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Macrophages drives fibrotic response via chemokine receptor Cxcr4 in a mouse model of kidney fibrosis

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Background: Renal fibrosis is the final common pathway for virtually every type of chronic kidney disease (CKD). Fibrosis is a result of the healing response that follows tissue inflammation that may be the result of simple wounding or a chronic inflammatory disease of an internal organ. Chronic renal inflammation ultimately leads to progressive tissue injury and renal scarring. Renal fibrosis consists of glomerular/vascular sclerosis and tubulointerstitial fibrosis. The histological picture of tubulointerstitial fibrosis is characterized by tubular atrophy and dilatation, interstitial leukocyte infiltration, fibroblast accumulation, vascular rarefaction and continuous deposition of matrix protein. A prominent feature in the biopsy specimens of CKD patients is that of significant macrophage M (Φ) infiltration that correlates directly with interstitial fibrosis and inversely with prognosis. Cxcr4 is a ubiquitously expressed G-protein coupled chemokine receptor that has a sole ligand, stromal derived factor-1, Sdf1.It is known for its role in stem cells homing to bone marrow and trafficking of immune cells. Cxcr4 is expressed at a low level in an adult kidney but following injury the tubular Cxcr4 expression is upregulated. We hypothesized that chronic upregulation of Cxcr4 will contribute to progression of fibrosis and interrupting this pathway will ameliorate the response.

Methods: Adult 8 weeks old male C57BL6/J mice underwent unilateral ureteral obstruction (UUO). Mice were administered a) FDA approved Cxcr4 antagonist AMD3100 (5 or 10 mg/kg/12hr by i.p.) or b) vehicle beginning on the day of UUO until one day before sacrifice. Kidneys were processed for Trichrome staining, (for fibrosis scoring); RNA isolation to determine the mRNA expression of various fibrotic markers by qRT-PCR and for macrophage analysis by FACS. To distinguish whether tubular or macrophage-derived Cxcr4 was essential for fibrotic response, mice lacking Cxcr4 in the collecting duct or macrophages were generated by Cre-loxP approach and UUO-mediated fibrosis was assessed.

Results: Following UUO, there was a progressive increase in the total kidney Cxcr4 expression. Quantitative mRNA analysis of FACS-sorted tubular cells and macrophages from UUO kidneys showed significant increase in Cxcr4 in both compartments. Administering 10mg/kg of AMD3100 reduced fibrosis score by ~40% compared to vehicle-treated mice. AMD3100-treated mice also had ~25% fewer macrophages and fibrocytes. Ablating Cxcr4 in collecting duct by Hoxb7Cre had no impact on UUO-mediated fibrosis. However, Cxcr4 ablation in macrophages by *LysMCre* resulted in significantly less fibrosis following 9 days of UUO. Furthermore, deleting Cxcr4 from macrophages reduced their pro-fibrotic gene expression. More importantly, mice in which macrophages lacked Cxcr4 had significantly less TGFb1 and *Inegrinb1mRNA* expression in their UUO kidneys. This is a novel finding. *In-vitro*, Cxcr4 activation in bone marrow-derived macrophages (BMMs) induced TGFb1 and *Integrinb1* mRNA expression. Furthermore, stimulating Cxcr4 activated STAT3, STAT5 signaling pathways in BMMs. *In-vivo*, AMD-treated mice showed decreased STAT3 activation, providing a potential mechanism by which Cxcr4 mediated signaling might be promoting fibrosis. Finally, analysis of peripheral mononuclear cells from CKD patients revealed several-fold upregulated Cxcr4 expression. Its significance is being determined.

Conclusion: Cxcr4 pathway is activated following UUO and may contribute towards the progression of fibrosis by modulating macrophage phenotype. Intervening this pathway or its downstream effectors may provide new therapeutic targets.

Biography

Anil Karihaloo completed his post-doc fellowships at the University of Michigan, Harvard Medical School and Yale University. Currently he is appointed as an Assistant Professor at the Yale University School of Medicine. His research focus has been on kidney fibrosis. He has been a recipient of many awards and also serves as a reviewer for American Journal of Physiology, Journal of American Society of Nephrology etc. He has published several articles in reputed international journals.

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