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Opening lines of communication in the distal nephron

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Commentary

The distal nephron is composed of two main cell types: principal cells and intercalated cells. These cells have distinct morphologic features that allow them to be readily distinguished by light microscopy, as well as distinct suites of proteins that facilitate cell-specific transport properties. In this issue of the *JCI*, Gueutin and colleagues describe a new mechanism by which β-intercalated cells, via release of ATP and prostaglandin E_2 (PGE_2), influence the activity of transporters in principal cells.

Although fasting insulin is used as a surrogate measure of insulin resistance, it has a stronger correlation with insulin clearance, which is highly heritable (19, 20). Future human genetic studies will be important for determining whether genetic variation in *SLC30A8* contributes to T2D entirely through its effect on insulin clearance and how much of the heritability of insulin clearance is due to *SLC30A8*.

These studies illustrate how in-depth phenotyping, which requires model organisms, can take clues from human genetics and provide mechanistic explanations for relationships between genetic variation and human disease. Results from these studies can now be used to study subphenotypes associated with diabetes susceptibility. In this case, it may motivate study of the relationship among inorganic physiology (such as the Zn^{2+} fluxes described here), genetic variation at the *SLC30A8* locus, and insulin clearance. Most importantly, these deeper phenotypes should be present in nondiabetics, and thus can be studied independently of the disease.

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Opening lines of communication in the distal nephron

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The distal nephron is composed of two main cell types: principal cells and intercalated cells. These cells have distinct morphologic features that allow them to be readily distinguished by light microscopy, as well as distinct suites of proteins that facilitate cell-specific transport properties. In this issue of the *JCI*, Gueutin and colleagues describe a new mechanism by which β-intercalated cells, via release of ATP and prostaglandin E_2 (PGE_2), influence the activity of transporters in principal cells.

Challenging tradition

The traditional view of the distal nephron considers principal cells to be primarily responsible for reabsorption of filtered Na^+ and for K^+ secretion into the ultrafiltrate, whereas intercalated cells account for urinary acidification. Sodium reabsorption by principal cells occurs via the Na^+/Cl^- cotransporter (NCC) in the early distal nephron and the epithelial Na^+ channel (ENaC) in later nephron segments. Potassium is secreted via the renal outer medullary K^+ channel (ROMK; Figure 1A). Intercalated cells are primarily responsible for urinary acidification, through H^+ secretion by the vacuolar H^+-ATPase or the H^+/K^+-ATPase found in α-intercalated cells. When required, HCO_3^- secretion into the ultrafiltrate occurs via the Cl^-/HCO_3^- exchanger pendrin (also known as SLC4A4) in β-intercalated cells (1, 2). This view presumes limited crosstalk between principal and intercalated cells, as a lack of gap junctions between these cell types limits their communication (3, 4).

As we learn more about properties of the distal nephron, distinctions between principal and intercalated cells are beginning to fade. Recent studies have shown

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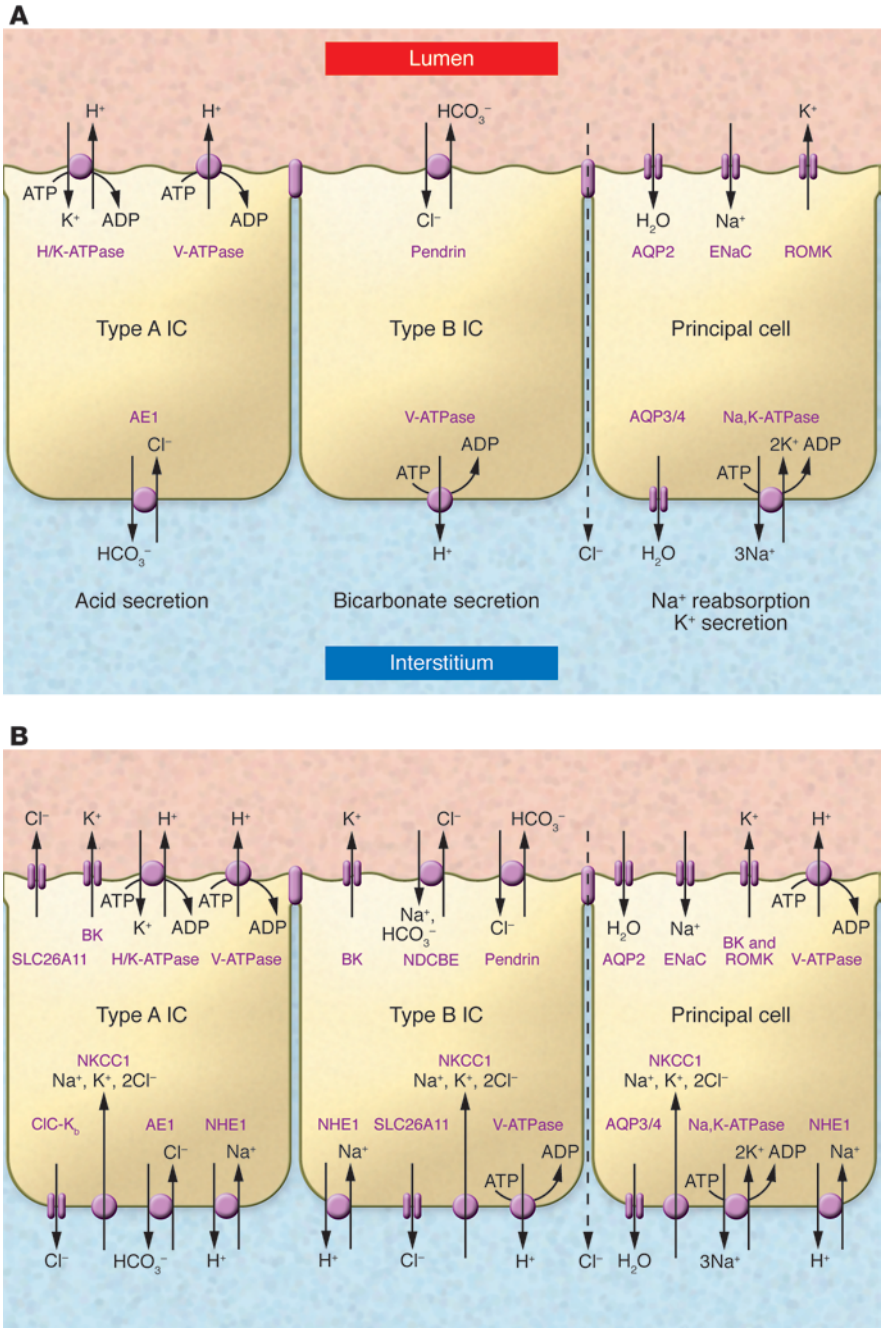

