


# Renal-Tubule Epithelial Cell Nomenclature for Single-Cell RNA-Sequencing Studies

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The assignment of cell type names to individual cell clusters in single-cell RNA-sequencing (RNA-seq; including single-nucleus RNA-seq) studies is a critical bioinformatic step because researchers will need to be able to reliably map the pertinent transcriptomes to other types of information in the literature. Ambiguous or redundant cell-type names would impede such mapping tasks. The solution to this problem is to create “controlled vocabularies”<sup>1,2</sup> that can be preferentially used in reports of single-cell RNA-seq data and other types of -omic data at a single-cell level. In this review, we provide such a controlled vocabulary for the epithelial cells that make up the mammalian renal tubule. The nomenclature list was not produced *de novo* in this review, but instead represents an adaptation of a prior, widely accepted nomenclature list for renal tubule segments published in 1988 in *Kidney International*.<sup>3</sup> This was done because historical consistency is important to assure that names assigned to clusters in single-cell RNA-seq studies mesh well with the “pregenomic” 20th century literature, which provides robust and well validated information on kidney cell structure and function. The 1988 article offered several alternative names for some of the segments and cell types. Our strategy here is to propose nomenclature that reflects the most common usage from 1988 to the present in each case. In this report, we not only describe preferred names for each cell type, but

also include information on the percentage of each epithelial cell type in mouse kidney and on widely accepted mRNA/protein markers that are considered prerequisites for identification of individual cell types.

The mammalian renal tubule is made up of at least 14 segments, containing at least 16 distinct epithelial cell types.<sup>4–6</sup> Each cell type has its own characteristic set of cellular functions (mostly related to transport and metabolism), which have been elucidated largely over the past 50 years since the development of single-tubule microdissection approaches by Burg *et al.*<sup>7</sup> and the expansion of the micropuncture technique to mammalian physiology.<sup>8,9</sup> Furthermore, each cell type has its own unique transcriptome as elucidated by recent RNA-seq studies carried out at the level of single microdissected tubules<sup>6</sup> and single cells.<sup>10–26</sup> The new transcriptomic data promises to expand and sharpen our understanding of renal tubule function, as the data are mapped to cellular processes responsible for the macroscopic function of each renal tubule segment.

To allow this mapping to be done accurately, it is imperative that the cell-type terminology used for single-tubule and single-cell gene expression studies be consistent with terminology used in the functional and biochemical studies done in the past. Here, we summarize recommended terminology for renal tubule epithelial cells derived from prior recommendations by the *Renal Commission of*

*the International Union of Physiologic Sciences* and published in in *Kidney International* in 1988.<sup>3</sup> The 1988 nomenclature was focused on what to call each renal tubule segment, and not necessarily what to call individual cell types. Accordingly, we refocused the recommended terminology to the individual cell types present in the various tubule segments.

Before presenting the list of recommended cell-type terminology, we summarize, in a greatly simplified manner, the current procedures for mapping gene expression lists from single-cell RNA-seq to the various known cell types. A single-cell RNA-seq dataset contains (for each cell) a list of expressed genes together with some measure of their mRNA expression levels. The initial task, carried out independently of cell type assignment, is to cluster the cells into groups that are similar on the basis of the lists of their expressed mRNAs along with their expression levels. These “clusters” are then mapped to cell-type names that are assigned on the basis of

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representation of cell-type selective marker genes. The problem we are addressing in this review is that there is presently no generally accepted “controlled vocabulary” for renal tubule epithelial cell types, *i.e.*, there is no standard list of acceptable terms. Consequently, terminology has been inconsistent among individual single-cell RNA-seq articles,<sup>10–26</sup> and the correct mappings to functional and biochemical studies done in the pregenomic era are uncertain.

