

TRPC6-Mediated Zn^{2+} Influx Negatively Regulates TGF- β -Induced Cell Differentiation: Pathophysiological Implications

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(TRPC6 を介した亜鉛イオン流入は TGF- β 誘導性の細胞分化を負に制御する : その病態生理学的意義の解明)

区 分 : 甲

論 文 内 容 の 要 旨

Cardiovascular diseases (CVDs) are characterized by complex pathological processes involving inflammation, fibrosis, and remodeling. Transforming growth factor- β (TGF- β) participates in these processes as a key molecular player. The hyperactivity of TGF- β in response to stress causes excessive extracellular matrix (ECM) deposition and changes in its mechanical properties, while stiffened ECM further triggers vascular smooth muscle disorder and multiple organ fibrosis.

Vascular smooth muscle cells (VSMCs) plasticity, characterized by reversible phenotypic switching between contractile and synthetic states in response to environmental stimuli, plays a central role in vascular homeostasis and pathological vascular remodeling. Our previous work demonstrated that suppression of canonical transient receptor potential 6 (TRPC6) channel-mediated cation influx preserves the contractile phenotype of VSMC and promotes the blood flow recovery in murine hindlimb ischemia models. We also established that TRPC6 activation mobilizes Zn^{2+} , which subsequently enhances cardiac contractility and attenuates pathological remodeling. The existing studies on the role of TRPC6 in vascular pathologies mainly focus on its mediated Ca^{2+} influx, while the role of TRPC6-mediated Zn^{2+} therein has been rarely mentioned. Therefore, it was studied whether TRPC6-mediated Zn^{2+} influx was involved in the phenotype switching of VSMC and vascular remodeling in the first section. Rat aortic smooth muscle cells (RAoSMCs) stably expressing wild type (WT) and Zn^{2+} only impermeable TRPC6 (KYD) mutant were established. I found that pharmacological TRPC6 activation by 2-[4-(2,3-dimethylphenyl)piperazin-1-yl]-N-(2-ethoxyphenyl)acetamide (PPZ2) prevented the TGF- β -induced reduction in the intracellular Zn^{2+} amount and contractile differentiation in RAoSMCs (WT), but failed in RAoSMCs (KYD). Moreover, treatment of mice with PPZ2 attenuated the progression of vascular remodeling caused by chronic angiotensin II infusion. These results suggested that TRPC6-mediated Zn^{2+} influx negatively regulated the TGF- β -induced contractile differentiation of VSMC and the progression of vascular remodeling in rodents (Figure 1).

Cardiac fibroblasts (CFs) are the essential cell type for the maintenance of the structural integrity and normal function of the heart tissues, but these changes are also associated with adverse pathological changes related to cardiac fibrosis. TGF- β stimulates CFs to differentiate into myocardial fibroblasts, eventually leading to cardiac

fibrosis characterized by excessive ECM deposition. Mitochondria as an important intracellular Zn^{2+} pool, the changes in its ultrastructure and function mediated by Zn^{2+} are related to fibrosis. Several studies provided evidence that the restoration of intracellular Zn^{2+} levels appears to be essential for the therapeutic response in fibrosis. However, the association among TRPC6-mediated Zn^{2+} and TGF- β -induced CFs differentiation as well as cardiac fibrosis is unclear. Therefore, I further investigated whether TRPC6-mediated Zn^{2+} influx modulated TGF- β -induced CFs differentiation and explored the underlying mechanisms. In the second section, I revealed that the increase in Zn^{2+} influx dependent on TRPC6 activation underlied prevention of cardiac fibrosis. In addition, results indicated that the inhibitory effect of Zn^{2+} on CFs differentiation was partially achieved by maintaining the redox homeostasis of cellular mitochondria (Figure 2).

Collectively, these findings identified TRPC6-mediated Zn^{2+} influx as a crucial negative regulator of TGF- β -induced pathological VSMC differentiation and differentiation of CFs to myofibroblasts. The maintenance of intracellular Zn^{2+} levels dependent on TRPC6 activation, particularly within mitochondria, alleviated the vascular remodeling and cardiac fibrosis.

