MiRNA 106b~25 is Essential for Functional Recovery in Limb Ischemia Model by Regulating Angiogenesis

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MicroRNAs are small non-coding RNAs that regulate a wide range of physiological and pathophysiological processes by post transcriptional gene silencing. microRNA-106b~25 cluster is highly expressed in endothelial cells and adult stem cells, but it's function is not fully understood.

In the current study we investigated the effect of miR-106b~25 deletion on blood flow, using a mouse model of hind limb ischemia. In addition, we isolated bone-marrow derived stem cells from miR-106b~25 knockout mice and examined their ability to expand in-vitro, their angiogenic capacity in Matrigel tube formation assay, as well as their apoptotic response following exposure to H2O2.

We observed an up-regulation of the 106b~25 cluster following limb ischemia as evident by Real-time PCR. Interestingly, 106b~25 knockout mice had reduced blood flow compared to the wild type controls, measured by Laser-Doppler imaging. Furthermore, partial salvage of the mutant phenotype was achieved by gene delivery of miR-106b~25 to ischemic muscles. In addition, bone-marrow derived stem cells isolated from 106b~25 KO mice had reduced proliferation rate and the cells were 3-fold more sensitive to H2O2-induced apoptosis. Finally, KO bone-marrow cell culture exhibited a reduced number of Sca-1 positive cells as compared to WT cells.

In summary, we have demonstrated that the 106b~25 microRNA cluster is essential for functional recovery of ischemic muscles in mice. A few possible mechanisms were identified including augmentation of post-ischemic vascularization, reduction in apoptosis levels and regulation of bone-marrow derived Sca-1 positive cells.

miR-106b~25 gene therapy may thus stand as a novel target for future gene based therapies for regeneration of ischemic tissues.