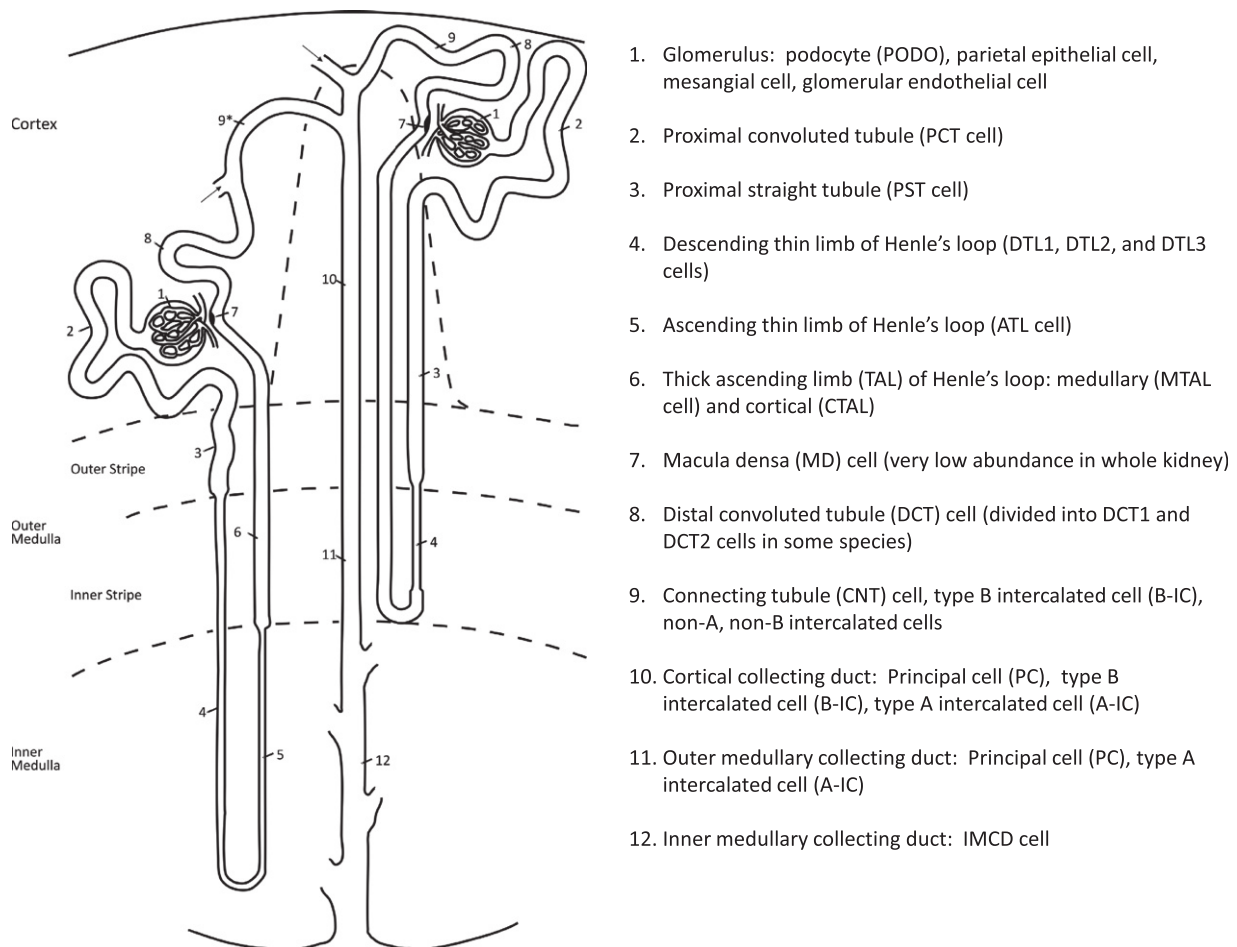
Recommended terms for renal tubule epithelial cell types in kidneys of mature mice, rats, or humans are given in Figure 1 and are listed on the Renal Epithelial Cell

Ontology (RECON) webpage (<https://hpcwebapps.cit.nih.gov/ESBL/Database/RECON/>). Figure 1 shows both a short-loop and a long-loop nephron superimposed on regional boundaries of the kidney. The structures that define the regional boundaries are the arcuate arteries (corticomedullary junction), the transition from proximal straight tubules (PSTs) to descending thin limbs (DTLs) of the loops of Henle (inner/outer stripe of outer medulla junction) and the transition from the ascending thin limbs of Henle of the long-loop nephrons to the medullary thick ascending limbs (MTALs) of the loops of Henle (inner-outer medullary junction).<sup>4</sup> Generally,

the latter two junctions are easily recognizable macroscopically, but the corticomedullary junction is obscure, at least in rodents, without benefit of a stereomicroscope. Here, we present the rationale for the terms presented, some alternative terminology, and some alternative terms to be avoided.

