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

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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

R.C. Harris reports having consultancy agreements with, and ownership interest in, Bayer; receiving research funding from Bayer; serving on the Bayer Scientific Advisory Board; and having patents and inventions relating to the eNOS db/db mouse.

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See related letter to the editor, "Heterogenous Role of IRF4 in Kidney Fibrosis," on pages 2971–2972, and original article, "Deletion of Myeloid Interferon Regulatory Factor 4 (Irf4) in Mouse Model Protects against Kidney Fibrosis after Ischemic Injury by Decreased Macrophage Recruitment and Activation," in Vol. 32, Iss. 5, on pages 1037–1052.

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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

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