precursors when co-cultured together ex vivo. Since then, research to understand how various microenvironments outside the BM govern the development of tissue-specific DC subtypes has become an intense and debated field of inquiry.1,4

Entering into the fray is the study by Huang et al.5 in this issue of JASN. Building on the growing appreciation that MSCs likely reside in all organs,6 Huang et al. asks whether MSCs could be isolated and propagated from normal mouse kidneys and, if so, whether these kidney-derived MSCs influence the differentiation of DCs in co-culture systems. Because little is known about which cells resident within the kidney influence the development, maintenance, and phenotype of renal DCs in steady state or during renal injury,7,8 knowledge that could be exploited for therapeutic benefit makes these questions timely.

Using a known battery of markers for murine MSCs,1 Huang et al. isolated adult mouse kidney cells, termed kidney sphere–derived cells (KSCs), with phenotypic characteristics very similar to BM-MSCs. The KSCs lack markers for leukocyte and epithelial lineages and weakly express those for mesenchymal lineages. Importantly, KSCs differentiate into different stromal cell types, a widely known potential of MSCs.

Then, using transwells to allow paracrine communication but not cell contact between the KSCs and BM cells ex vivo, the authors studied the differentiation of DCs from hematopoietic precursors. In the absence of GM-CSF, KSCs fail to induce DCs, indicating that KSCs alone do not provide competent soluble poietins for the development of DCs; however, in the presence of GM-CSF, paracrine factors released from the KSCs induce the development of GM-CSF–derived DCs with a more regulatory phenotype. This latter method of differentiation produces DCs with reduced MHC II expression, increased IL-10 production, and an inability to stimulate the proliferation of CD4+ T lymphocytes when compared with GM-CSF–derived DCs differentiated alone. Neutralization of candidate soluble mediators suggests that secretion of IL-6 by KSCs contributes to this modulation.

Understanding how these observations gathered ex vivo apply to the kidney in vivo poses some challenges. Although Huang et al. do not explore where in normal kidneys KSCs reside, knowledge of this anatomy will become critically important in deciphering whether kidney MSCs provide cues to resident or recruited renal DC precursors at steady state or during periods of renal injury.8 Renal DCs reside in the renal interstitium, intimately apposed to the renal epithelium and renal endothelium and intertwined with renal fibroblasts.7,9 These renal cell types constitute the nearest known neighbors for renal DCs and likely play a central role in creating the cytokine milieu for differentiating renal DC precursors in steady state.8 Of these, renal fibroblasts are intriguing in that they may be a stromal lineage of the KSCs isolated by Huang et al.; studies of fibroblasts in other organs have shown their ability to secrete competent poietins for the development of DCs.3

Unlike the steady state, however, the observations by Huang et al. may be more applicable to periods of renal inflammation. GM-CSF has long been used as a conventional growth factor for DCs ex vivo; however, recent studies indicated that GM-CSF–derived

**Interfacing Kidney Stroma with Dendritic Cells**

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The vast majority of ongoing clinical trials using multipotent, mesenchymal stromal cells (MSCs) seek to harness their immunomodulatory properties,1 attesting to the regulatory interface that exists between MSCs and their stromal cell lineage and immunocytes. Specifically regarding extramedullary dendritic cells (DCs), this interface was first recognized in 1997 from reports showing that splenic stroma could support the differentiation of immature DCs from bone marrow (BM)-derived hematopoietic...
DCs are the equivalent of inflammatory DCs. Thus, the co-culture systems developed by Huang et al. more closely mimic a resolving state of renal inflammation, in which recruited inflammatory renal DC precursors are modulated by kidney MSCs toward a more regulatory phenotype. Indeed, inflammatory GM-CSF-derived DCs can be induced into regulatory DCs in the presence of IL-10 and TGF-β.

If the latter scenario holds true, then one can envision that niches of kidney MSCs play an important role in returning the injured kidney to a state of immunologic homeostasis and repair. Kidney MSCs may be recruited locally to replace damaged and dying kidney stroma after renal injury. In the process, these recruited MSCs may also contribute to microenvironments that favor the development of regulatory, not inflammatory, renal DCs, thereby promoting resolution of renal inflammation. These are exciting questions for future inquiry, and the groundbreaking studies by Huang et al. provide the rationale to move forward.

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DISCLOSURES

None.

REFERENCES


Are We Ready to Screen the General Population for Microalbuminuria?

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The United States Preventive Services Task Force does not recommend screening for proteinuria in adults; however, this recommendation has not be reviewed since 1989 and therefore cannot take into consideration newer information on benefits of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in slowing the progression of kidney disease. It is already accepted practice to screen all individuals with diabetes for microalbuminuria. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative recommends screening with standard urine dipstick for individuals not at increased renal risk and screening for microalbuminuria for individuals who are at increased risk. Standard risk factors to identify individuals at increased risk for kidney disease include diabetes, hypertension, older age, family history of kidney disease, and possibly race/ethnicity. The recommendation to screen healthy adults with dipstick proteinuria was opinion not evidence based. Is there enough new data since these recommendations were made to justify screening the general population without risk factors for microalbuminuria?

In this issue of JASN, van der Velde et al. analyze outcomes in the Prevention of Renal and Vascular End-stage Disease (PREVEND) study, a cohort study designed to evaluate the association of albuminuria with cardiovascular disease (CVD) and ESRD in the general population of Groningen, Netherlands. They found that a urine albumin concentration >20 mg/L predicted initiation of renal replacement therapy (RRT) over 10 yr, although risk was modest in individuals with levels 20 to 100 mg/L (hazard ratio 3.0 versus 47 for urine level 100 to 200 mg/L). Approximately half of the individuals who ultimately required RRT had microalbuminuria. They used the data from this cohort to evaluate albuminuria as a screening test in both high-risk individuals (known CVD, diabetes, or hypertension or age >55) or the general population. Screening only high-risk individuals identified 55% of individuals with

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