## PROXIMAL TUBULE NOMENCLATURE

There are two sets of terms commonly used to describe proximal tubule cells. One divides the proximal tubule into three



**Figure 1.** Renal tubule cell nomenclature. The scheme shows the connection of both a short-looped nephron and a long-looped nephron to the collecting duct system. The numbers point to different renal tubule segments and the cell types that they contain are listed on the right of the scheme. Dashed lines indicate regional boundaries. The corticomedullary junction is defined by the arcuate arteries (not shown in this diagram). The division between the outer stripe and inner stripe of the outer medulla is defined by the transitions from PSTs to DTLs of the loops of Henle. The junction between the outer medulla and inner medulla is defined by the transitions from the ascending thin limbs (ATL) of Henle of the long-loop nephrons to the MTALs of the loops of Henle. The division between the cortical labyrinth and cortical medullary rays is indicated but not labeled. Drawing is on the basis of the original Renal Commission of the International Union of Physiologic Sciences publication.<sup>3</sup>

segments called S1, S2, and S3 on the basis of differences in morphology, topology, and location in the kidney.<sup>27,28</sup> Functionally, the S2 is recognized as the segment responsible for para-aminohippurate secretion and, by implication, responsible for general organic anion and cation secretion.<sup>28</sup> A limitation of this classification is the lack of a discrete transition from one to the other morphologically. This lack of clear transitions suggests that there are probably intermediate cell types, which would preclude clear-cut clustering into three distinct groups of cells. The S3 segment is found chiefly in the outer stripe of the outer medulla, allowing it to be separated from S1 and S2 simply by selecting the outer stripe as starting material for single-cell isolation. An alternative classification divides the proximal tubule into the proximal convoluted tubule (PCT) and PST on the basis of the course of the tubule (convoluted versus straight) and the location in the cortex (the PCT is found in the cortical labyrinth whereas the PST is found in the medullary ray of the cortex and the outer stripe of the outer medulla). Thus, in tissue sections and microdissection experiments, the two can be readily discriminated. The PCT includes the S1 (early PCT) and S2 (late PCT), whereas the PST includes the S2 (cortical PST) and S3 (medullary PST).

### LOOP OF HENLE NOMENCLATURE

The loop of Henle spans from the DTL to the cortical thick ascending limb (CTAL) (Figure 1). It is made up of six distinct segments corresponding to seven morphologically distinct cell types. Three of these are the cells of the three DTL segments, *viz.* DTL1, DTL2, and DTL3.<sup>3,29</sup> The DTL1 segment makes up the entire DTL in short-loop nephrons, whereas the DTL of long-loop nephrons is made up of DTL2 in the outer medulla and DTL3 in the inner medulla. The transition between the two is indistinct, occurring various distances into the inner medulla. The fourth thin limb segment, the ascending thin limb of the loop of Henle is morphologically and

topologically distinct from the other three thin limb segments.<sup>29</sup> All of the thin limb segments are difficult to microdissect from the kidney and difficult to study by micropuncture, limiting the amount of functional information we have about them.

In contrast, the thick ascending limb (TAL) is relatively easy to study in isolation and has well defined functional roles.<sup>30–32</sup> The TAL is normally divided into the MTAL and the CTAL on the basis of a difference in morphology, location, and function.<sup>30</sup> The transition between these cell types occurs in the outer stripe of the outer medulla. Near the end of the TAL, the CTAL comes into contact with its own glomerulus. At this point, special epithelial cells called macula densa cells transduce feedback signals to the afferent arterioles, regulating GFR and renin production.<sup>33</sup> The macula densa consists of only 14–24 cells per nephron in rodent species,<sup>34,35</sup> and so has been elusive in single-cell RNA-seq studies. In several recent studies using single-cell RNA-seq, clusters were labeled “loop of Henle cells.” This is an ambiguous label because it could apply to any of seven cell types discussed in this section. Thus, the term loop of Henle cells should generally be avoided in cluster labeling.

