signaling system. This is notable because RSK also phosphorylates BAD on Ser-155 (Figure 2). PGE_2, acting through EP2/EP4, has been shown to activate Rap1 through an EPAC signaling pathway;[8] Rap1 is upstream of MEK/ERK/RSK. In unrelated studies, Wang *et al.*[9] found that EPAC acts coordinately with PKA in renal inner medullary collecting duct cells to alter urea movement and potentially other transport processes that are important for renal-cell osmoregulation. While the study did not examine the potential involvement of PGE_2, it demonstrated that hypertonicity activates the EPAC pathway in the inner medulla. When considered altogether, these studies suggest that PGE_2 can modulate BAD activity and apoptosis in the renal tubular epithelial cells in the inner medulla by activating parallel signaling pathways involving EPAC and PKA.

Although the hypertonicity-induced increase in COX-2 activity can antagonize the apoptotic action of BAD, the potential negative effects of COX-2 should not be ignored. In situations where increased PGE_2 would be detrimental, there are alternate means by which BAD can be phosphorylated that offer an alternate control of apoptosis for the kidney.[7] Ser-155 can be phosphorylated by RSK following activation of protein kinase C (Figure 2). Phosphatidylinositol-3-kinase (PI3K) and heat-shock proteins HSP90 and HSP27 stimulate AKT to inactivate BAD by phosphorylating it on Ser-136.

In conclusion, the work of Küper *et al.*[2] provides new insights into the mechanisms responsible for the deleterious effects of reducing COX-2 activity pharmacologically or genetically in the kidney, by characterizing the key roles of PGE_2 and BAD in the survival responses of renal epithelial cells to hypertonic stress. The study suggests that inhibition of COX-2 by NSAIDs could be detrimental to inner medullary epithelial cells by increasing the pro-apoptotic actions of BAD and ultimately cell death. Given the complexity of responses that can be evoked by COX-2-generated prostaglandins, and the potential for non-prostaglandin-mediated regulation of BAD function, caution should be exercised not to oversimplify the control of apoptosis in the renal medulla and the role of NSAIDs in this process.

DISCLOSURE
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A new regulator of the vacuolar H^+-ATPase in the kidney

Dominique Eladari[1,2,3] and Jacques Teulon[1]

Xu *et al.* identify Slc26a11, a novel member of the Slc26 anion exchanger family, as an electrogenic $(Cl^-)_n/HCO_3^-$ exchanger. Functional characterization of this transporter suggests that Slc26a11 mediates classical electroneutral Cl^-/HCO_3^- exchange but also exhibits an electrogenic Cl^- conductance. In the kidney, Slc26a11 colocalizes with the vacuolar H^+-ATPase in intercalated cells, emphasizing the cooperation of the proton pump with chloride transporters.

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Vacuolar H^+-ATPases (V-ATPases) are large multiprotein complexes that use the energy produced by adenosine triphosphate (ATP) breakdown to pump protons across cell membranes. In eukaryotic cells, the V-ATPases are expressed ubiquitously in intracellular organelles, where they play a critical role in their acidification and intracellular trafficking. They are also present at the plasma membrane of some specialized cells, such as osteoclasts and kidney epithelial cells, where they mediate acidification of the extracellular space or are involved in acid–base transport. A large set of published data indicates that Cl^- channels or transporters might influence the activity of V-ATPases, via several possible mechanisms.

In this issue, Xu *et al.*[1] identify Slc26a11, a member of the Slc26 exchanger superfamily, as a novel partner of the V-ATPase

[1]*Centre de Recherche des Cordeliers, Équipe de Recherche Labellisée (ERL) Centre National de la Recherche Scientifique (CNRS) 7226, INSERM UMRS 872 (Équipe 3), Université Pierre et Marie Curie, Paris, France;* [2]*Département de Physiologie, Hôpital Européen Georges-Pompidou–Necker Enfants Malades, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France and* [3]*Faculté de Médecine Paris Descartes, Université Paris Descartes, Paris, France*
Correspondence: *Dominique Eladari, INSERM U872, Équipe 3, 15 Rue de l'École de Médecine, Esc. E RDC, F-75006 Paris, France.*
E-mail: dominique.eladari@crc.jussieu.fr

in the kidney, thus giving new insight into a complex issue. The authors nicely show that the Slc26a11 protein, exclusively present in the collecting duct, colocalizes with the V-ATPase in three different cell types: Slc26a11, like the V-ATPase, is apically expressed in A-intercalated cells, whereas both proteins are on the basolateral side in B-intercalated cells. In addition, some cells, probably representing non-A-, non-B-intercalated cells, display colocalization on their apical and basolateral membranes. This common localization in three different types of cells by itself suggests that Slc26a11 and the V-ATPase might functionally interact. Indeed, in a second set of experiments, the authors demonstrate that Slc26a11 expressed into COS7 cells activates endogenous V-ATPase by a chloride-dependent mechanism.

