KIDNEY DISEASE

Comment on “Nuclear receptor PXR targets AKR1B7 to protect mitochondrial metabolism and renal function in AKI”

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The nuclear pregnane X receptor may not protect against ischemia/reperfusion-induced acute kidney injury in mice.

In a Science Translational Medicine paper by Yu et al. (1), the authors describe the pregnane X receptor (PXR) as a potential therapeutic target in acute kidney injury (AKI). This discovery is interesting due to the high morbidity and mortality of AKI and the lack of effective treatments (2). However, our group have performed similar studies but obtained different results.

PXR is a mammalian xenosensor critically involved in detoxification of chemicals and drugs (3). The structure of PXR includes an N-terminal transactivating domain, a DNA binding domain and a C-terminal ligand-binding domain (LBD). Although PXR is conserved across vertebrates, the LBD of the PXR varies considerably among species, resulting in marked differences in ligand recognition and activation profiles in response to xenobiotics and some functional differences among different species (4, 5). Increasing evidence has suggested that PXR may represent an attractive pharmacological target for treating liver diseases due to its abundance in the liver and its wide spectrum of transcriptional activities in regulating enzymes important for drug oxidation and conjugation and transporters for xenobiotic and endobiotic compounds. In addition to the liver, PXR is also expressed in the small intestine. The presence of PXR in tissues other than the liver and small intestine may also open a therapeutic window for promoting or suppressing the functions of PXR in tissues other than the liver and small intestine may also open a therapeutic window for promoting or suppressing the effects and consequences of hPXR activation, we generated a strain of transgenic mice expressing the hPXR (Fig. 1, G and H). hPXR expression was specifically driven by an endogenous mouse PXR promoter, and thus, its expression pattern naturally copied that of the deleted mouse PXR gene. We treated the hPXR transgenic mice with rifampicin, a widely used hPXR agonist. As expected, rifampicin induced PXR activation in the liver and kidneys of hPXR transgenic mice (fig. S1). After continuous oral gavage of hPXR transgenic mice with rifampicin (50 mg/kg) for 4 days, the mice were subjected to uninephrectomy, and then renal ischemia was induced for 35 min, followed by reperfusion. Rifampicin treatment showed no effect on I/R-induced renal dysfunction including no effect on elevated blood urea nitrogen (BUN) and serum creatinine (sCr) (Fig. 1I). To assess renal histological damage, hematoxylin and eosin (H&E)–stained sections of renal tissue were prepared. Mice in the sham group showed normal renal morphology, whereas the kidneys from the mice subjected to I/R renal injury exhibited typical features of acute renal tubule damage, such as the loss of the brush border, extensive necrosis of the proximal tubular cells, cells denuded of tubules, and protein cast in tubular lumens. Consistent with these findings, rifampicin treatment showed no beneficial effect on morphological and histological damage of the proximal tubules induced by renal I/R injury (Fig. 1I).

Thus, in contrast to the findings reported by Yu et al. (1), our results do not support a protective effect of PXR against I/R-induced AKI. The discrepancy between their results and ours may be because they used rats instead of mice in their renal I/R injury experiments. However, as the goal of their study and our study was to investigate PXR as a potential therapeutic target for human AKI, the results from the hPXR transgenic mice are relevant. It has long been debated whether PXR could represent a druggable target for human kidney diseases particularly nephrotoxic AKI. Activation of PXR in renal tubular cells would be expected to reduce accumulation and increase metabolism of nephrotoxic drugs, leading to decreased toxic renal injury. However, since the first cloning of hPXR (7, 10), tissue expression profiling of PXR has not shown expression of PXR in human kidneys. Neither Northern blotting nor RT-PCR has detected PXR mRNA including its several isoforms in human kidneys (7, 8). Thus, a fundamental question—that is, whether PXR

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is present in human kidneys—needs to be answered. Yu et al. (1) may have oversimplified their results by using immunostaining with an unverified antibody against hPXR to claim the presence of PXR in human kidneys and to conclude that PXR expression was decreased according to the severity of AKI. Moreover, PXR activation in patients with trauma has been shown to potentially exacerbate hemorrhagic shock–induced hepatic injury, indirectly suggesting that PXR activation may not be beneficial in ischemic tissue injury (11).

In summary, PXR in humans and rodents exhibits species-specific tissue distribution patterns and responds differently to xenobiotics and endobiotics. One should be cautious about considering the translational applications of PXR agonists for treating kidney diseases in human patients based on data from rodent studies. According to our results, we find it difficult to support the conclusion by Yu et al. (1) about the beneficial effect of PXR on ischemic renal injury. Currently, there is no solid evidence to support the use of PXR agonists for AKI in human patients.

**REFERENCES AND NOTES**


Funding: This work was supported by National Natural Science Foundation of China Grants 81970595 (to Y.G.) and 81722010 (to X.Z.), Dalian Young Star of Science and Technology 2019RQ116 (to Z.L.), and Education Department of Liaoning Province, China 507123 (to Z.L.).

Author contributions: Y.G. contributed to the conception of the study. Y.G. and Z.L. designed the experiments. Z.L., W.M., C.Z., and X.H. performed the experiments. Z.L. and W.M. analyzed and interpreted the data. Z.L. and X.Z. prepared the figures. Z.L. drafted the original manuscript. Y.G. and F.Z. revised the manuscript. All authors approved the final version of the manuscript. Competing interests: The authors declare that they have no competing interests.

Data and materials availability: All data associated with this study are present in the paper or the Supplementary Materials.

Submitted 27 May 2020
Accepted 23 April 2021
Published 12 May 2021
10.1126/scitranslmed.abd0214

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Sci Transl Med 13, eabd0214.
DOI: 10.1126/scitranslmed.abd0214