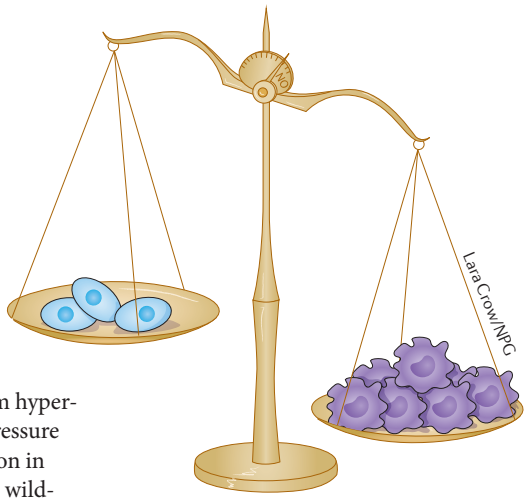
Nature Reviews Nephrology | Published online 19 Jan 2016; doi:10.1038/nrneph.2016.1

HYPERTENSION

IL-1 receptor-induced sodium reabsorption in hypertension



Hypertension is recognized to be mediated, at least in part, by inflammatory processes; however, the mechanisms by which immune cells regulate hypertension remain unclear. New findings suggest that IL-1 can potentiate hypertensive responses by stimulating the activity of the renal sodium transporter NKCC2 through IL-1-receptor (IL-1R1)-mediated suppression of nitric oxide (NO). The researchers say that translational testing of IL-1R1 blockade could lead to new immunomodulatory therapies to lower blood pressure in patients with resistant hypertension.

> “IL-1R1 activation drives salt retention in the kidney by enhancing the activity of the NKCC2 sodium transporter”

Steven Crowley and colleagues initiated their study following the observation that IL-1 levels were elevated in the kidneys of hypertensive mice. “To investigate if activation of IL-1R1 promoted hypertension we subjected wild-type mice and IL-1R1-knockout mice to hypertension by removing one kidney to sensitize the animal to salt followed by chronic infusion of angiotensin II,” explains Crowley. “We believe this model is relevant to humans because medicines that block the main receptor for angiotensin lower blood pressure in the majority of patients with hypertension.”

The researchers found that mice lacking IL-1R1 were partially protected from hypertension, with lower blood pressure and reduced sodium retention in knockout mice compared to wild-type mice following angiotensin II infusion. “We interpreted these findings to mean that IL-1R1 activation exacerbates angiotensin-dependent salt retention and hypertension,” explains Crowley. “Our ancillary studies suggested that IL-1R1 activation drives salt retention in the kidney by enhancing the activity of the NKCC2 sodium transporter.”

Bioavailability of NO, which suppresses NKCC2 activity and thereby stimulates renal sodium excretion, was enhanced in IL-1R1-knockout mice compared to wild-type mice, and disruption of NO generation attenuated the protective effect of IL-1R1 deletion on angiotensin II-induced hypertension. The researchers also found increased numbers of NO-generating macrophages concurrently with fewer immature myeloid cells in the kidneys of IL-1R-knockout mice, suggesting that IL-1R1 activation potentiates angiotensin II-induced hypertension by suppressing the differentiation of progenitor myeloid cells to NO-producing macrophages, leading to increased NKCC2 activity and sodium reabsorption.

Crowley says that future research will focus on understanding more precisely which cells in the kidney or the circulation contribute to hypertension by responding to IL-1. “We would also like to explore the relevance of this signalling pathway to human hypertension,” he adds.

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ORIGINAL ARTICLE Zhang, J. *et al.* Interleukin-1 receptor activation potentiates salt reabsorption in angiotensin ll-induced hypertension via the NKCC2 co-transporter in the nephron. *Cell. Metab.* http://dx.doi.org/10.1016/j.cmet.2015.11.013