The multiple roles of pendrin in the kidney

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ABSTRACT

The Cl− /HCO3− exchanger pendrin (SLC26A4, PDS) is located on the apical membrane of B-intercalated cells in the kidney cortical collecting duct and the connecting tubules and mediates the secretion of bicarbonate and the reabsorption of chloride. Given its dual function of bicarbonate secretion and chloride reabsorption in the distal tubules, it was thought that pendrin plays important roles in systemic acid–base balance and electrolyte and vascular volume homeostasis under basal conditions. Mice with the genetic deletion of pendrin or humans with inactivating mutations in PDS gene, however, do not display excessive salt and fluid wasting or altered blood pressure under baseline conditions. Very recent reports have unmasked the basis of incongruity between the mild phenotype in mutant mice and the role of pendrin as an important player in salt reabsorption in the distal tubule. These studies demonstrate that pendrin and the Na+–Cl− cotransporter (NCC; SLC12A3) cross-compensate for the loss of each other, therefore masking the role that each transporter plays in salt reabsorption under baseline conditions. In addition, pendrin regulates calcium reabsorption in the distal tubules. Furthermore, combined deletion of pendrin and NCC not only causes severe volume depletion but also results in profound calcium wasting and luminal calcification in medullary collecting ducts. Based on studies in pathophysiological states and the examination of genetically engineered mouse models, the evolving picture points to important roles for pendrin (SLC26A4) in kidney physiology and in disease states. This review summarizes recent advances in the characterization of pendrin and the multiple roles it plays in the kidney, with emphasis on its essential roles in several diverse physiological processes, including chloride homeostasis, vascular volume and blood pressure regulation, calcium excretion and kidney stone formation.

Keywords: hypertension, oxalate stone, renal tubular acidosis, salt excretion, volume depletion

INTRODUCTION

The reabsorption of sodium and chloride represents a major function of kidney tubules and is essential for the vascular volume homeostasis and blood pressure regulation. The bulk of filtered sodium and chloride is reabsorbed in the proximal tubule and the thick ascending limb of Henle (TALH), with the remaining load being reabsorbed in the more distal tubule segments, including the collecting duct [1–9]. Both trans- and para-cellular pathways participate in the reabsorption of salt with varying proportions in different kidney segments [1–9].

The trans-cellular reabsorption of sodium is predominantly mediated via the Na+/H+ exchanger NHE3 in the proximal tubule, by the apical Na+–K+–2Cl− cotransporter (NKCC2) and NHE3 in the TALH, through the Na+–Cl− cotransporter (NCC; SLC12A3) in the distal convoluted tubule (DCT) and by the epithelial sodium channel (ENaC) in the connecting tubule (CNT) and collecting duct [1–4].

Chloride reabsorption involves both para- and trans-cellular pathways, with the trans-cellular pathway mediated via apical chloride/base exchangers in the proximal tubule and the collecting duct, by NKCC2 (SLC12A2) in TALH and through NCC (SLC12A3) in the DCT [1–9]. The para-cellular reabsorption of chloride is predominantly secondary to the gradients generated by trans-cellular absorption of sodium and occurs through tight junctions [9–11]. The apical chloride/base exchangers in the proximal tubule work in tandem with NHE3 [1, 5, 7, 8], whereas in the collecting duct they primarily function in collaboration with the ENaC and in part with the sodium-dependent chloride/bicarbonate exchanger (NDCBE; SLC4A8) to mediate the reabsorption of NaCl [5–9, 12].

In addition to salt reabsorption, the kidney plays an essential role in systemic acid–base homeostasis by eliminating excess acid and reabsorbing the filtered bicarbonate through the synchronized action of specific acid–base transporters that are expressed on the apical and basolateral membranes of various tubular segments [1, 2, 4–7, 9, 12–15]. The net effect
of the action of these transporters is the maintenance of the systemic pH within a narrow physiological range, which is vital for the normal functioning of cells and tissues.