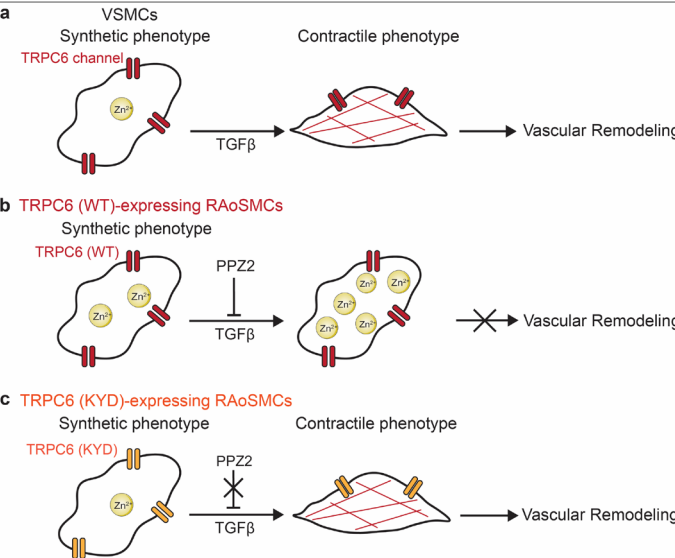


Figure 1. Schema of the role of TRPC6-mediated Zn^{2+} influx in negative regulation of TGF- β -induced VSMC contractile differentiation and vascular remodeling

(a) TGF- β promotes VSMC contractile differentiation, which further drives vascular remodeling. (b) Activation of TRPC6 channel by PPZ2 suppresses TGF- β -induced contractile differentiation in TRPC6 (WT)-expressing RAOsMCs. (c) This effect is abolished when TRPC6 Zn^{2+} permeability is inhibited.

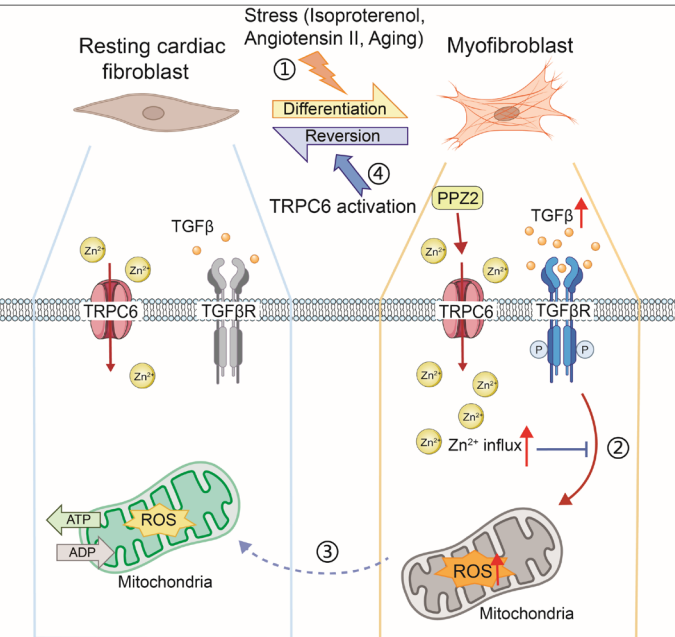


Figure 2. Schema of the role of TRPC6-mediated Zn^{2+} influx in the prevention of cardiac fibrosis by maintaining redox homeostasis

Various stresses (isoproterenol, angiotensin II, aging) induce cardiac fibroblast to differentiate into myofibroblast (1). TGF- β induces excessive generation of mitochondrial ROS in myofibroblast (2). TRPC6-mediated Zn^{2+} influx alleviates the excessive generation of ROS induced by TGF- β (3). Pharmacological TRPC6 activation by PPZ2 reverses TGF- β -induced cardiac fibroblast differentiation (4).