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Mobilization and differentiation of multipotent nestin+ stem cells during arterial remodeling

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Multipotent mesenchymal stem cells (MSCs) can mobilize into the circulating blood under many circumstances, such as serious disease, injury, or stress. MSCs then migrate to the remodeling sites and differentiate toward distinct lineages of cells. However, the primary factors and signaling pathways that control MSCs recruitment to the injured sites and their commitment/differentiation into lineage-specific local cells are largely unknown. Here we show that active TGFβ controls the mobilization of MSCs to circulating blood in response to arterial injury and their recruitment to the target sites, where the cells give rise to either endothelial cells to repair the damaged endothelium or smooth muscle cells (SMCs)/myofibroblasts contributing to intimal hyperplasia. In our animal models of arterial injury, about 50% of the neointimal cells were derived from MSC lineages. Using an *ex vivo* cell migration assay established in our laboratory, we found that TGFβ activated from the injured vessels induces MSC migration, and this effect is mediated by Smad-MCP1 signaling cascade. Moreover, active TGFβ produced from the injured vessels also activated RhoA-ROCK signaling in MSCs and induced their differentiation to SMC/myofibroblastic neointimal cells. Inactivation of ROCK maintains the stemness of MSCs and their differentiation capacity to endothelial cells. Importantly, treatment of the arterial injured mice with ROCK inhibitor promoted re-endothelialization and inhibited neointima formation of the vessels. Thus, pharmacotherapies that inhibit RhoA-ROCK signaling offer a new therapeutic target for treating cardiovascular disease by promoting endothelium repair and inhibiting pathological intimal hyperplasia.

Biography

Mei Wan is an Associate Professor of the Center for Musculoskeletal Research, Department of Orthopaedic Surgery at Johns Hopkins University School of Medicine. She obtained her PhD in Pathophysiology at Hebei Medical University in 1997. Her research for the past 17 years focuses on characterizing the mechanisms by which bone marrow mesenchymal stem cells (MSCs) are regulated in various physiological and pathological conditions such as bone remodeling, cancer development, vascular disorders, and tissue repair/remodeling. At earlier years of her career, she demonstrated that the role of proteosome degradation pathway in the regulation of TGFβ signaling. She also identified the central mechanism through which parathyroid hormone stimulates bone formation, which had been the major unresolved question in bone field. In recent years, she found that active TGFβ can be released from tissue in response to perturbations to the local environment such as bone remodeling (*Nat. Med. 2009, Cell Stem Cell 2011*), arterial injury (*Stem Cells 2012, Stem Cell Dev. 2014*), and lung injury (*J. Immunol. 2014*). The released active TGFβ stimulates the migration of MSCs to participate in tissue repair or remodeling. Currently, she is an Editorial Board Member for *Journal of Bone and Mineral Research and Bone Research*.

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