THE KOREAN SOCIETY OF NEPHROLOGY
APCN & KSN 2024
June 13(Thu) - 16(Sun), 2024 Coex, Seoul, Korea
APSN
Promoting Sustainable Kidney Health: The Asia-Pacific and Beyond

Abstract Submission No.: A-1080

Flt3L from Tubular Epithelial Cells Drives Dendritic Cell Responses in Acute Kidney Injury: A Protective Mechanism for Novel Immunotherapeutic Strategies

Na Li[1], Zhihua Zheng[1], Zhizhuang Joe Zhao[3], Yun Chen[4]
[1]Department of Internal Medicine-Nephrology, Sun yat-sen unveristy, China
[2]Department of Scientific Research Center, Sun yat-sen University, China
[3]Department of Emergency and Disaster Medical Center, Sun yat-sen University, China
[4]Department of Department of Pathology, University of Oklahoma Health Sciences Center, United States

Objectives : Dendritic cells (DC) accumulate in the kidneys of patients with acute kidney injury (AKI), but the Fms-like tyrosine kinase receptor 3 ligand (Flt3L)-dendritic cell axis is poorly defined in kidneys with AKI.
Methods : 1) Blood specimens and urine collected from two patient cohorts: a) patients with pre-renal AKI. b) patients with acute myocardial infarction (AMI) developed with or without AKI. 2) AKI mouse model constructed by IR surgery. 3) Mice treated with rFlt3L or Flt3 inhibitor gilteritinib.
Results : We observed a notable increase in serum FLT3L levels in patients with AKI. This increase was particularly pronounced for acute myocardial infarction (AMI) patients with AKI, rather than those without AKI or healthy individuals. This elevation in serum FLT3L correlated significantly with increases in Creatinine (CREA) and Blood Urea Nitrogen (BUN) within 48 hours post-admission. In our experimental models, we observed a significant upregulation of Flt3L in both wild-type (WT) and T cell-deficient ($Tcra^{KO}$) mice following IRI-induced AKI, suggesting alternative mechanisms beyond T cell contribution. Notably, this elevation in Flt3L was observed at both the protein and mRNA levels, predominantly in the proximal tubules of kidneys damaged by IRI and in HK-2 cells subjected to hypoxia-reoxygenation in vitro, showing the key role of tubular expression in this context. Treatment with recombinant Flt3L (rFlt3L) in WT mice increased kidney type 1 conventional DC (cDC1) and $CD64^{+}$DC populations, correlating with reduced tubular injury. Conversely, treatment with Gilteritinib, an inhibitor targeting FLT3 signaling, reduced these DC populations, exacerbated tubular injury. Similarly, $Irf8^{KO}$ mice, characterized by deletion of kidney cDC1s, showed worsened kidney injury, not mitigated by rFlt3L supplementation.
Conclusions : These findings suggest that Flt3L, upregulated in both human and mice during IRI-AKI and produced by tubular epithelial cells, promotes accumulation of protective dendritic cell subsets, thereby attenuating AKI severity.