

EVOLUTIONARY STRATEGIES OF CARDIAC GROWTH: THE ICEFISH HEART AS A MODEL TO CONTRAST PATHOLOGICAL CELLULAR MALADAPTATION

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The PNRA0000022-ICEHEART project investigates the molecular strategies that allow Antarctic icefish (Channichthyidae)—the only vertebrates lacking hemoglobin and often myoglobin—to maintain cardiac performance under extreme conditions. These species represent a unique model to identify pathways relevant for human hypertrophic and dilated cardiomyopathies. The absence of respiratory pigments requires profound cardiovascular remodeling, leading to marked cardiomegaly, vascular expansion and high cardiac output. Transcriptomic analyses show strong upregulation of Col8A1B and Fosl2, indicating active extracellular matrix remodeling and vasculogenesis, while enrichment of miR-214, miR-223 and miR-10a-5p defines a pro-angiogenic and pro-survival profile. Conversely, qRT-PCR reveals down-regulation of miR-1/133, key repressors of cardiomyocyte growth in mammals; this pattern resembles human pathological hypertrophy and zebrafish cardiac regeneration,

suggesting a release of molecular brakes that normally limit myocardial renewal. Immunohistochemistry supports these findings: increased GATA4 and NFAT2 confirm activation of hypertrophic programs; WT1 indicates persistent epicardial plasticity; elevated cTNT and HSP70 reflect reinforcement of the contractile apparatus and maintenance of proteostasis under chronic cold stress. Overall, icefish display a state of permanent physiological hypertrophy in which growth signals, vascular remodeling and cytoprotection remain chronically active. Unlike humans, where sustained hypertrophy often progresses to dysfunction, the icefish heart preserves a stable, adaptive phenotype. In conclusion, the pathways activated in icefish provide critical insights into the mechanisms required to contrast or redirect maladaptive remodeling in human cardiac disease.

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