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Valsartan ameliorates tacrolimus-induced vascular injury via cellular senescence

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Objectives : To understand the underlying mechanisms of CNI-induced renal vascular injury and hypertension.
Methods : Changes in mouse arterial blood pressure (BP) were monitored under anesthesia via a pressure transducer attached to a carotid artery cannula. BP in conscious mice was measured by a noninvasive tail-cuff system. Microperfusion was used to assess the contractile and dilatory function of renal afferent arterioles (Af-Art).
Results : Long-term administration of Tac lead to the activation of renin-angiotensin system (RAS). Tac-induced vascular remodeling of renal arterioles could be rescued by valsartan, an AT_1R inhibitor. In mice treated with Tac, vasoconstriction in response to angiotensin II was markedly enhanced , which was abolished by valsartan. Notably, the expression of senescence-related biomarkers was upregulated in mesenteric and renal resistance arteries from Tac-treated mice. However, Tac co-administration with valsartan or ABT-263, a senolytic agent, rescued Tac-induced vascular injury and hypertension. Moreover, valsartan and ABT-263 also alleviated Tac or Ang II induced cellular senescence in vitro.
Conclusions : Long-term administration of Tac induces renal vascular injury and hypertension, which is rescued by valsartan, possibly via the inhibition of cellular senescence.

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