Beta-catenin C-terminus inhibition reduces vascular remodeling by precluding the expression of sphingosine-1-phosphate receptor-1

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Vascular remodeling is associated with target organ damage and fatal cardiovascular events. The molecular mechanisms that control vascular remodeling are still poorly understood, limiting effective therapeutic approaches. Vascular smooth muscle cells (SMCs), in part via activation of the Wnt/β-catenin signaling pathway, contribute importantly to vascular remodeling. The β-catenin C-terminal domain is required in SMCs for artery formation during embryogenesis, but its role in vascular remodeling in adulthood is unknown. Thus, the aim of this study was to define the importance of β-catenin C-terminus in SMCs during vascular remodeling and the underlying mechanisms. We found that mice expressing a C-terminus-deficient β-catenin in SMCs show reduced vascular remodeling and decreased SMC proliferation after arterial injury. In line with these findings, we observed that treatment with E7386, a novel β-catenin C-terminus inhibitor, reduces cell proliferation of both human and mouse vascular SMCs. RNA-seq analysis revealed a downregulation of the sphingosine-1-phosphate receptor 1 (S1pr1) transcript in β-catenin C-terminus-deficient SMCs. This receptor is known to be important in vascular remodeling, but its regulation is not fully elucidated. Interestingly, we found that β-catenin interacts with the S1pr1 promoter and acts through its C-terminal domain to activate S1pr1 transcription and protein expression, resulting in enhanced SMC proliferation. Consistent with these observations, S1PR1 expression was markedly decreased in SMCs of arteries from mice lacking the β-catenin C-terminus, and re-establishing S1PR1 expression in SMCs restored vascular remodeling in those mice. Taken together, these findings identify the β-catenin C-terminal output as a novel upstream regulator of S1PR1 expression and define a functional interaction between the canonical Wnt and sphingosine-1-phosphatase signaling pathways that drives vascular remodeling after injury. Our study suggests that targeting β-catenin C-terminus/S1PR1 axis could provide a therapeutic strategy to reduce vascular remodeling and cardiovascular disease.

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