPAF2-KO) mice. cATPAF2-KO exhibited an approximately 50% reduction in cardiac ATPAF2 expression, confirmed by western blot. Mice were assessed for cardiac function using echocardiography and biomolecular analysis. Furthermore, cardiac mitochondrial ultrastructure was assessed by electron microscopy (EM), and images were analyzed using ImageJ.

RESULTS: Echocardiographic assessment shows that cATPAF2-KO mice exhibited significantly increased left ventricular mass and left ventricle dilation, along with significantly reduced cardiac function. Although total cardiac ATP synthase α -subunit (ATP5A1) levels remained unchanged, the α -subunit incorporated into the ATP synthase complex was significantly reduced, validating ATPAF2's role in facilitating α -subunit assembly. EM indicated that cATPAF2-KO mitochondria have significantly reduced cristae density, larger surface areas, and reduced circularity, highlighting alterations in mitochondrial structural integrity. cATPAF2-KO expressed significantly increased ATP synthase c-subunit (ATP5G1/2/3) and adenine nucleotide translocase (ANT), suggesting a compensatory response to impaired ATP synthase capacity. cATPAF2-KO also showed significantly reduced PTEN-induced kinase 1 (PINK1), whereas dynamin-related protein 1 (DRP1) and light chain 3 beta (LC3B) were significantly increased, indicating altered mitochondrial homeostasis with possible secondary implications from impaired ATP synthase bioassembly.

CONCLUSION: Our findings show that ATPAF2 is essential for maintaining cardiac function and mitochondrial homeostasis by regulating proper ATP synthase bioassembly. Further investigation is needed to understand how ATPAF2 contributes to mitochondrial adaptation under pathological conditions such as heart failure.