### DISTAL CONVOLUTED TUBULE VERSUS DISTAL TUBULE

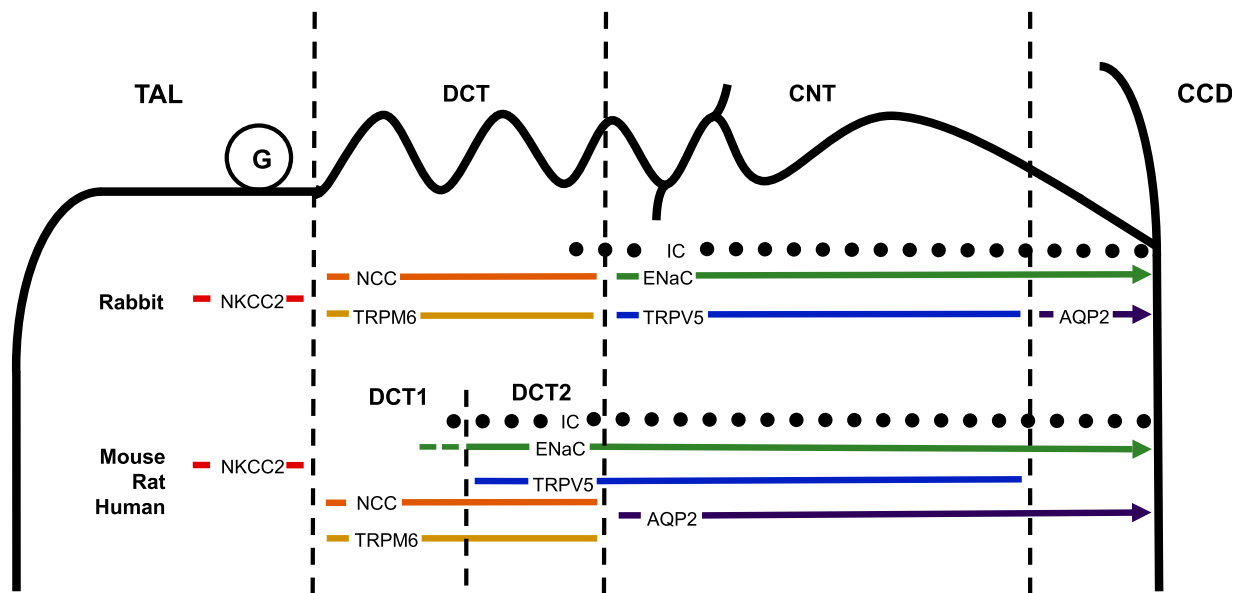
The distal convoluted tubule (DCT) is a short segment that follows the CTAL a few cells beyond the macula densa. It transports NaCl at a high rate in a regulated manner, and is the chief target for thiazide diuretics.<sup>36–38</sup> Morphologically, DCT cells are quite distinct from any other cell type in the kidney, on the basis of the unique subapical location of its nucleus. The term “distal convoluted tubule” should be distinguished from the nonspecific term “distal tubule.” The latter is defined differently in different contexts, sometimes referring to all tubule segments beyond the proximal tubule, sometimes denoting the region between the macula densa and the initial collecting tubule<sup>38</sup> and sometimes

considered to include the aquaporin-2 (AQP2) expressing cells of the collecting duct. Hence, the term distal tubule is ambiguous and should be avoided in RNA-seq studies. Another similar term is “distal nephron,” commonly used to designate the portion of the renal tubule from the macula densa through the end of the inner medullary collecting duct (IMCD), thereby comprised of multiple cell types.

Rabbits exhibit a distinct transition point at the end of the DCT that allow unambiguous dissection of a uniform DCT epithelium (Figure 2).<sup>39,40</sup> Rodents, however, exhibit a transition region<sup>41</sup> that includes cells expressing markers normally attributed to downstream segments, such as the three subunits of the epithelial sodium channel (ENaC) (Figure 2). The DCT in human kidney also has such a transition region (Figure 2), leading investigators to divide the DCT into two subsegments, referred to as DCT1 and DCT2.<sup>41,42</sup> The rodent and human DCT1 appears equivalent to the rabbit DCT with a single unique cell type. In addition, the DCT2 region contains interspersed intercalated cells (ICs; see below). Whether there are uniquely defined DCT2 cells remains an unresolved issue and is certainly addressable in future single-cell RNA-seq studies. This scientific question is complicated by the marked plasticity of the DCT segment, undergoing changes in cell number and tubule length under different physiologic circumstances.<sup>43,44</sup> It seems possible, therefore, that the cell types present in the DCT can change with physiologic state. An ancillary question is: “What cells in this region are derived from the metanephric mesenchyme and what cells are derived from the ureteric bud?” Careful studies are needed to address this question.