The cortical collecting duct (CCD) plays a major role in acid–base regulation through acid or bicarbonate secretion in specialized intercalated cells. The acid is secreted into the lumen in A-intercalated cells predominantly via apical H⁺-ATPase, and bicarbonate is transported to the blood via basolateral AE1 (SLC4A1) [16, 17]. Bicarbonate secretion into the lumen occurs in B-intercalated cells and is mediated via pendrin [18, 19], which exchanges luminal chloride for cellular bicarbonate [20]. Na⁺ reabsorption in these nephron segments and in the CNT is trans-cellular and is mediated by ENaC located on the apical membrane of the principal cell.

Recent studies have demonstrated an important role for pendrin in acid–base regulation and/or systemic electrolyte homeostasis and blood pressure regulation in pathophysiological states. The focus of this review is on pendrin, a member of a large, conserved family of anion transporters called SLC26, and the multiple roles it plays in the kidney, with emphasis on important contributions to several diverse physiological processes, including chloride homeostasis, vascular volume and blood pressure regulation, acid–base regulation, calcium excretion and kidney stone formation.

**SLC26 family of anion transporters**

The main apical chloride/base exchangers in epithelial tissues, including the kidney and gastrointestinal tract, belong to the family of solute transporters SLC26A [21–30]. This family is genetically distinct from the SLC4 family of anion transporters, which encompasses AE1, AE2, AE3 and AE4, and can function as Cl⁻/HCO₃⁻ exchangers [31]. The SLC26 family comprises 11 distinct members (SLC26A1–11) [21–30]. Modes of transport mediated by SLC26 members include the exchange of chloride for bicarbonate, hydroxyl, sulfate, formate, iodide or oxalate with variable specificity [5, 7, 32–36].

Several SLC26 family members can specifically function as Cl⁻/HCO₃⁻ exchangers. These include SLC26A3 (DRA), SLC26A4 (pendrin), SLC26A6 (PAT1 or CFEX), SLC26A7, SLC26A9 and SLC26A11 [32–42]. In addition to mediating chloride/base exchange, SLC26A7, SLC26A9 and SLC26A11 can also function as chloride channels [41–47].

Five well-known SLC26 isoforms that show distinct tubule segment distributions are SLC26A4, SLC26A6, SLC26A7, SLC26A9 and SLC26A11 [7, 46–50]. SLC26A4 is expressed on the apical membrane of a subset of intercalated cells (B-IC) and mediates chloride/bicarbonate exchange [6, 7, 18–20, 48–50]. SLC26A6 is expressed on the apical membrane of kidney proximal tubule cells and mediates chloride/oxalate and chloride/bicarbonate exchange [51–54]. SLC26A7 is expressed on the basolateral membrane of A-intercalated cells in the outer medullary collecting duct and can function as a chloride channel as well as a chloride/bicarbonate exchanger [45, 55–57]. SLC26A9 is expressed on the apical membrane of principal cells in the outer medulla and initial inner medullary collecting duct and can function as a chloride channel, an electronegic chloride/cation cotransport and an electronegic chloride/bicarbonate exchange [40, 41, 43, 44, 46, 58].

SLC26A11 is expressed on the apical membrane of A-intercalated cells and the basolateral membrane of B-intercalated cells in the collecting duct and can function as a chloride channel, an electronegic chloride transporter and a chloride/bicarbonate exchanger [42, 47]. In addition to the above three isoforms, SLC26A3 (DRA) can also function as a chloride/bicarbonate exchanger but is primarily expressed in the intestine and is absent in the kidney [32, 38]. Figure 1 compares the expression pattern of the main SLC26 members between kidney and intestine and their predominant functional modes in native tissues.

**SLC26A4 (pendrin): a multifaceted transporter**

**Cloning and localization.** The SLC26A4 gene was first identified by linkage analysis and positional cloning studies in patients with Pendred syndrome [24], a genetically inherited, autosomal recessive disorder characterized by deafness and thyroid enlargement or goiter [59, 60]. The pendrin gene SLC26A4 transcribes an mRNA of ~5 kb which encodes a protein of ~95–100 kDa [24]. Pendrin is abundantly expressed in the thyroid and inner ear [24], with very low levels in the kidney [24]. The gene encoding pendrin is located next to the gene encoding DRA (SLC26A3) on chromosome 7 [24]. They show 45% homology, suggesting ancient gene duplication.

