Peripheral artery disease (PAD) is highly prevalent in patients with diabetes and associates with a high rate of limb amputation and poor prognosis. Surgical and catheter-based revascularization have failed to improve outcome in diabetic patients with PAD. Hence, a need exists to develop new treatment strategies able to promote blood vessel growth in the ischemic limb of diabetic patients. Mono-methylation of histone 3 at lysine 4 (H3K4me1) - a specific epigenetic signature induced by the methyltransferase SETD7 - favours a chromatin active and open state thus enabling the gene transcription. Patients with diabetes and HG in presence of SETD7-siRNA and Scr.siRNA.

Primary human arterial endothelial cells (HAECs) were exposed to normal glucose (NG, 5 mM) or high glucose (HG, 20 mM) concentrations for 48 hours. In vitro angiogenic assays like migration assay & tube formation assay were performed. Pharmacological blockade of SETD7 was achieved by using the highly selective inhibitor called (R)-PFI-2 HG + (R)-PFI-2. T1D mice (streptozotocin-induced diabetes) was orally treated with (R)-PFI-2 and with vehicle for 21 days and followed by induction of hindlimb ischemia. Blood flow recovery was analysed at 30 minutes, 7 and 14 days by laser doppler imaging. Gastrocnemius muscle samples from patients with and without T2D were employed to translate our experimental findings.

**Purpose**

Peripheral artery disease (PAD) is highly prevalent in patients with diabetes and associates with a high rate of limb amputation and poor prognosis. Surgical and catheter-based revascularization have failed to improve outcome in diabetic patients with PAD. Hence, a need exists to develop new treatment strategies able to promote blood vessel growth in the ischemic limb of diabetic patients. Mono-methylation of histone 3 at lysine 4 (H3K4me1) - a specific epigenetic signature induced by the methyltransferase SETD7 - favours a chromatin active and open state thus enabling the gene transcription. Patients with diabetes and HG in presence of SETD7-siRNA and Scr.siRNA.

**RESULTS**

Primary human arterial endothelial cells (HAECs) were exposed to normal glucose (NG, 5 mM) or high glucose (HG, 20 mM) concentrations for 48 hours. In vitro angiogenic assays like migration assay & tube formation assay were performed. Pharmacological blockade of SETD7 was achieved by using the highly selective inhibitor called (R)-PFI-2 HG + (R)-PFI-2. T1D mice (streptozotocin-induced diabetes) was orally treated with (R)-PFI-2 and with vehicle for 21 days and followed by induction of hindlimb ischemia. Blood flow recovery was analysed at 30 minutes, 7 and 14 days by laser doppler imaging. Gastrocnemius muscle samples from patients with and without T2D were employed to translate our experimental findings.

**CONCLUSIONS**

Targeting SETD7 represents a novel epigenetic-based therapy to boost neovascularization in diabetic patients with PAD.