### THE COLLECTING DUCT SYSTEM

The collecting duct system consists of the connecting tubule (CNT), cortical collecting duct (CCD), outer medullary collecting duct (OMCD), and IMCD. These collecting duct segments contain different cell types that are interspersed in the same epithelium.



**Figure 2.** Distributions of transporters in the renal tubule segments from CTAL to CCD in rabbit, mouse, rat, and human kidney. A uniform DCT epithelium expressing NCC (*Slc12a3*) is present in rabbit, whereas the DCT in mouse, rat, and human has a transitional region (DCT2) expressing NCC and ENaC subunits (*Scnn1a*, *Scnn1b*, and *Scnn1g*). Thus, in rodents and humans, but not rabbit, the DCT is divided into DCT1 and DCT2. The distribution of ICs (mostly type B ICs expressing pendrin [*Slc26a4*]) is indicated by large dots. AQP2 (*Aqp2*), vasopressin-dependent water channel aquaporin 2; ENaC (*Scnn1a*, *Scnn1b*, and *Scnn1g*), amiloride-sensitive epithelial Na channel; G, glomerulus; NKCC2 (*Slc12a1*), bumetanide-sensitive Na-K-2Cl cotransporter; NCC (*Slc12a3*), thiazide-sensitive Na-Cl cotransporter; TRPM6 (*Trpm6*), magnesium channel of distal convoluted tubule, TRPV5 (*Trpv5*), calcium channel of CNT cells.

These cell types are usually classified as principal cells (PCs) and ICs. The latter are of two general types, the type A (or  $\alpha$ ) ICs that secrete acid and the type B (or  $\beta$ ) ICs that secrete base (bicarbonate) and reabsorb chloride. The collecting duct segments appear to be quite plastic, and even in adult kidneys PCs and ICs were reported to be interconvertible.<sup>13,45–54</sup> In accordance with that observation, hybrid PC/IC cells have been reported.<sup>13,14</sup>

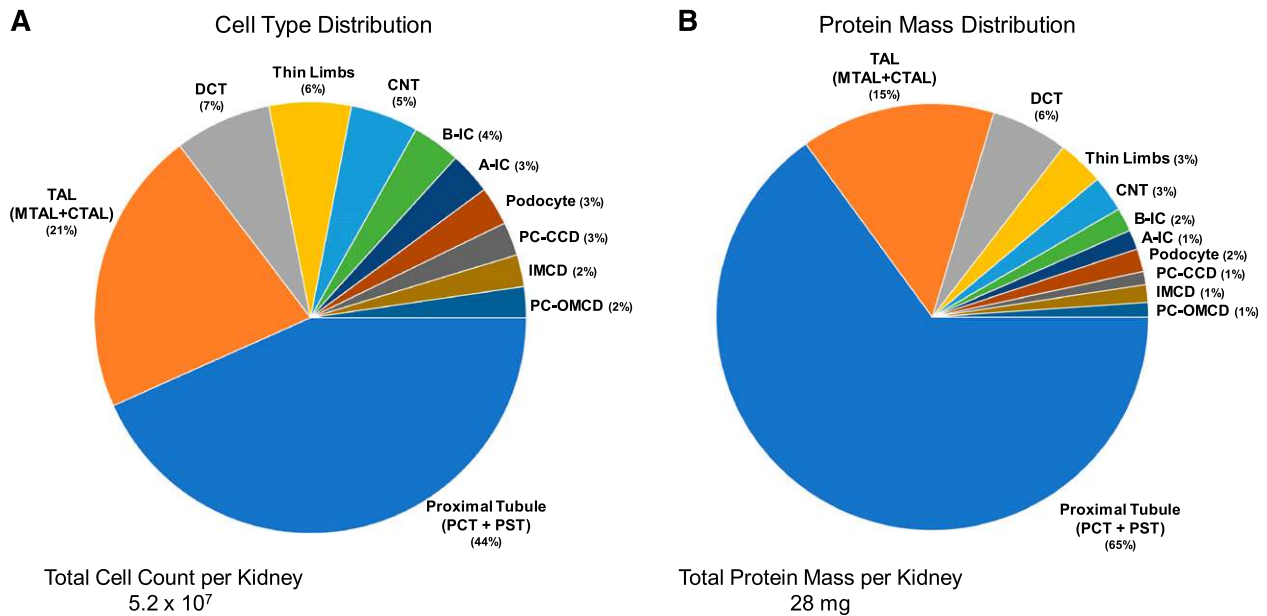
Type A ICs predominate in the OMCD, whereas type B ICs predominate in the CCD and CNT.<sup>55</sup> There have been reports of noncanonical ICs (so called “non-A, non-B cells”) that are distinguished on the basis of the distribution of acid-base transporters between the apical and basolateral plasma membrane,<sup>56</sup> but specific protein markers for these cells that could be used to sort cells within RNA-seq datasets were not well established. It is possible that these represent hybrid type A IC/type B IC cells, although existing single-cell RNA-seq studies failed to identify cells with markers for both.<sup>14</sup>

