The PAR-1 antagonist Vorapaxar protects against kidney injury and tubulointerstitial fibrosis in the progression of AKI to CKD

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Background

Protease-activated receptor-1 (PAR-1) has been reported as a coagulation regulator in the pathophysiology of AKI. Beyond its function in normal haemostasis, abberant PAR-1 signaling may lead to the development of tubulointerstitial fibrosis, and subsequently CKD.

Methods

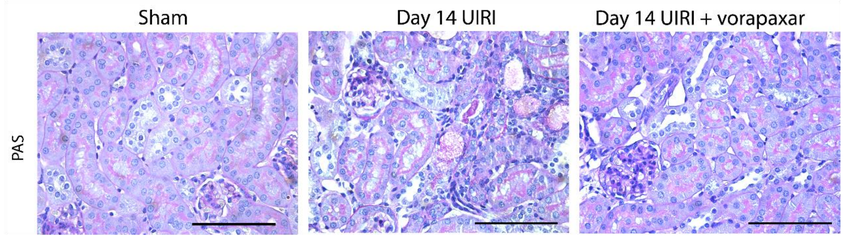
We investigated whether the administration of PAR-1 antagonist vorapaxar, an FDA-approved drug for reducing thrombotic cardiovascular events, has renoprotective effect on a robust kidney fibrotic murine model of chronic kidney disease at 14 days after unilateral ischemia reperfusion injury (UIRI), as well as in hypoxia-induced cultured rat proximal tubular epithelial cells (NRK-52E) under a condition of 1% O2, 5% CO2 and 95% humidity .

Funding

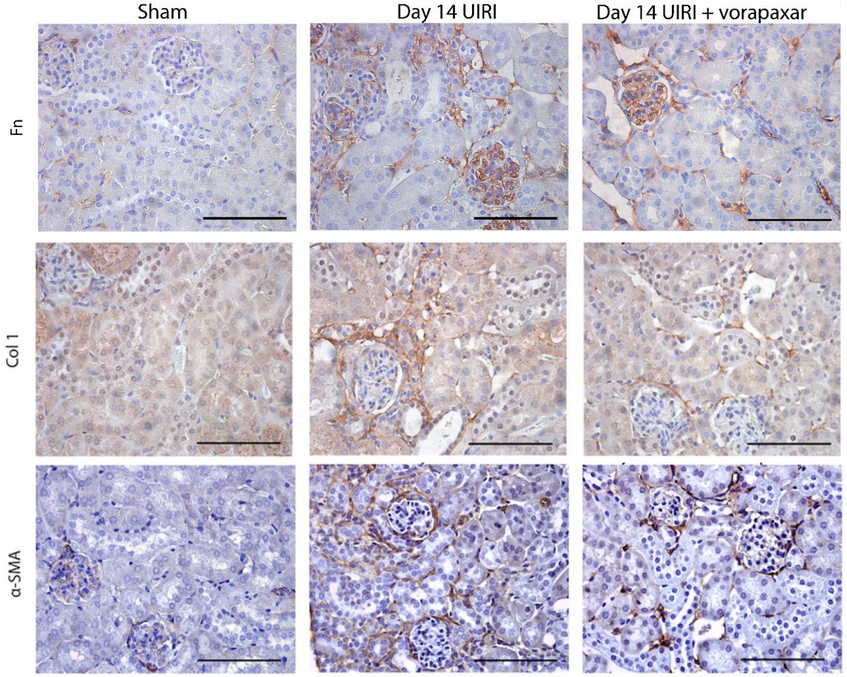
Health and Medical Research Fund (HMRF) of Hong Kong (grant no. 05163596), Research Grants Council of Hong Kong (Collaborative Research Fund, grant no. C7018-16G), and Hong Kong Society of Nephrology/HK Kidney Foundation Research Grant 2018.

Results

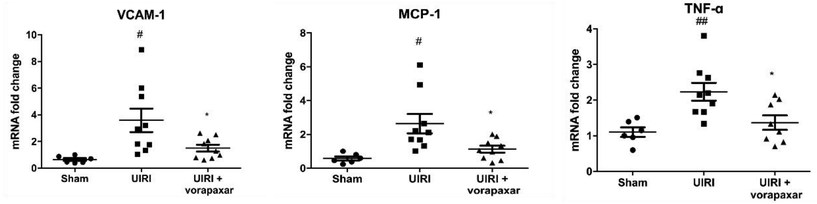
1. Vorapaxar ameliorated kidney injury in UIRI kidneys.



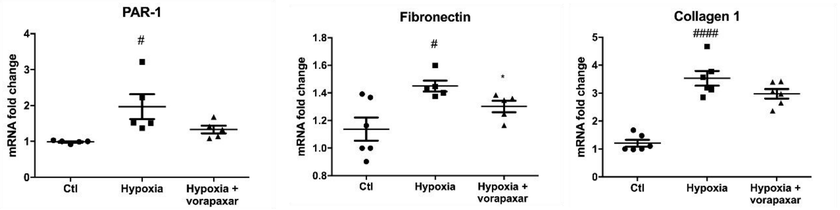
2. Vorapaxar alleviated kidney fibrotic changes in UIRI mice.



3. IR-induced endothelial cell activation and inflammation were reduced by vorapaxar treatment.



4. PAR-1 expression was upregulated during hypoxic condition and associated with ECM protein production in NRK-52E cells.



Conclusion

Vorapaxar diminishes UIRI-induced renal fibrosis, and protects against tubular injury during the process of AKI to CKD. Targeting PAR-1 for the treatment of CKD in human warrants further investigation.