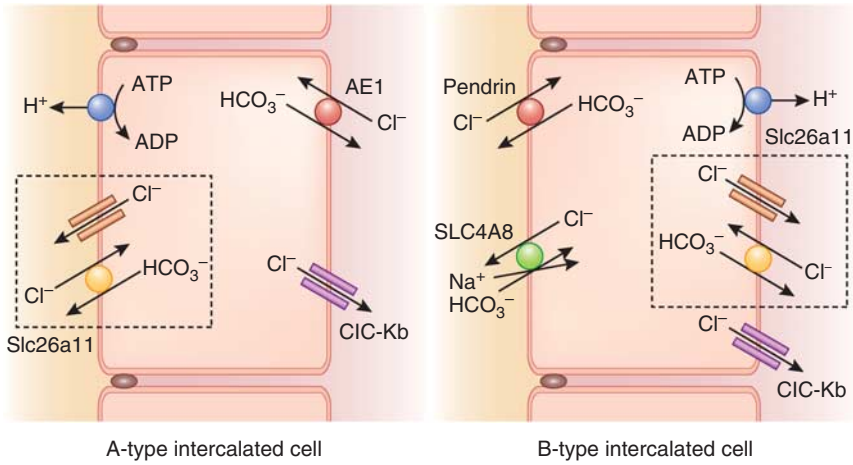

Figure 1 | Complex arrangement of ion transport systems in intercalated cells. The newly identified Slc26a11 protein is expressed on the same membrane as the H^+-ATPase, that is, in the apical membrane of A-type intercalated cells and in the basolateral membrane of B-intercalated cells. It may function as a Cl^- channel or Cl^-/HCO_3^- exchanger. Note the presence in these cells of other Cl^-/HCO_3^- exchangers and, on the basolateral membrane, of the ClC-Kb chloride channel.

The Cl^- dependence of V-ATPase activity is generally accepted when it concerns intracellular membranes but is more speculative for the V-ATPase in plasma membranes. However, a few studies have proposed a role for Cl^- conductance in the regulation of the V-ATPase in the proximal convoluted tubule and the distal convoluted tubule.[2,3] Translocation of H^+ across membranes by V-ATPases is electrogenic. In intracellular organelles, the accumulation of positive charges into a limited space may generate a large transmembrane potential difference, resulting in pump self-inhibition in the absence of an electric shunt. Several Cl^- transporters and channels have been implicated in this process, following pioneer observations in Golgi vesicles isolated from rat liver,[4] or in secretory granules of parathyroid cells,[5] showing that Cl^- conductance is strictly necessary to V-ATPase activity. The molecular identity of the Cl^--conducting pathways remains elusive. However, CFTR and ClC-5, which are widely distributed along the nephron, where they colocalize largely with the V-ATPase, particularly in intracellular organelles, are attractive candidates in the kidney. Accordingly, a recent study demonstrated that the knockdown of ClC-5 or CFTR significantly decreased V-ATPase-mediated proton secretion in isolated proximal tubules.[2] However, other studies have provided evidence for direct modulation of V-ATPase activity by luminal Cl^-, independent of voltage. For instance, acidification of renal endosomes[6] or V-ATPase activity in renal proximal tubule cells[2] remains dependent on the presence of Cl^- when membrane potential difference is dissipated artificially with valinomycin. The role of vesicular Cl^- has been further demonstrated in two elegant studies in which ClC-5 and ClC-7 were mutated within a single residue to change transport activity from Cl^-/H^+ exchange into uncoupled Cl^- conductance. In these studies, the authors showed that the mutated ClCs (although acting as electric shunts) were not able to improve the activity of the V-ATPase to higher levels than in animals devoid of ClC-5[7] or ClC-7.[8] Thus, the mechanisms by which chloride transporters/channels can activate the intracellular V-ATPase are unclear and may well include modulation of the intravesicular Cl^- concentration, or additional unknown mechanisms.