Pendrin, as well as other SLC26 isoforms, contains a C-terminal cytoplasmic fragment organized around a central Sulfate Transporter and Anti-Sigma factor antagonist (STAS) domain [7, 8]. Published reports indicate that STAS domain plays an important role in surface trafficking and functional expression for SLC26 isoforms [7, 8].

Expression of SLC26A4 in cultured kidney cells showed that it can function in Cl⁻/HCO₃⁻ exchange, Cl⁻/OH⁻ exchange and Cl⁻/formate exchange modes [20]. Northern hybridization and nephron segment distribution studies showed that pendrin mRNA expression was exclusively detected in the cortex of the kidney, with high levels in the CCD and lower levels in the proximal tubule [20]. Immunofluorescence studies localized pendrin to the apical membrane of B-intercalated cells as well as non-A, non-B- intercalated cells in the CNT and CCDs, with no protein expression in the proximal tubule [18, 19, 49, 50].

Figure 2A is a schematic diagram depicting the nephron segment distribution of pendrin. Figure 2B demonstrates the cellular and subcellular distribution of pendrin in the CCD.

**Mutations and structure–function relationship.** The SLC26A4 gene encodes a transmembrane protein of 780 amino acids, with either 11 or 12 membrane-spanning domains [24]. More than 60 mutations have been reported in the SLC26A4 gene, predominantly distributed throughout the coding sequence. The mutations are primarily missense, with a smaller number of deletions, frame-shift or insertions also reported [60, 61].

Functional analysis of wild-type and several mutations of pendrin have been carried out in various expression systems. The majority of these mutations show loss-of-function phenotypes due to misfolding and lack of membrane targeting, with some others displaying the loss of function, but with normal
membrane insertion. A considerable number of patients with Pendred syndrome lack mutations in the SLC26A4 coding region in one or both alleles. Mutations in both FOXI1, a transcriptional activator of SLC26A4, and the SLC26A4 promoter that binds FOXI1, have been shown to interfere with FOXI1-binding and FOXI1-mediated transcriptional activation of the SLC26A4 gene, resulting in reduced activity of pendrin [62]. No detailed studies have been performed on kidney functions, including salt excretion, divalent ion (calcium or magnesium) excretion or urine concentrating ability, in patients with Pendred syndrome.

**Pendrin-deficient mice.** The generation of mice with a genetic deletion of pendrin has significantly advanced our understanding of the role of this exchanger in normal physiology and pathophysiological states.

**Pendrin and bicarbonate loading.** Pendrin knockout (KO) mice showed impaired ability to excrete bicarbonate in response to bicarbonate loading, indicating an important role for this transporter in bicarbonate secretion in the kidney [18]. Studies in microperfused kidney collecting ducts showed significant down-regulation of apical Cl⁻/HCO₃⁻ exchanger activity in B-intercalated cells in pendrin KO mice, directly verifying that pendrin is the dominant apical Cl⁻/HCO₃⁻ exchanger in the kidney collecting duct [19]. Consistent with an important role for pendrin in bicarbonate secretion under basal condition in mice kept under standard laboratory conditions is the fact that pendrin KO mice have an acidic urine pH versus WT littermates [19, 63]. This latter observation is important, as it suggests that pendrin may be active under baseline conditions, and its inactivation or inhibition causes acidic urine. Alternative possibilities such as enhanced ammonium excretion in pendrin KO mice should be considered as possible explanation for reduced urine pH in these mutant animals [19, 63].

**Pendrin and salt depletion.** Kidney functions, including salt excretion, glomerular filtration and systemic blood pressure, are all within the normal range in pendrin KO mice under basal conditions [18, 19, 63]. Pendrin KO mice, however, develop volume depletion, metabolic alkalosis and hypotension when subjected to salt restriction [63]. These results are congruent with a recent report indicating the development of metabolic alkalosis in a patient with Pendred syndrome during vascular volume depletion [64] and clearly support an important role for pendrin in salt absorption and bicarbonate secretion in volume-depleted states.

