PARIETAL EPITHELIAL CELLS

Biology of glomerular parietal epithelial cells (PECs):

The study and understanding of PECs has lacked significantly compared to other kidney cells, such that their functions and roles in the pathobiology of glomerular diseases have only been delineated in the past 5+ years, and as a community, we likely have only scratched the surface. We have made several important contributions to the field to date.

1) we showed that by expressing several tight junction proteins, PECs serve an important role in limiting the passage of protein from the urinary space to the extraglomerular space (*a*). Indeed, when tight junctions are disrupted in disease, albumin and other proteins escape into the extra-glomerular space, where they contribute to the peri-glomerular inflammation and fibrosis that characterized progressive proteinuric glomerular diseases.
2) we developed the first immortalized mouse PEC line for study in cell culture (*b*). These cells are now widely used by numerous groups internationally, from which many publications have arisen.
3) we have several publications showing that the expression profile, and likely biological functions of PECs, changes in settings where podocytes are the primary target of disease (*c*). Our data shows that in states of podocyte depletion, PECs lining Bowman's capsule begin to co-express several proteins considered specific for podocytes. A subset of PECs co-expressing podocyte proteins migrate to the glomerular tuft, suggesting that they may serve as adult podocyte progenitors. We have also published three additional manuscripts showing that when mice are given either dexamethasone, ACE-inhibitors or retinoids, that the improvement in podocyte number coincides with an increase in the subset of PECs expressing podocyte proteins. These studies strongly suggest an adult podocyte progenitor function for PECs in states of podocyte depletion.
4) the exact genetic makeup of PECs is not known, and the field needs to better understand what genes are constitutively expressed by PECs. We have reported on the transcriptional landscape for PECs, and how this profile differs from neighboring podocytes (d). These studies have already benefited the community, as many are using this dataset for further studies.

(a) Ohse T, Chang AM, Pippin JW, Jarad G, Hudkins KL, Alpers CE, Miner JH, **Shankland S**J. A new function for parietal epithelial cells: a second glomerular barrier. Am J Physiol Renal. 2009;297(6):F1566-74. *PMID 19794110. PMCID: 2801333.*

(b) Ohse T, Pippin JW, Vaughan MR, Brinkkoetter PT, **Shankland SJ**. Establishment of conditionally immortalized mouse glomerular parietal epithelial cells in culture. J Am Soc Nephrol. 2008;19(10):1879-90. *PMID: 18596122. PMCID: 2551564*

(c) Zhang J, Pippin JW, Krofft RD, Naito S, Liu ZH, **Shankland SJ**. Podocyte repopulation by renal progenitor cells following glucocorticoids treatment in experimental FSGS. Am J Physiol Renal 2013;304(11):F1375-89. *PMID: 23486009. PMCID: 3680690.*

(d) Gharib SA, Pippin JW, Ohse T, Pickering SG, Krofft RD, **Shankland SJ**. Transcriptional landscape of glomerular parietal epithelial cells. PLoS One. 2014 Aug 15;9(8) *PMID: 25127402. PMCID: 4134297.*

How PECs might contribute to glomerular disease

When PECs or APEMPs are activated or dysregulated, identified by *de novo* CD44 expression, they can either lead to glomerulosclerosis by migrating and producing ECM proteins unique to the parietal basement membrane (also called Bowman's capsule) or undergoing proliferation leading to crescent and/or pseudocrescent formation. Proliferation of a subset of dysregulated PECs expressing CD133 and CD24, so called APEMPs, might also contribute to crescent and/or pseudocrescent formation. This pathway is dependent on intracellular retinoic acid, levels of which can be decreased (represented by dashed line) by albumin endocytosis by PECs. The latter has additional consequences, including apoptosis, a reduction in the levels of tight junction proteins or both, leading to increased albumin permeability beyond the PEC–parietal basement membrane barrier, and to peri-glomerular inflammation. The consequences of EMT are not yet understood. Abbreviations: APEMP, adult parietal epithelial multipotent progenitor; ECM, extracellular matrix; EMT, epithelial–mesenchymal transformation; glycCD133, glycosylated CD133; PEC, parietal epithelial cell.