Fibrosis after Ischemic Injury by Decreased Macrophage Recruitment and Activation," in Vol. 32, Iss. 5, on pages 1037–1052.

Zhenyu Liu and Jingbo Zhang

Department of Nephrology, Key Laboratory for the Prevention and Treatment of Chronic Kidney Disease of Chongqing, Chongqing Clinical Research Center of Kidney and Urology Diseases, Xinqiao Hospital, Army Medical University (Third Military Medical University), Chongqing, People's Republic of China

Authors' Reply

We appreciate Liu and Zhang's interest in our recent study. We agree that, given previous studies by Lassen et al.[1] and Lorenz et al.,[2] our findings that selective myeloid deletion of interferon regulatory factor 4 (IRF4) decreased development of tubulointerstitial fibrosis[3] after ischemic kidney injury were somewhat unexpected. However, there are two crucial differences between our study and the two previous studies. Whereas we only deleted IRF4 expression in myeloid cells, both Lassen et al.[1] and Lorenz et al.[2] used mice with global IRF4 deletion, and IRF4 is also expressed in cells of nonmyeloid lineage.[4] In addition, we used a model of moderate kidney ischemia, whereas the ischemic injury in the previous studies was more severe. Therefore, we agree with Liu and Zhang that global IRF4 deletion and a more proinflammatory milieu may overcome the migratory defect in IRF4−/− myeloid cells and lead to persistent renal macrophage activation and subsequent fibrosis. Whether or not myeloid IRF4 deletion is deleterious in other models of CKD is an area of ongoing study in our laboratory.

DISCLOSURES

FUNDING

REFERENCES

1. Lassen S, Lech M, Römmele C, Mittruecker HW, Mak TW, Anders HJ: Ischemia reperfusion induces IFN regulatory factor 4 in renal dendritic cells, which suppresses postischemic inflammation and prevents acute renal failure. J Immunol 185: 1976–1983, 2010
2. Lorenz G, Moschovaki-Filippidou F, Würf V, Metzger P, Steiger S, Batz F, et al.: IFN regulatory factor 4 controls post-ischemic inflammation and prevents chronic kidney disease. Front Immunol 10: 2162, 2019
3. Sasaki K, Terker AS, Pan Y, Li Z, Cao S, Wang Y, et al.: Deletion of myeloid interferon regulatory factor 4 (Irf4) in mouse model protects against kidney fibrosis after ischemic injury by decreased macrophage recruitment and activation. J Am Soc Nephrol 32: 1037–1052, 2021
4. Huber M, Lohoff M: IRF4 at the crossroads of effector T-cell fate decision. Eur J Immunol 44: 1886–1895, 2014

Raymond C. Harris and Ming-Zhi Zhang
Vanderbilt University, Nashville, Tennessee

Need for a Validation Study before Using the Two-Step Algorithm for dd-cfDNA to Screen for Acute Rejection

The study by Bunnapradist et al.[1] proposes using a two-step algorithm threshold for donor derived cell free DNA (dd-cfDNA) to increase sensitivity for detection of acute rejection. Although this hypothesis is both tenable and biologically plausible, we have concerns if this study allows for any rigorously derived conclusions. Of the 41 patients in the study, 16 had (for cause) biopsies and 9 had biopsy-proven rejections. The new algorithm detected all nine acute rejections. Even though pre-ordained separate cutoffs were utilized, this is the first study to test this algorithm and thus must be considered as discovery and merely the first of many steps in biomarker assessment and ultimately utilization.[2] In addition, the improved test performance was accompanied by large confidence intervals and thus has a high risk of type 1 error due to the small sample size.[3] Given that many of the rejections were severe, it is unclear if this algorithm would retain this performance in the general transplant population.

The main challenge now will be conducting an adequately powered validation study upholding these results.[2] This can be difficult given the low prevalence of acute

Correspondence: Dr. Aditi Gupta, Associate Professor of Medicine, Division of Nephrology and Hypertension, Department of Internal Medicine, University of Kansas Medical Center, 3901 Rainbow Blvd, Kansas City, KS 66160. Email: agupta@kumc.edu

Correspondence: Dr. Raymond C. Harris, Vanderbilt University, Nashville, TN. Email: ray.harris@vumc