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Role of Wall Stress-Responsive Cation Channels in the Maturation of Peripheral Blood Vessels

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Summary

Collateral arterial growth (arteriogenesis) through efficient phenotype switching of vascular smooth muscle cells (SMCs) is an endogenous compensatory mechanism for the progressive occlusion of large conductance arteries. However, why arteriogenesis is retarded during severe ischemia remains obscure. Here we found that an increased abundance of transient receptor potential canonical 6 (TRPC6) proteins in SMCs during ischemia negatively regulates arteriogenesis in mice. TRPC6 deficient mice showed improvement of peripheral blood circulation as well as walking activities after hind-limb ischemia, without affecting capillary formation and macrophage infiltration. Suppression of TRPC6 channel activity through endothelium-dependent and -independent phosphorylation of TRPC6 at Thr69 promoted arteriogenesis through increasing muscular differentiation of SMCs while maintaining proliferative and migrating activities. Marked TRPC6 phosphorylation was observed in neonatal gastrocnemii, but it declined with age. The magnitude of TRPC6 phosphorylation level was well co-related with the strengths of resilience to ischemic stress among three mouse strains. These results strongly suggest that TRPC6 phosphorylation at Thr69 is a key indicator of arterial growth during ischemic arteriogenesis, and will provide a new strategy to prevent retardation of arteriogenesis after hind-limb ischemia.