alternative enzymatic pathways such as ACE2.[1] This monocarboxypeptidase is abundantly expressed on the proximal tubule brush border, and its enzymatic activity cleaves the C-terminal amino acid from Ang I. ACE2 might, therefore, provide an alternative pathway for Ang I degradation.[1] ACE2 also converts Ang II to Ang1-7 which may bind to its own receptor and act as an endogenous inhibitor of Ang II type 1 receptor signaling.[1] ACE2 might, therefore, have a major impact on renal RAS activity.

Lastly, liver-specific AGT KO in the study by Matsusaka *et al.* had a modest beneficial effect on glomerular injury in Nep25 mice as assessed by glomerular nephrin expression.[7] In contrast, tubulointerstitial injury was exacerbated in these mice. The authors suggest that this tubulointerstitial damage may be the result of hypotension and tubular ischemia in the liver AGT KO mice. An alternative explanation, however, is that AGT synthesis by the kidney contributed to the more severe tubular dilation and increased tubulointerstitial cell proliferation in this group. Unfortunately, more definitive evidence of glomerular and tubulointerstitial injury could not be assessed in the study by Matsusaka *et al.*[7] because of the short duration of the experimental protocol. In future studies, a more comprehensive histologic evaluation of the renal phenotype may provide additional useful information on the relative impact of liver- and kidney-derived AGT on the disease process.

In summary, the findings of Matsusaka *et al.*[7] demonstrate an important role for liver-derived AGT in renal Ang II generation using a model with a severe defect in glomerular permselectivity. In this model, renal Ang II generation was dependent on AGT synthesis by the liver despite upregulation of AGT mRNA in the kidney. An important caveat to these findings is that the large defect in glomerular permselectivity in the Nep25 model likely promoted high concentrations of both AGT and renin in the tubular fluid. Given prominent expression of ACE on the proximal tubule brush border, all the components necessary for robust Ang II generation were present in the tubular lumen in this model. As a result, the contribution of renal AGT synthesis to renal Ang II generation in the kidney was minimized and probably difficult to detect. It will be critical to test the generalizability of the findings of Matsusaka *et al.*[7] in other animal models.

DISCLOSURE
The authors declared no competing interests.

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The heterogeneous mononuclear phagocyte system of the kidney

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The kidney has a diverse repertoire of cells that make up the mononuclear phagocyte system (MPS). Wu *et al.* identify a population of CD8αα$^+$CD11c$^+$MHC-II$^+$ blood precursors that display dendritic cell-like characteristics in the glomeruli. These cells show increased recruitment in a rat anti-glomerular basement membrane glomerulonephritis model and were able to attenuate disease. This study highlights the importance of the MPS in kidney disease and the need to better understand it to develop immunotherapeutics translatable to the renal patient.

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The mononuclear phagocyte system (MPS) was established in 1968 by van Furth and Cohn and can be grouped into myeloid precursors in the bone marrow, circulating blood monocytes, tissue macrophages, and dendritic cells (DCs).[1,2]

Macrophages are classically defined as tissue-resident phagocytic cells that contribute to steady-state tissue homeostasis by performing functions such as clearing apoptotic material and producing growth factors. During infection, they can also perform antimicrobial effector functions such as phagocytosis and production of toxic metabolites, chemokines, and cytokines. DCs are largely defined by the specialized functions of antigen presentation and regulation of immune effector cells.[2]

Bone marrow-derived monocytes are classically thought to differentiate into tissue macrophages, and some populations of DCs. However, recent data show that, like macrophages (M1 and M2) and DCs, monocytes have heterogeneous phenotypes in mammals, which have multiple sub-populations and display independent effector functions. Moreover, populations of monocytes may not differentiate into macrophage/DC tissue effector cells but can independently contribute to immunity.[3] Importantly, some populations of macrophages/DCs are not derived from bone marrow progenitors but spatially occupy organs and tissue, including the kidney, from embryonic origins and can proliferate *in situ*. This, along with studies demonstrating blood monocyte maturation or conversion, has increased the complexity of studying the MPS.[2,4]

Flow cytometry studies in murine, swine, and human samples have described in detail the vast range of independent (but not necessarily exclusive) and overlapping receptors and proteins that are expressed by cells of the MPS.[1–4] Although not described here in detail, these include CD43, CX3CR1, F4/80, CD11b, Ly6C (GR1), CD14, CD16, CD8, CCR2, CD68, CD103, CD206, CD11c, and MHC-II, to name but a few.

