Uncovering Novel VEGF-B Regulated Molecular Mechanisms in Myocardial Infarction

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Cardiovascular disease remains the leading global cause of mortality, with myocardial infarction resulting in permanent myocardial loss due to the limited regenerative capacity of adult cardiomyocytes. Vascular Endothelial Growth Factor B (VEGF-B), a lesser-focused VEGF isoform, has emerged as a regulator of cardiac survival and regeneration through receptor-mediated interactions. This study aims to investigate the specific molecular mechanisms by which VEGF-B signaling mitigates ischemic injury and promotes myocardial regeneration. AC16 human cardiomyocytes were treated with Cobalt Chloride (CoCl2) to model the hypoxic stress that occurs during myocardial infarction, with recombinant VEGF-B overexpression treatment. Functional assays demonstrated VEGF-B's potential to significantly enhance cell viability and reduce apoptosis. Bulk RNA-seq analysis identified key genes significantly implicated in VEGF-B pathways, with upregulation of proliferative genes (MYCN, MKI67) and suppression of apoptotic and inflammatory genes (PDCD2, IL6R). Western blot analysis revealed activation of pro-survival signaling via AKT and p38 MAPK pathways. In Situ Hybridization in zebrafish embryo revealed spatial MYCN expression in developmening muscular and neural tissue, supporting its relevance in cardiac regeneration. Integrating in vitro, ex vivo, and in silico approaches, this work identifies MYCN and related targets as promising mediators of VEGF-B's cardioprotective function. These findings support the therapeutic potential of VEGF-B signaling mechanisms as a next-generation strategy to restore myocardial function following infarction.

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