**IDH2 DEFICIENCY IMPAIRS MITOCHONDRIAL FUNCTION IN ENDOTHELIAL CELLS AND ENDOTHELIUM-DEPENDENT VASOMOTOR FUNCTION**

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Mitochondrial NADP(+)-dependent isocitrate dehydrogenase (IDH2) plays an essential role protecting cells against oxidative stress-induced damage. A deficiency in IDH2 leads to mitochondrial dysfunction and the production of reactive oxygen species (ROS) in cardiomyocytes and cancer cells. However, the function of IDH2 in vascular endothelial cells is mostly unknown. In this study the effects of IDH2 deficiency on mitochondrial and vascular function were investigated in endothelial cells. IDH2 knockdown decreased the expression of mitochondrial oxidative phosphorylation (OXPHOS) complexes I, II and III, which lead to increased mitochondrial ROS (mtROS). In addition, the levels of fission and fusion proteins (Mfn-1, OPA-1, and Drp-1) were significantly altered and MnSOD expression also was decreased by IDH2 knockdown. Furthermore, knockdown of IDH2 decreased eNOS phosphorylation and nitric oxide (NO) concentration in endothelial cells. Interestingly, treatment with Mito-TEMPO, an mtROS-specific scavenger, blunted mitochondrial fission, fusion and mtROS production, and reduced the IDH2 knockdown-induced decrease in MnSOD expression, eNOS phosphorylation and NO production in endothelial cells. Endothelium-dependent vasorelaxation was impaired, and the concentration of bioavailable NO decreased in the aortic ring in IDH2 knockout mice. These findings suggest that IDH2 deficiency induces endothelial dysfunction through the induction of dynamic mitochondrial changes and impairment in vascular function.