**Pendrin and salt-sensitive hypertension.** Published reports indicate that pendrin plays an important role in aldosterone-mediated hypertension. In detailed studies, Verlander et al. demonstrated that under enhanced salt intake, the aldosterone analog, deoxycorticosterone acetate, causes translocation of pendrin to the apical membrane in mouse kidney CCD and increases systemic blood pressure [65]. The same maneuver in pendrin KO mice failed to increase systemic blood pressure [65]. These results convincingly show that pendrin enhances salt absorption in the kidney collecting duct in the presence of increased aldosterone and contributes to enhanced systemic blood pressure [6, 65].

A recent report examined the role of pendrin overexpression in the pathogenesis of hypertension. Using a mouse transgenic model, the authors showed that pendrin overexpression along the length of the collecting duct increases systemic blood pressure when animals are subjected to increased dietary salt intake [66]. Whether gain-of-function mutations in human pendrin can result in systemic hypertension remains speculative. There are no published linkage analysis studies identifying pendrin as a candidate gene product in salt-sensitive hypertension.
Regulation of pendrin in acid–base and electrolyte disorders

**Pendrin and acid–base disorders.** Pendrin is up-regulated in bicarbonate loading and down-regulated in acidosis [67–73]. These results are consistent with an adaptive role for pendrin in eliminating excess bicarbonate in alkalosis and conserving bicarbonate in acidosis. An alternative view suggests that the up-regulation of pendrin in alkalosis could be secondary to decreased chloride intake (secondary to the consumption of a chloride-free diet and HCO₃⁻/Cl⁻-rich drinking water). Conversely, the down-regulation of pendrin in acidosis is attributed to increased chloride intake in the form of NH₄Cl added to the drinking water [74, 75]. A possible direct effect of systemic pH (acidosis or alkalosis) on pendrin expression needs to be investigated in carefully controlled experiments.

**Pendrin and potassium depletion.** Pendrin expression is down-regulated in rats on a potassium restricted diet [67, 72]. Whether this is an adaptive or a maladaptive process remains speculative. Given the role of pendrin as a bicarbonate-secreting transporter in the collecting duct, we speculate that its down-regulation may contribute to the maintenance of metabolic alkalosis in conditions such as hypokalemia. It should be noted that the induction of potassium depletion in rodents has been generally achieved by dietary potassium restriction [76], which results in reduced aldosterone secretion. However, some of the well-known pathophysiological states associated with potassium depletion (hypokalemia) are due to the treatment with diuretics, such as furosemide, which cause hypovolemia and result in enhanced aldosterone release [77], which can subsequently activate pendrin [65].

It is noteworthy to mention that potassium homeostasis has a unique effect on NCC expression and regulation. Published reports indicate that both dietary K⁺ depletion and dietary K⁺ loading provoke renal Na⁺ retention and increase blood pressure in Na⁺ replete mice, but these occur through different kinase signaling pathways and Na⁺ transporting molecules [78, 79]. While K⁺ loading decreases NCC expression and activity [78], K⁺ depletion activates NCC to promote sodium retention [79]. This latter view was recently emphasized at the American Society of Nephrology (Atlanta, November 2013), where well-designed studies were presented which showed that in conditions of total body potassium depletion NCC is up-regulated (Dr. David Ellison, Robert W. Schrier Endowed lecture, ASN 2013 and Andrew Terker, Chao-Ling Yang, David H. Ellison. A Western diet activates NCC to promote sodium retention. ASN annual 2013, Atlanta). The differential regulation of NCC and pendrin by potassium depletion (above and Refs. 67, 72 and 79) suggests the decoupling of these two transporters in sodium absorption in the distal tubule. It is plausible that the activation of NCC in potassium depletion is meant to maximize sodium absorption in the DCT and minimize potassium secretion in the CCD. Hypothetically, it is also plausible that NCC up-regulation in potassium depletion is secondary to the down-regulation of NKCC2 in the thick ascending limb in the same condition [76], and is an attempt to prevent massive salt wasting.