PCs uniquely express the water channel AQP2. AQP2-expressing cells can be divided into four morphologically and functionally distinct cell types: CNT cells, CCD PCs, OMCD PCs, and IMCD cells. Many kidney morphologists consider the CNT cell a unique cell type different from the PC on the basis of morphologic differences.<sup>57</sup> Likewise, some kidney morphologists do not consider the IMCD cell a PC, largely because it is the only cell type throughout most of the IMCD length.

### ABSOLUTE AND RELATIVE NUMBERS OF EACH RENAL TUBULE CELL TYPE

Assignment of names to individual cell clusters in single-cell RNA-seq studies can benefit from knowledge of the relative number of each cell type in a kidney. Figure 3 shows the absolute and relative numbers of each renal tubule cell type (including podocytes) in a mouse kidney as well the absolute and relative protein

amounts. These data are taken from Clark *et al.*,<sup>58</sup> who compiled morphometric data from multiple sources including the classic comparative morphology study of Sperber<sup>59</sup> (available at <https://esbl.nhlbi.nih.gov/Databases/Sperber/>). As expected, proximal tubule cells (combination of S1, S2, and S3) are the most abundant cell type amounting to 43% of all renal tubule epithelial cells and 65% of the total renal tubule protein mass. The second most abundant cell type is the TAL cell (combination of MTAL and CTAL), amounting to 21% cell count and 15% protein mass. DCT cells account for 7% of tubule epithelial cells and AQP2-expressing cells (CNT, PC, and IMCD) account for 12%. In the present context, podocytes can be considered a “minority” cell type accounting for only 3% of cells. If one makes this calculation for cortex rather than whole kidney, the percent of proximal tubule cells increases to 57% and the percent of podocytes increases to 4% (see Supplemental Figure 1). Thus, despite their importance to overall kidney function,



**Figure 3.** Cell type and protein mass distribution among mouse renal epithelial cells. (A) The contributions of individual mouse renal epithelial cell types to whole kidney epithelial cell count (given at bottom). (B) The contributions of individual mouse renal epithelial cell types to whole kidney tubule protein mass (given at bottom). A-IC, type A intercalated cell; B-IC, type B intercalated cell; Thin Limbs, thin limbs of the loop of Henle (sum of DTL1, DTL2, DTL3, and ascending thin limbs). The data are from Clark *et al.*<sup>58</sup>

podocyte transcriptomes may be expected to be rare in whole-kidney shotgun single-cell RNA-seq studies and it may be necessary to isolate glomeruli before cell dissociation to get large numbers of podocyte transcriptomes.<sup>24</sup> In general, isolation of cells from solid tissue can distort the proportions of cell types because some cells are more fragile than others, less easily dissociable than others, or less metabolically stable than others. Consequently, the distribution of cell types that can be successfully analyzed by single-cell RNA-seq are unlikely to match the actual distribution displayed in Figure 3.

