Nature Reviews Nephrology **11**, 198 (2015); published online 24 February 2015; doi:10.1038/nrneph.2015.24

HYPERTENSION

Lymphocyte adaptor protein puts the 'brakes' on hypertension

A recent report by Meena Madhur and colleagues describes a role for lymphocyte adaptor protein (LNK; also known as SH2B3) in angiotensin II (Ang II)-induced hypertension and associated vascular and renal dysfunction. LNK functions as a negative regulator of cytokine signalling and cellular proliferation, but prior to this latest study, how the protein might affect blood pressure (BP) was unknown.

"Our interest in LNK was based on genome-wide association studies that found polymorphisms in *LNK* to be strongly associated with hypertension as well as autoimmune and cardiovascular disorders," explains Madhur. "We therefore decided to investigate the role of LNK in hypertension using *Lnk*$^{-/-}$ mice."

The researchers first determined the effect of Ang II infusion on BP in their mouse model. Infusion of 490 ng/kg/min Ang II for 14 days resulted in a 35 mmHg increase in systolic BP and profound hypertension (>200 mmHg) in *Lnk*$^{-/-}$ mice compared to wild-type. Moreover, infusion of 140 ng/kg/min Ang II—a dose that does not raise BP in wild-type mice—resulted in BPs approaching 180 mmHg in *Lnk*$^{-/-}$ animals.

> "...LNK might serve as a therapeutic target in the future treatment of hypertension"

Renal and vascular infiltration of immune cells was assessed in *Lnk*$^{-/-}$ and wild-type mice using flow cytometry and immunohistochemistry. At baseline, kidneys from *Lnk*$^{-/-}$ mice showed increased T-cell infiltration in the renal cortex and medulla compared to wild-type, despite no difference in BP. This effect was also observed in the aorta, and was exacerbated in both by Ang II exposure.

The researchers next transplanted bone marrow from *Lnk*$^{-/-}$ mice into irradiated wild-type mice, and vice versa, to determine in which cell types loss of *Lnk* contributes to hypertension. "These experiments showed that loss of *Lnk* in hematopoietic cells predisposes mice to develop aggravated hypertension, renal inflammation and renal dysfunction," explains Madhur. "This effect was mediated in part through elevated production of interferon–γ." Replica analyses in *Lnk*$^{+/-}$ mice indicated a gene-dosage effect, demonstrating that loss of one allele of *Lnk* can increase BP and promote renal injury.

The researchers hope to use the *Lnk*$^{-/-}$ model to further explore the role of the immune system in cardiovascular and renal disorders. "Patients with certain autoimmune disorders have elevated risk of cardiovascular disease," says Madhur. "Our study provides a 'LNK' between inflammation and cardiovascular disease. Furthermore, LNK might serve as a therapeutic target in the future treatment of hypertension."

Jessica K. Edwards

Original article Saleh, M. A. *et al.* Lymphocyte adaptor protein LNK deficiency exacerbates hypertension and end-organ inflammation. *J. Clin. Invest.* doi:10.1172/JCI176327