**Pendrin-dependent, sodium absorption pathways in the collecting duct: electrogenic versus electroneutral pathway.** The accepted belief, based on published studies, was that pendrin-mediated Cl⁻/HCO₃⁻ exchange in B-intercalated cells is primarily coupled to sodium absorption via ENaC in principal cells [6, 65]. However, that view has been revisited. A recent publication indicated that pendrin could work in tandem with the NDCBE to absorb sodium [12, and reviewed in 80], although the exact localization of NDCBE in CCD cells (B-intercalated cells or principal cells) remains unresolved. Such a coordinated mechanism would be electroneutral, could provide an ENaC-independent salt reabsorption pathway in the collecting duct and is not associated with net potassium secretion [12, 80], whereas the pendrin-dependent ENaC salt absorption is associated with a net K⁺ secretion. The schematic diagram in Figure 3A and B depicts the two modes of salt absorption via pendrin. It is plausible that the ENaC-dependent, pendrin-mediated functional complex plays a dominant role in salt absorption in the collecting duct, specifically in the setting of NCC inactivation or inhibition. Whether the ENaC-
independent (NDCBE-dependent), pendrin-mediated salt absorption could function as a substitute for the former (i.e. in the absence of ENaC) or is differentially regulated in pathophysiological states remains to be determined.

Published studies indicate that in NCC KO mice, the expression levels of both pendrin and ENaC in the distal nephron are increased [74, 81–83]. A recent study from our laboratory shows that treatment with amiloride caused significant diuresis in NCC KO but not in wild-type mice, strongly supporting an important role for ENaC in compensatory salt absorption in the setting of NCC inactivation (M. Patel-Chamberlin, K. Zahedi, S. Barone and M. Soleimani. The role of ENaC and the apical Cl–/HCO3– exchanger pendrin in compensatory salt absorption in the distal nephron in NCC KO mice, manuscript under review; abstract presented at the ASN 2013 in Atlanta). Coupled with the massive diuresis found in pendrin/NCC double KO (dKO) mice, but not in NCC or pendrin only KO mice (see below and 83), it was proposed that pendrin-dependent, ENaC-mediated salt absorption is the dominant salt absorbing pathway in the distal nephron in the setting of NCC deletion or inactivation. These results do not conflict with published studies that show ENaC deletion in the collecting duct does not cause excess salt wasting in wild-type mice [84]. Whether pendrin-dependent, NDCBE-mediated salt absorption is differentially regulated and plays an important role in salt absorption in certain pathophysiological states remains to be determined. It is worth mentioning that for pendrin to operate in tandem with ENaC and the apical Cl–/HCO3– exchanger pendrin in the context of NCC inactivation or inhibition [83, 89]. The results demonstrated that the treatment of rats with acetazolamide for 1 week down-regulated the expression of pendrin, leaving NCC as the major salt absorbing transporter in the distal nephron in the setting of increased delivery of salt from the proximal tubule [89]. Under these circumstances, the inhibition of NCC with the use of hydrochlorothiazide caused profound salt wasting and resulted in volume depletion and renal failure [89]. Treatment with hydrochlorothiazide alone did not cause significant diuresis [89]. These results confirm the essential role of pendrin in salt absorption in the distal nephron in the presence of enalapril or enalaprilat [81, 85]. Whether thiazide in combination with pendrin inhibitors is more advantageous than thiazide in combination with amiloride remains to be determined.

**Pendrin and signaling transduction pathways.** The effect of protein kinase A and C on pendrin expression and/or function has been examined. In oocytes injected with pendrin cRNA, phorbol ester only mildly inhibited pendrin (SLC26A4) activity whereas it had a significant inhibitory effect on PAT-1 (SLC26A6) activity [91]. In cultured CCDs pendrin protein abundance increased in the presence of adenylyl cyclase agonist forskolin, a cAMP analog [92]. In cultured kidney cells stably transfected with pendrin cDNA and in isolated microperfused CCDs, stimulation of the cAMP–PKA pathway by isoproterenol increased the apical abundance of pendrin at the cell surface along with its transport activity [93]. These effects were mediated via increased trafficking of pendrin and were associated with its phosphorylation. These studies strongly suggest that pendrin activation by the cAMP–PKA pathway could contribute to enhanced NaCl reabsorption in the kidney collecting duct by β-adrenergic agonists [93].

