Are Some Nephrons More Equal Than Others?: Perspective on “Viewing Cortical Collecting Duct Function Through Phenotype-Guided Single-Tubule Proteomics”

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The human kidney consists of about a million nephrons, arranged in parallel. Although each nephron contains multiple segments that do different things, one generally assumes that each parallel unit has qualitatively and quantitatively the same functions carried out by the same proteins (except for the obvious distinction between cortical and juxtamedullary nephrons). This, however, is a default assumption, supported mainly by the lack of detailed information on differences among all these anatomically similar structures. An article by Himmerkus et al.,1 in this inaugural issue of Function, starts from a contrary position that defined tubular segments may have important quantitative differences in both function and protein expression.

Figure 1. Functions and Omics of the Cortical Collecting Duct. This tubular segment helps control the volume and composition of body fluids by regulating transport of ions and water. Numbers for mRNA and protein species are detected from Chen et al., Himmerkus et al., Höhne et al., and Lee et al.1–4 PC, principal cell; A-IC, A-type intercalated cell; B-IC, B-type intercalated cell.

For starters, they measured amiloride-sensitive voltage (reflecting ENaC-mediated Na⁺ reabsorption), transtubular resistance and diffusion potentials (reflecting tight-junction permeability and its selectivity) in isolated, perfused CCDs. Not unexpectedly for such physiological experiments, ΔV_{amil} ranged 3-fold, from −7 to −30 mV. In the same tubules, they assessed a panel of 17 proteins, including very abundant ones such as the

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Na/K-ATPase and relatively scarce ones such as the β-subunit of ENaC. These also showed considerable variability. Having both datasets from the same tubules permitted calculations of correlations between different parameters. For example, expression of the beta subunit of the epithelial Na channel (βENaC) correlated positively with ΔVamil, which at first seems logical but is nonetheless interesting since the βENaC is not much altered by aldosterone, the main regulator of ENaC in the kidney.7

Other relationships were more surprising, particularly the negative correlation between ΔVamil and the expression of aquaporin 2 (AQP2), the water channel that inserts into the apical membrane of principal cells to control ADH-dependent H2O transport and urine osmolarity.5 This suggests that some CCDs may commit to Na transport or to H2O transport at the expense of the other, although a lot more work will need to be done to sort this out.

Another strength of the approach entails the definition of sets of proteins that change their expression together. B-type intercalated cells use the anion exchanger pendrin to secrete HCO3− into the urine in exchange for Cl−, particularly during alkalosis.8 Expression of pendrin correlated positively with that of the B2 subunit of the vacuolar ATPase that pumps H+ from the cell to the blood and with barttin, a regulator of the anion channels that move Cl− from cell to blood to maintain electroneutrality. All of these proteins are part of the same overall transport pathway, and also tend to change in concert when the pendrin gene is knocked out. These responses to genomic manipulation may give clues about causalities underlying the correlations. More surprising was the positive correlation with another anion exchanger, slc4A1 (AE1), which resides on a different cell type, namely the A-type intercalated cell, and mediates urinary acidification. This and other findings argue against the simple idea that the correlations simply reflect changes in the numbers of various cell types, a phenomenon known to occur in the CCD.9

These results demonstrate the possibility of studying variations in protein expression and function among tubular segments from the same animal under nominally identical conditions. This would both define differences in physiology among nominally identical structures and help to explain those differences in terms of protein abundance. Ultimately, this approach could be applied at the level of the single renal cell, as is currently done with transcriptomics. With advances in the sensitivity of proteomics techniques, this achievement may not be far away.

Conflict of interest statement
The author has no conflicts of interest to declare.

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