A biomarker (MicroRNA-126) for diabetic retinopathy.

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Introduction

MiR-126 is a highly preserved, non-coding RNA that is expressed primarily in human endothelial cells and is a key regulator of angiogenesis and vasculogenesis. MiR-126 is found in human genomes within intron 7 of the gene Epidermal Growth Factor-Like Domain 7 (EGFL7) on chromosome 9. Pre-MiR-126 processing, i.e., the miRNA precursor, produces two mature strands: (a) MiR-126-3p with the sequence: UCGUACCGUAGUAAUAAUGCG and (b) MiR-126-5p with the sequence: CAUUAUUACUUUUGGUACGCG. In the eye, by regulating the expression of VCAM1 (Vascular Cell Adhesion Molecule 1) and the pro-apoptotic marker BCL2L11 (B-Cell Lymphoma 2-Like 11), MiR-126 maintains the integrity of the Blood-Retina-Barrier (BRB). MiR-126 protects against apoptosis of retinal endothelial cells, retinal vascular leakage, and retinal permeability under ischemic conditions in the retina. Furthermore, MiR-126 protects Muller cells against hypoxic retinal damage. Mature blood vessels express abundant levels of MiR-126, which controls the signaling cascades of VEGF- and Angiopoietin, thus regulating angiogenesis and vasculature development.

Discussion

MiR-126 promotes angiogenesis in endothelial cells by inhibition of the repressors of endogenous VEGF (Vascular Endothelial Growth Factor), i.e. SProuty-Related EVH1 Protein 1 (SPRED1) and PhosphoInositol-3 Kinase Regulatory Subunit 2 (PIK3R2) domain-containing proteins, both of which antagonize VEGF effects and obstruct angiogenesis. SPRED1 suppresses activation of MAPK (Mitogen-Activated Protein Kinase) induced by growth factor and thus negatively regulates hematopoiesis; PIK3R2 regulates the pathway of PI3 kinase negatively. MiR-126 suppression results in impaired vascular integrity and attenuated phosphorylation of VEGF-induced ERK and AKT (a serine/threonine-protein kinase). In addition, MiR-126 controls the migration of endothelial cells, cytoskeleton reorganization, the stabilization of the capillary network, and the proliferation and survival of endothelial cells. MiR-126 inhibits VCAM1 expression and prevents endothelial cell adherence to leukocytes, thereby indicating its role in vascular inflammation control. MiR-126 3p/-5p overexpression attenuates VCAM-1 and E-selectin, suppresses pro-inflammatory cytokine production and maintains in vivo the integrity of the Blood-Brain-Barrier (BBB) in ischemic brains.

A recent study showed that targeted vascular transfection improved vascular density, tissue perfusion, vessel maturation, and arteriolar development with limited off-target effects through ultrasound-mediated gene delivery of MiR-126-3p micro particles in chronic ischemia. Endothelial proliferation is promoted by MiR-126-5p and leads to the pro-angiogenic effect of BMP4 on endothelial cells. The delivery of functional MiR-126 endothelial micro particles promotes vascular endothelial repair through SPRED1. Serum sample analysis of patients with proliferative diabetic retinopathy showed that serum MiR-126 levels are proportional to the degree of retinal damage; serum MiR-126 steadily decreases with the development of retinal damage caused by the disease. For early diagnosis of proliferative diabetic retinopathy and screening for retinal endothelial injury, this study indicated that serum MiR-126 could serve as a non-invasive biomarker.

Substantive deregulation of MiR-126 was observed in pediatric type 1 diabetes patients relative to controls, as demonstrated by decreased levels of MiR-126 in plasma and urinary samples. Furthermore, it has been shown that retinal expression of MiR-126 is significantly reduced in an in vivo streptozotocin-induced diabetic model and that MiR-126 prevents hypoxia-induced retinal neovascularization by down regulation of MMP-9 (Matrix Metallopeptidase-9) and VEGF-9. In a study in which MiR-126 suppressed IRS-1 (Insulin Receptor Substrate-1) expression and the PI3K/AKT pathway, inhibiting cell invasion and subsequent angiogenesis in retinal pericytes and endothelial cells in an in vivo diabetic retinopathy model, MiR-126 was identified as a potential candidate for diabetic retinopathy care. Restoration of decreased endogenous MiR-126 levels under ischemic conditions results in inhibition of VEGF, HIF-1 alpha and IGF-2 by down regulation of p38 and ERK signaling molecules; and decreased retinal neovascularization by intravitreal MiR-126 injection in an oxygen-induced retinopathy model. In addition, in Diabetic Retinopathy, MiR-126 leads to vascular repair caused by Niaspan therapy.

Conclusion

In conclusion, while additional researches, including clinical trials that further validate preclinical evidence, are necessary to assess the therapeutic potential of MiR-126 in retinal diseases, the studies carried out to date highlight the crucial role of MiR-126 in the retina and recognize MiR-126 as a promising candidate for diabetic retinopathy therapy.

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