Interestingly, whereas most of the Slc26a transporters mediate classical Cl^-/anion exchange, Xu *et al.*[1] demonstrate the existence of two independent modes of Cl^- transport for Slc26a11, electroneutral Cl^-/HCO_3^- exchange and Cl^- conductance, by manipulating transmembrane potential. The fact of a transporter displaying associated conductance properties has already been reported for the Na^+-HCO_3^- cotransporter NBCn1, which harbors a Na^+ current,[9] and for the two glutamate transporters EAAT1 and EAAT3, which possess a Cl^- conductance.[10] Within the Slc26a11 family, two members, Slc26a7 and Slc26a9, display Cl^- channel properties. It is yet unclear, since all transporters were expressed in heterologous cells for characterization, whether these channel-like activities reflect intrinsic properties of these different transporters. Nevertheless, several members of the Slc26 family, including Slc26a3, Slc26a6, and Slc26a9, have been shown to associate and establish a functional cooperation with CFTR. Since previous reports have shown the potential stimulatory effects of CFTR on the V-ATPase, it would be worthwhile to test whether Slc26a11 chloride conductance reflects an association with CFTR or a CFTR-like channel. The mechanism by which chloride transporters/channels can activate the V-ATPase remains unclear. As is indicated above, at least two possibilities have been already proposed: (1) chloride transporters might act as chaperone, regulating the expression of the V-ATPase or its interaction with a channel critical for its function, such as CFTR; and (2) chloride ions moving in parallel to protons may dissipate the electrical gradient across membranes and thereby avoid self-limitation of the pump. Xu *et al.*[1] demonstrate that chloride depletion of the cells abolishes the activation of the V-ATPase by Slc26a11. Further, they demonstrate that the stimulatory effect of

Slc26a11 on the V-ATPase is only mildly affected by alteration in the membrane potential. Taken together, these observations suggest that the V-ATPase is activated by intracellular chloride and put forward a critical role of Slc26a11 in modulating intracellular Cl^-.

In summary, Xu *et al.*[1] have identified a possible novel regulator of the V-ATPase in renal intercalated cells. This study raises a number of exciting possibilities for identifying new regulatory mechanisms of renal acidification. Particularly interesting is the fact that Slc26a11 may function in Cl^- conductance mode or Cl^-/HCO_3^- exchange mode, under conditions that remain to be determined. Incidentally, these results also emphasize the complex arrangement of transport proteins in the various types of intercalated cells, altogether indicating that the functions of these cells are not yet totally understood (Figure 1).

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Choice of dialysis modality

Rajnish Mehrotra[1,2]

Few medical decisions have as profound an impact on every aspect of a patient's life as the selection of dialysis modality by a patient with end-stage renal disease. It remains uncertain whether the outcome differences seen between hemodialysis and peritoneal dialysis patients, if any, in observational studies are attributable to the dialysis modality. Such studies, thus, are insufficient to deny patients a choice in selecting their dialysis modality.

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Over the past three decades, scores of single-center, multicenter, and national-registry studies have compared the outcomes of end-stage renal disease patients treated with hemodialysis (HD) and peritoneal dialysis (PD). Even though the results have not always been consistent, a few common themes emerged from the studies using cohorts from the 1990s.[1] First, although the early risk for death was lower in PD patients, the long-term patient and technique survival was not as good as achieved with HD. Second, the relative outcomes varied by age, diabetic status, and comorbidity status of patients—younger, nondiabetic patients with no additional comorbidity treated with PD had a considerably lower risk for death than those treated with HD, but older diabetic PD patients had a higher risk for death than the corresponding HD patients.[1] These results, however, have limited applicability for our current clinical practice, as improvements in outcomes of PD patients have outpaced those seen with HD. Thus, in contemporary cohorts in the United States there is no significant difference in the 4-, 5-, and 10-year survival of patients treated with HD or PD.[2,3] The overall equivalency in outcomes with the two therapies in more recent cohorts has also been reported from Australia, New Zealand, Taiwan, and Colombia, regions with higher rates of PD utilization than seen in the United States.[3] The differential improvement in outcomes has been seen for every subgroup of patient such that the higher risk for death in the older diabetics has attenuated in comparison with earlier cohort periods.[2] Despite the multitude of these comparisons, the central question meant to be answered by these studies remains: are any of the differences in outcomes seen in any cohort or any subgroup thereof attributable to the dialysis modality or a result of unmeasured differences in the characteristics of the patients who choose a given modality? And is it appropriate to use data from such observational studies when discussing the dialysis treatment options with an individual patient?

It is with this background that one should interpret the results of the analyses

[1]*Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, California, USA and* [2]*David Geffen School of Medicine at UCLA, Los Angeles, California, USA*
Correspondence: *Rajnish Mehrotra, Los Angeles Biomedical Research Institute at Harbor-UCLA, 1124 W. Carson Street, Torrance, California 90502, USA. E-mail: rmehrotra@labiomed.org*