**Pendrin and cystic fibrosis.** Cystic fibrosis (CF) is the most common lethal genetic disease in the USA. It is caused by mutations in CFTR (cystic fibrosis transmembrane regulator), a CAMP-activated chloride channel, which is widely expressed
in epithelial tissues. CFTR plays an important role in HCO₃⁻ secretion in the duodenum and pancreatic duct by activating the apical Cl⁻/HCO₃⁻ exchangers SLC26A3 (DRA), and SLC26A6 (PAT-1) [94]. Published reports indicate that CFTR and SLC26 bicarbonate transporters construct a bicarbonate-secreting complex via binding at their PDZ-binding ligands [94]. While there are conflicting reports on nephron segment distribution of CFTR in the kidney [95–100], several studies in primary cultures, patches from kidney collecting duct and cultured cells show that CFTR is abundantly expressed in various nephron segments, including the CCD [95, 97–100]. However, the exact role of CFTR in kidney physiology remains speculative. Patients with cystic fibrosis on many occasions present with metabolic alkalosis, specifically at a young age [101, 102]. While the generation of metabolic alkalosis has been attributed to volume depletion subsequent to the loss of electrolytes through the skin, it is highly plausible that pendrin, which plays a major role in chloride reabsorption and bicarbonate secretion in the distal nephron in volume-depleted states, remains inactive in patients with cystic fibrosis, resulting in the inability of the kidney to secrete HCO₃⁻. In support of this hypothesis, recent studies demonstrated that CFTR and pendrin mutually activate each other [103, 104]. These studies showed that a functional, but not a mutant CFTR activates pendrin-mediated Cl⁻/HCO₃⁻ exchange [103, 104]. While the interaction of CFTR and pendrin was specifically demonstrated in cultured tracheal and parotid epithelial cells [103, 104] such a synergy could be at work in CCD cells, where abundant levels of CFTR and pendrin are expressed. It is interesting to note that the highest expression levels of CFTR in the collecting duct are observed in B-intercalated cells, which are the exclusive site of pendrin expression in the kidney [95]. The schematic diagram in Figure 5A and B depicts a hypothetical interaction between CFTR and pendrin in the CCD to facilitate HCO₃⁻ secretion.

**Figure 3:** Pendrin-dependent salt absorption in the collecting duct. Left (A) Pendrin functioning in conjunction with the ENaC. The net effect of this synergy is the absorption of sodium and chloride and the secretion of bicarbonate. Right (B) Pendrin functioning in collaboration with NDCBE (Na⁺-dependent chloride/bicarbonate exchanger). The net effect of this interaction is the absorption of sodium and chloride, with the recycling of bicarbonate via NDCBE and pendrin.

**Figure 4:** A schematic diagram highlighting the synergistic effects of pendrin and NCC inhibition on salt and water excretion. (A) Normal condition: salt reabsorption by NCC and pendrin (working in tandem with ENaC) minimizes the amount of salt that is excreted. (B) Combined inactivation or inhibition of pendrin and NCC causes severe salt wasting.
secretion. Chloride is reabsorbed across the apical membrane via pendrin and transported to the blood via the basolateral chloride channel CLC-K.

**Pendrin-deficient mice and hypercalciuria.** Calcium reabsorption in the DCT and CNT is mediated via apical ECaC (TRPV5), cytosolic Calbindin 28 and basolateral Na/Ca exchange and Ca\(^{2+}\) ATPases [105, 106]. A recent study examined the impact of pendrin deletion on calcium excretion and the expression of calcium-absorbing proteins in the distal nephron [107]. These results demonstrated that the expression of calcium-absorbing molecules (TRPV5, Calbindin 28 and the Na/Ca exchanger) were all decreased in the kidneys of pendrin KO mice [107]. These changes were associated with significant hypercalciuria [107]. Bicarbonate loading for 7 days increased the expression of calcium-absorbing proteins and improved the hypercalciuria in pendrin KO mice [107]. It is plausible that the acidic urine in pendrin KO mice causes hypercalciuria subsequent to the down-regulation of calcium-absorbing molecules in the distal nephron. This is congruent with published reports indicating the down-regulation of ECaC (TRPV5) by acidic pH [81]. The authors [107] proposed that humans with unexplained acidic urine and hypercalciuria [108, 109] could have decreased pendrin activity. It is worth mentioning that in a rat model of hypercalcemia and hypercalciuria, triggered by PTH infusion, urinary excretion of acid increased subsequent to enhanced activity of H\(^{+}\)-ATPase, likely to prevent stone formation [110].

