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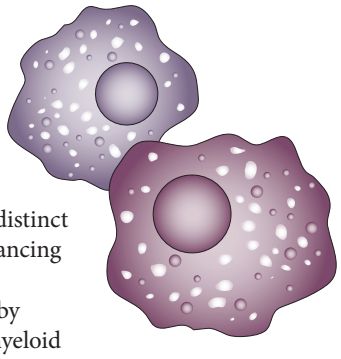
ACUTE KIDNEY INJURY

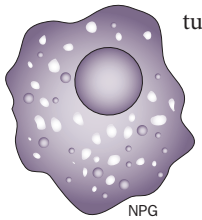
IL-34 promotes persistent ischaemia-induced AKI



Colony stimulating factor 1 (CSF-1) is central to macrophage-mediated renal repair during inflammation, but little is known about the function of IL-34, with which it shares a receptor (c-FMS). Now, data from Vicki Rubin Kelley and colleagues support a mechanism by which macrophages can promote persistent ischaemia–reperfusion (I/R)-induced acute kidney injury (AKI) that can progress to chronic kidney disease (CKD), through an IL-34-dependent pathway.

Given that CSF-1 is a mediator of kidney fate during injury, the investigators questioned whether IL-34 promoted or inhibited renal repair. They first noted that expression of IL-34 was robustly induced in renal tubule epithelial cells (TECs) acutely after I/R-induced injury in mice. Conversely, both IL-34 receptors (c-FMS and PTP-ζ), were maximally induced in the chronic phase after I/R. The researchers claim these findings provide the first evidence of PTP-ζ expression in the kidney.

The investigators next evaluated the phenotype of *Il-34*$^{-/-}$ and wild-type mice following I/R-induced AKI and CKD. Following I/R, wild-type mice exhibited dramatically decreased kidney weight, increased tubular pathology, leucocyte infiltration in the interstitium, and elevated loss of tubules compared to *Il-34*$^{-/-}$ mice. In addition, kidney injury molecule 1 was more robustly expressed in wild-type TECs than in *Il-34*$^{-/-}$ TECs during the acute phase after I/R. The researchers propose that these data implicate IL-34 in the initiation of macrophage-mediated tubule injury.



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"IL-34 generated by TECs, promotes macrophage-mediated TEC destruction during AKI that worsens to subsequent CKD by two distinct mechanisms: first by enhancing intra-renal macrophage proliferation and second by elevating bone marrow myeloid cell proliferation, thereby increasing circulating monocytes that are drawn into the kidney by chemokines," explains Kelley. "Furthermore, we found that CSF-1 expression in TECs does not compensate for the absence of IL-34, as *Il-34*$^{-/-}$ and wild-type TECs showed similar levels of CSF-1."

The researchers then assessed the expression of IL-34 in engrafted and rejected human kidney tissue within the first 6 months after transplantation. The expression of IL-34, c-FMS, and PTP-ζ, and the number of macrophages and neutrophils, were upregulated in engrafted and rejected kidneys compared to untransplanted donor kidneys, and increased further with advancing renal inflammation.

"Our study provides the first causal evidence that IL-34 mediates inflammation, and has an impact on AKI and CKD," claims Kelley. "Moreover, our findings are highly translational, as I/R is an inevitable consequence of the kidney transplantation procedure."

The researchers now plan to determine the effects of blocking IL-34 expression in the kidney and circulation. They hope this strategy might provide a suitable therapeutic approach for patients with AKI, CKD, and other forms of macrophage-mediated tissue injury.

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Original article Baek, J. H. *et al.* IL-34 mediates acute kidney injury and worsens subsequent chronic kidney disease. *J. Clin. Invest.* doi:10.1172/JCI81166