**A CRUCIAL ROLE OF PDGF-C IN IMPAIRED ANGIOGENESIS OF DIABETES**

**Background:** Platelet-derived growth factor-C (PDGF-C) is known to promote angiogenesis independently of vascular endothelial growth factor (VEGF), although its significance in postnatal angiogenesis in vivo remains poorly understood.

**Methods and Results:** We employed murine model of hind limb ischemia and found that expression of PDGF-C and its receptor PDGFR-alpha were markedly up-regulated in ischemic limbs. Treatment with a neutralizing antibody against PDGF-C significantly impaired blood flow recovery and neovascularization after ischemia almost to the same extent as treatment with a VEGF neutralizing antibody. Moreover, PDGF-C deficient mice showed a reduced blood flow recovery after ischemia compared to wild-type mice, confirming a strong pro-angiogenic activity of PDGF-C. Next, we injected an expression vector encoding the PDGF-C gene into ischemic limbs. Blood flow recovery and neovascularization after ischemia were significantly improved in the PDGF-C treated group compared with the control group. It has been reported that angiogenic response to ischemia is attenuated in diabetes even after VEGF treatment, although a precise mechanism remains unknown. We hypothesized that PDGF-C might relate to the impaired angiogenesis of diabetes. To test this hypothesis, we created murine model of diabetes by intraperitoneal injection of streptozotocin (STZ). We found that expression levels of PDGF-C at baseline and after ischemia were both significantly lower in limb tissues of diabetic mice than in those of control mice, while expression levels of other members of the PDGF family and VEGF were not changed or even higher in diabetic mice. Consequently, introduction of VEGF gene into ischemic limbs did not improve blood flow recovery in diabetic mice. However, these changes were effectively reversed by additional introduction of the PDGF-C gene.

**Conclusion:** These results indicate that down-regulation of PDGF-C expression in limb tissues of diabetic mice contribute to impaired angiogenesis and suggest that introduction of PDGF-C would be a novel strategy for therapeutic angiogenesis, especially when VEGF treatment is ineffective, such as in the diabetic state.