Based on published studies, the working model elucidating chloride reabsorption pathways in the collecting duct indicates the following major mechanisms: first, an active trans-cellular reabsorption by pendrin in B-intercalated cells, which is coupled to the basolateral Cl channel CIC-K (Figure 2) [9]. Second, a passive diffusion of chloride down its electrochemical gradients via the para-cellular pathway [9–11]. This is secondary to a lumen-negative, trans-epithelial electrical potential difference (Vte) generated via Na absorption across the apical membrane through the ENaC (Figure 2) and likely involves claudins [9–11]. Third, the recycling of Cl\(^{-}\) across the basolateral membrane of acid-secreting A-intercalated cells. This is accomplished via the electroneutral Cl\(^{-}\)/HCO\(_3\)^{−} exchanger AE1 (SLC4A1) working in tandem with the basolateral Cl\(^{-}\)channel CLC-K (Figure 2) [16, 17, 31]. Taken together, these studies demonstrate that Cl\(^{-}\) transport is required for both the acidification and alkalization of the urine. The simultaneous operation of these pathways allows the fine-tuning of acid–base excretion. In addition, recent published studies indicate the presence of an apical sodium-dependent chloride/bicarbonate exchange that can function in tandem with pendrin [12]. Studies examining the role of NDCBE in salt absorption in the collecting duct in salt deplete/salt replete states or in the setting of NCC inactivation in NDCBE KO mice are wanting.

In conclusion, pendrin is a multifaceted transporter that plays important roles in various functions of the kidney, including chloride homeostasis, vascular volume and blood pressure regulation, acid–base balance and calcium excretion. Furthermore, recent studies demonstrate that pendrin plays an essential role in distal tubule salt reabsorption in the setting of NCC inactivation. We propose that pendrin could provide a novel target for a new class of diuretics that, in conjunction with thiazide derivatives, can be an effective regimen for patients with fluid overload, such as those with congestive heart failure.

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One hundred ways to kill a podocyte

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ABSTRACT

The podocyte is a highly specialized cell, forming within the developing glomerulus from a mesenchymal origin, acquiring some but not complete features of an epithelial cell as it matures. Once mature, this cell has the potential to receive signals from several different directions and sits within a dynamic microenvironment. By taking an overview of many lines of evidence, it is clear that we already know many signals that are tightly controlled in keeping the podocyte healthy. For example, vascular endothelial growth factor, insulin and integrins are all known to have bidirectional effects on podocyte functionality, depending on whether there is too much or too little. It is of little surprise therefore that disrupting this delicate balance can result in a dramatic loss of function, and manifestation of glomerular disease originating from many different primary insults. The cues directing podocyte phenotype and functionality for the purpose of this review will be divided into four main sources: (i) genetic, (ii) paracrine signals from endothelial and mesangial cells, (iii) direct contact signals to/from the glomerular basement membrane and (iv) signals from circulating plasma. Of course there are other influences, which we still know little about, such as flow and shear stresses, signals from the urinary space that should all be considered in the overall healthy environment.

Keywords: endothelin, endothelial, integrin, mesangial, nephrotic, podocyte

WHAT MAKES A PODOCYTE A PODOCYTE?

In order to approach the question of what kills a podocyte, we need to address the important elements of what keeps a podocyte alive, and phenotypically healthy in normal physiology (Figure 1). These influences are discussed in the following sections.

Genetic influences

A great deal has been learnt from genetic studies, both in mouse and man, about molecules that are crucial for podocyte health and survival. Podocyte-specific knockout (KO) models have allowed the testing of many proteins for their relevance in podocyte biology. Some of the deleterious results discovered are understandable in the context of disrupting important cell survival pathways (e.g. [1, 2]). However, landmark discoveries of podocyte-restricted proteins, in particular nephrin and...