Circulation丨南模生物助力广州妇儿中心科研成果登上国际心脏和心血管系统研究领域顶级期刊

2020年11月19日，广州市妇女儿童医疗中心儿科研究所心血管疾病实验室邓伟豪课题组在国际心脏和心血管系统研究领域顶级杂志Circulation发表题为Circular RNA CircMAP3K5 acts as a microRNA-22-3p sponge to promote resolution of intimal hyperplasia via TET2-mediated SMC differentiation的科研论文，中心儿科研究所曾智博士为第一作者，中山大学孙逸仙纪念医院心外科和耶鲁大学心血管研究中心作为合作单位同时参与研究。南模生物为该研究构建了miR-22-KO 小鼠模型。

动脉粥样硬化是导致冠心病全球发病率和死亡率的主要原因。 当前，许多干预措施用于治疗动脉粥样硬化，包括气囊血管成形术，动脉内膜切除术和冠脉搭桥术。但是，这些干预措施可能会因内膜增生引起的支架术后再狭窄而失败。已有研究证实了TET2在动脉粥样硬化和血管再狭窄中的关键作用，因此阐明TET2调节血管损伤和修复的机制非常重要 。

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Circular RNA CircMAP3K5 Acts as a MicroRNA-22-3p Sponge to Promote Resolution of Intimal Hyperplasia via TET2-Mediated SMC Differentiation

Zhi Zeng, Luoxing Xia, Shunyang Fan, Junmeng Zheng, Jinhong Qin, Xuejiao Fan, Yunfeng Liu, Jun Tao, Yingying Liu, Kang Li, Zhenwei Ling, Yun Bu, Kathleen A. Martin, John Hwa, Renjing Liu, and Wai Ho Tang

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Abstract

Background: Aberrant expression of circular RNA (CircRNA) contributes to human diseases. CircRNAs regulate gene expression by sequestering specific microRNAs (miRNAs). In this study, we investigated whether CircMAP3K5 could act as a competing endogenous miR-22-3p sponge and regulate neointimal hyperplasia.

Methods: CircRNA profiling from genome-wide RNA sequencing data was compared between human coronary artery smooth muscle cells (HCASMCs) treated with or without PDGF. Expression levels of circular MAP3K5 (CircMAP3K5) was assessed in human coronary arteries from autopsies on patients with dilated cardiomyopathy (DCM) or coronary heart disease (CHD). The role of CircMAP3K5 in intimal hyperplasia was further investigated in mice with AAV9-mediated CircMAP3K5 transfection. SMC-specific Tet2 knockout mice and global miR-22-3p knockout mice were used to delineate the mechanism by which CircMAP3K5 attenuated neointimal hyperplasia using the femoral arterial wire injury model.

Results: RNA sequencing demonstrated that treatment with PDGF-BB significantly reduced expression of CircMAP3K5 in HCASMCs. Wire-injured mouse femoral arteries and diseased arteries from CHD patients (where PDGF-BB is increased) confirmed in vivo downregulation of CircMAP3K5 associated with injury and disease. Lentivirus-mediated overexpression of CircMAP3K5 inhibited the proliferation of HCASMCs. In vivo AAV9-mediated transfection of CircMap3k5 specifically inhibited SMC proliferation in the wire-injured mouse arteries, resulting in reduced neointima formation. Using a luciferase reporter assay and RNA pull-down, CircMAP3K5 was found to sequester miR-22-3p, which in turn inhibited the expression of TET2. Both in vitro and in vivo results demonstrate that the loss of miR-22-3p recapitulated the anti-proliferative effect of CircMap3k5 on VSMCs. In SMC-specific Tet2 knockout mice, loss of Tet2 abolished the CircMap3k5-mediated anti-proliferative effect on VSMCs.

Conclusions: We identify CircMAP3K5 as a master regulator of TET2-mediated VSMC differentiation. Targeting the CircMAP3K5/miR-22-3p/TET2 axis may provide a potential therapeutic strategy for diseases associated with intimal hyperplasia including restenosis and atherosclerosis.

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该研究在小鼠体内的血管特异性过表达CircMAP3K5，利用miR-22-KO ，SMC-Tet2-KO等小鼠模型进一步实验证明了CircMAP3K5对血管新生内膜形成的明显抑制作用，为新生内膜形成提供新的治疗手段，为后续临床研究提供了理论依据。

血管内膜增生在支架术后再狭窄的发生发展中扮演着重要角色，同时也是动脉粥样硬化、静脉移植、高血压等疾病的共同病理生理学基础。因此，深入了解血管新内膜形成的机制有助于发现新的有效靶点，进而开发更有效地靶向治疗，具有重要的临床意义。

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