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HYPERTENSION

Haematopoietic COX-2 in salt-sensitive hypertension

Inhibition of the cyclooxygenase–prostaglandin (COX–PG) pathway has been linked to salt-sensitive hypertension. New findings now demonstrate a key role for haematopoietic cells in this process. "Our studies indicate that inhibition of the COX–PG pathway in haematopoietic cells leads to salt-sensitive hypertension through several mechanisms, including renal macrophage and T-cell infiltration with altered macrophage polarization; increased activity of the renal sodium chloride cotransporter (NCC); and aberrant skin lymphangiogenesis," explains researcher Raymond Harris.

The effect of COX-2 inhibition on blood pressure has been previously attributed to inhibition of intrinsic renal COX-2 activity. "Our previous studies had shown that high salt intake increases COX-2 expression in the kidney medullary stroma, and preliminary data showed that salt also increases COX-2 expression in renal macrophages," says Harris. "In addition, other studies have implicated infiltrating inflammatory cells and skin macrophages in the pathogenesis of salt-sensitive hypertension."

To investigate the role of immune cells in COX-2-mediated blood pressure regulation, Harris and colleagues transplanted bone marrow from wild-type or *Cox2*$^{-/-}$ mice into syngeneic animals. Wild-type mice transplanted with bone marrow from *Cox2*$^{-/-}$ mice and fed a high-salt diet showed increased blood pressure; kidneys from these mice showed increased expression of pro-inflammatory M1 macrophages and infiltration of T-cells, and decreased expression of anti-inflammatory M2 macrophages. These effects were mimicked by treatment with a COX-2 inhibitor. Mice with macrophage-specific deletion of the major PGE_2 receptor, EP_4, also developed salt-sensitive hypertension, with aberrant macrophage polarization and increased NCC activity. Examination of skin from mice transplanted with *Cox2*$^{-/-}$ bone marrow revealed salt-dependent increases in sodium content, proinflammatory macrophages, and abnormal lymphangiogenesis.

The researchers now plan to dissect the relative contribution of skin and kidney macrophages to the development of salt-sensitive hypertension. "We also plan to investigate whether a selective EP_4 agonist might be effective in the treatment of salt-sensitive hypertension," says Harris.

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ORIGINAL ARTICLE Zhang, M.-Z. *et al.* Inhibition of cyclooxygenase-2 in hematopoietic cells results in salt-sensitive hypertension. *J. Clin. Invest.* doi:10.1172/JCI81550