### PROTEIN AND MRNA MARKERS FOR INDIVIDUAL CELL TYPES

Identification of the cell types corresponding to individual clusters in single-cell RNA-seq data depends in part on matching the transcriptomes of the cells included in each cluster to prior information about what proteins are functionally important in the cells. For example, the thiazide sensitive NaCl cotransporter (Slc12a3) is well established

to mediate the major function of the DCT cells, namely reabsorption of NaCl, and has been found to be expressed exclusively in DCT cells.<sup>36</sup> Thus, this single marker is considered necessary and sufficient to identify a DCT cell. Table 1 lists these *sine-qua-non* identifiers for the cell types described in this review, known before the invention of the RNA-seq technique. An important characteristic of such identifiers is that their mRNAs must be very abundant because (depending on the platform) single-cell RNA-seq does not always capture the full transcriptome of each cell (discussed by Clark *et al.*<sup>58</sup>) and it is important for discriminating markers to be detectable at their native expression levels. In Supplemental Figure 2 and Supplemental Appendix 1, we show a set of additional markers found in RNA-seq studies of microdissected rat renal tubule segments<sup>6</sup> (panel A) in combination with mouse single-cell RNA-seq<sup>14</sup> (panel B). In theory, a combination of these markers can be used to specifically identify any renal tubule cell type.

### SUMMARY

In this review, we have provided a set of terms for each renal tubule epithelial cell type, recommended for use in cluster naming in single-cell RNA-seq studies. A consistent nomenclature is critical to ensure accurate mapping of the pertinent transcriptomes to other types of information in the literature accrued over many decades. We have pointed out examples of ambiguous cell-type names (*i.e.*, loop of Henle cells and distal tubule cells) that impede such mapping tasks. The controlled vocabulary introduced here is likely to be useful for naming tasks that extend beyond single cell RNA-seq studies as measurements in single cells expand to other modalities, *e.g.*, chromatin accessibility measurements using ATAC-seq.<sup>60</sup> In this report, we not only described preferred names for each cell type, but also included information on widely accepted mRNA/protein markers that are considered pre-requisites for identification of individual cell types and on the percentage of each epithelial cell type in mouse kidney.

**Table 1.** Classic cell type selective markers

Cell Type <sup>a</sup>	Gold Standard Marker(s)
Podocyte	Nphs1 (nephrin), Nphs2 (podocin)
Proximal S1 cell	Slc5a2 (SGLT2)
Proximal S2 cell	Slc22a6 (OAT1)
Proximal S3 cell	Agt (angiotensinogen)
All proximal tubule	Slc34a1 (Na-Pi2), Lrp2 (megalin)
DTL type 1 cell	Slc14a2 (UT-A2)
DTL type 2 cell	Slc14a2 (UT-A2)
DTL type 3 cell	Slc14a2 (UT-A2)
Ascending thin limb cell	Clcnka (chloride channel Ka)
MTAL limb cell	Slc12a1 (NKCC2), Umod (Tamm-Horsfall protein)
CTAL cell	Slc12a1, Umod
Macula densa cell	Slc12a1, Oxt (oxytocin receptor), Nos1 (nitric oxide synthase 1)
Distal convoluted tubule cell	Slc12a3 (NCC)
CNT cell	Aqp2 (aquaporin-2), Scnn1g (γ-ENaC), Calb1 (calbindin)
PC (CCD)	Aqp2, Scnn1g
PC (OMCD)	Aqp2, Scnn1g
Type A IC	Slc4a1 (anion exchanger 1)
Type B IC	Slc26a4 (pendrin)
IMCD cell	Aqp2, Slc14a2 (UT-A1)

<sup>a</sup>Cell type markers identified in the pregenomic era.

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Dr. Chen, Dr. Clark, and Dr. Knepper outlined the paper. Dr. Chen, Dr. Clark, and Dr. Knepper wrote the paper. Dr. Clark made the webpage. Dr. Chen, Dr. Clark, and Dr. Kaissling made the figures. All authors edited the text and approved the final version.

## DISCLOSURES

None.

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## SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at <http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2019040415/-/DCSupplemental>.

Supplemental Figure 1. Cell type and protein mass distribution among mouse renal epithelial cells.

Supplemental Figure 2. Selected marker transcript expression in different renal tubule/cell types.

Supplemental Appendix 1. Additional markers found in RNA-seq studies.