Kidney biology is no exception to this repertoire of MPS cell phenotypes (Figure 1). This may account for why many investigators, whether originating from monocyte/macrophage or DC disciplines, may have unknowingly studied the same resident kidney MPS cell, while often overlooking data from other fields. Further, the term 'resident' requires some thought; whether this cell is tissue resident from recruited precursors, proliferation, and/or trafficking is an important distinction. Currently there is no consensus on organ-specific definitions of resident cells or the characteristics of residency, either in the steady state or under inflammatory responses.

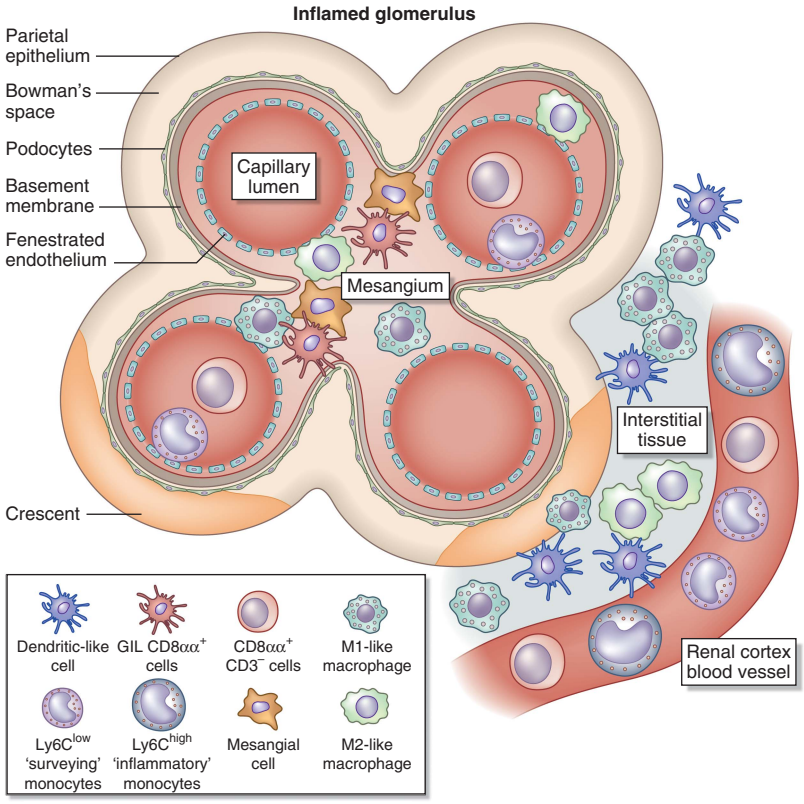

Figure 1 | Heterogeneous MPS cells of the kidney. This simplified schematic represents some of the cells that make up the mononuclear phagocyte system (MPS) in the kidney during glomerulonephritis (GN). Sub-populations of monocytes and macrophages—in particular, inflammatory M1-like macrophages or Ly6C^{high} monocytes—can be recruited both into the kidney interstitial tissue and to the glomerular endothelium. Unique subsets of M2-like macrophages and 'surveying' Ly6C^{low} monocytes that can crawl along the endothelial interface within the renal cortex in the steady state may also play a role in GN. Multiple sub-populations of DCs in specific compartments of the kidney have been identified as having effector functions in autoimmune and inflammatory GN. Wu *et al.* identify a unique precursor CD8αα$^+$CD11c$^+$MHC-II$^+$CD3$^-$ DC-like cell that circulates in peripheral blood but can enter the glomeruli (glomeruli-infiltrating leukocyte (GIL) CD8αα$^+$) in the presence of GN and can modulate disease. Further work is needed to understand their complex recruitment, retention, trafficking, and fate in GN, and, importantly, whether these cell populations are involved in human GN.

Important knowledge of the kidney MPS began in the 1980s with studies in normal animal kidneys that identified dendritic-like cells within the renal interstitium. These cells were designated antigen-presenting DCs on the basis of MHC-II expression, or resident macrophages because of F4/80 expression. Further, MHC-II-positive globular macrophages were identified in the periarterial connective tissue, glomerulus, and subcapsular regions.[5] These early studies could not predict the variety of additional functions now attributed to the kidney MPS or the fact that functional plasticity might exist depending on cues provided to the kidney MPS from the environment. This is important, as emerging data show that the tissue specificity and hence environment of the MPS is an important factor governing phenotype.[6] Moreover, the kidney MPS at steady state changes dramatically