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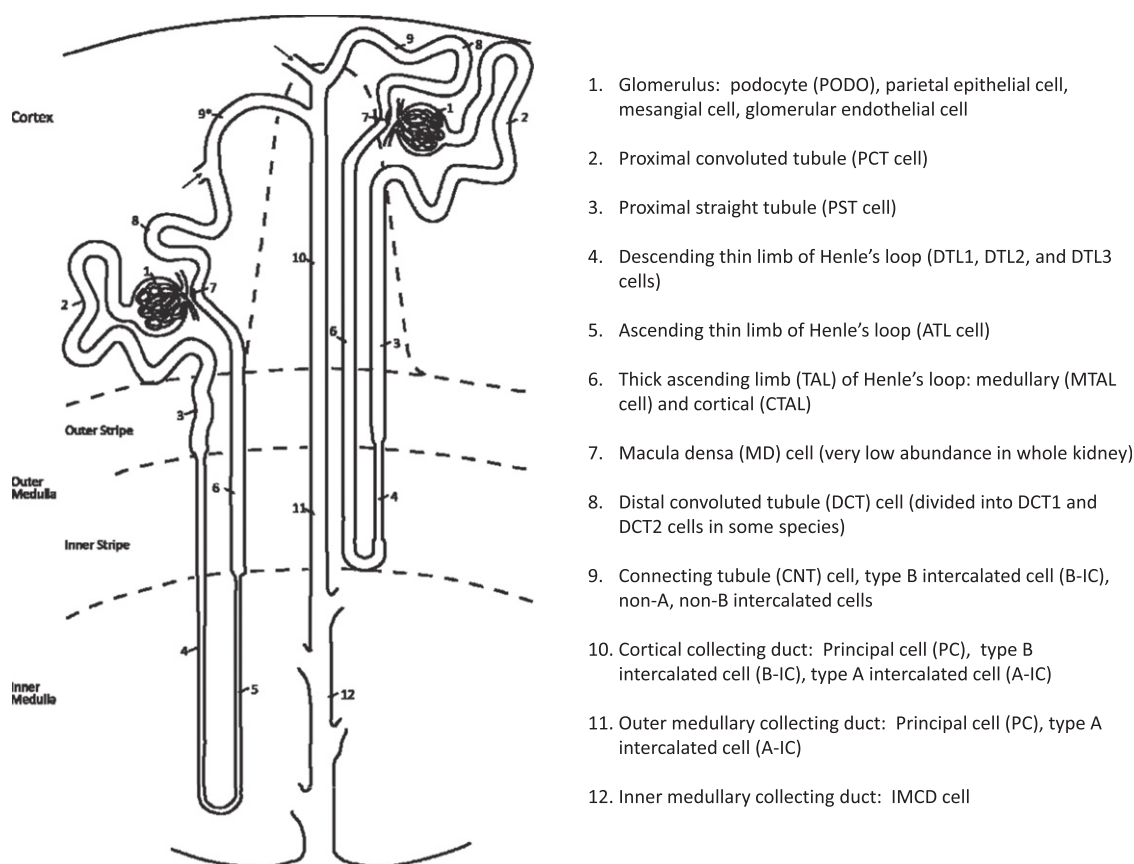
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**CORRECTION**

Lihe Chen, Jevin Z. Clark, Jonathan W. Nelson, Brigitte Kaissling, David H. Ellison, and Mark A. Knepper: Renal-Tubule Epithelial Cell Nomenclature for Single-Cell RNA-Sequencing Studies. *J Am Soc Nephrol* 30: 1358–1364, 2019.

Figure 1 of our article in the August issue of *JASN* lacked a numerical label indicating the position of the thick ascending limb of Henle in short-looped nephrons. The corrected figure is provided below and at <https://hpcwebapps.cit.nih.gov/ESBL/Database/RECON/>.



**Figure 1.** Renal tubule cell nomenclature. The scheme shows the connection of both a short-looped nephron and a long-looped nephron to the collecting duct system. The numbers point to different renal tubule segments and the cell types that they contain are listed on the right of the scheme. Dashed lines indicate regional boundaries. The corticomedullary junction is defined by the arcuate arteries (not shown in this diagram). The division between the outer stripe and inner stripe of the outer medulla is defined by the transitions from PSTs to DTLs of the loops of Henle. The junction between the outer medulla and inner medulla is defined by the transitions from the ascending thin limbs (ATL) of Henle of the long-loop nephrons to the MTALs of the loops of Henle. The division between the cortical labyrinth and cortical medullary rays is indicated but not labeled. Drawing is on the basis of the original Renal Commission of the International Union of Physiologic Sciences publication.