Figure 1

Evolving understanding of the distal nephron. (**A**) Traditional view, highlighting key transport proteins involved with acid/base, salt, and water balance in kidney collecting duct α (type A) and β (type B) intercalated cells (ICs) and principal cells. (**B**) Updated view, based on studies performed in mice, rats, or rabbits. Although SLC26A11 is represented as a Cl^- channel, there is evidence that it may also function as a Cl^-/HCO_3^- exchanger. AE1, anion exchanger 1; AQP, aquaporin; ClC-K_b, Cl^- channel, kidney-specific (type B); NDCBE, Na^+-dependent Cl^-/HCO_3^- exchanger; NHE1, Na^+/H^+ exchanger 1; NKCC1, $Na^+/K^+/2Cl^-$ cotransporter 1; V-ATPase, vacuolar H^+-ATPase.

that intercalated cells are capable of reabsorbing filtered Na^+ and Cl^- via a luminal Na^+-dependent Cl^-/HCO_3^- exchanger, SLC4A8, which operates in parallel with pendrin (Figure 1B and refs. 2, 5). Reabsorption is not blocked by amiloride, a prototypic ENaC inhibitor, but is blocked by thiazide diuretics, which are also inhibitors of NCC. The finding that mice overexpressing pendrin develop salt-sensitive hypertension suggests that this NaCl transport system has an important role in the reabsorption of filtered NaCl and regulation of extracellular fluid volume and blood pressure (6).

Evidence also suggests that intercalated cells, along with principal cells, participate in K^+ secretion that is activated by increased tubular flow rates. In this context, K^+ secretion is mediated by the luminal large-conductance Ca^{2+}-activated K^+ channel (referred to as the BK channel) and the basolateral $Na^+/K^+/2Cl^-$ cotransporter (7, 8). The findings that both individuals with Bartter syndrome as a result of ROMK loss-of-function mutations and mice lacking ROMK expression have robust renal K^+ secretion highlight the importance of this BK channel–mediated K^+ secretory pathway (9). Although neonates with loss of function ROMK mutations may exhibit early hyperkalemia (10), this likely reflects a delay in BK channel expression in the immediate postnatal period. Finally, identification of a luminal H^+-ATPase in principal cells, although modest compared with intercalated cell H^+-ATPase, raises the possibility that these cells may contribute to renal H^+ secretion (11).

Working together

Given the recent findings that principal and intercalated cells transport similar cations, it is likely that mechanisms have evolved to coordinate the transport of specific ions across these distinct cell types. For example, pendrin-dependent transport of HCO_3^- into the tubular lumen by intercalated cells enhances ENaC activity in principal cells (12). High tubular flow activates autocrine/paracrine prostaglandin E_2 (PGE_2) release in the distal nephron, presumably via activation of cytosolic phospholipase 2 (cPLA2), which in turn regulates flow-stimulated Na^+ and K^+ transport in cortical collecting ducts (13). Gueutin and colleagues address the issue of functional crosstalk between intercalated and principal cells of the distal nephron in this issue of the *JCI* (14). Distal renal tubular acidosis is a clinical disorder associated with reduction or loss of distal nephron acid secretion. In humans, this disorder is accompanied by increased urinary Ca^{2+} losses, nephrocalcinosis, and chronic kidney disease. It is not surprising that humans with this disorder also exhibit enhanced renal Na^+ and K^+ losses, as this

could simply reflect damaged cells within the distal nephron (15). The authors studied a mouse model of distal renal tubular acidosis in which the gene encoding the B1 subunit of the vacuolar H^+-ATPase was disrupted (16). Previous characterization determined that these animals have a blunted response to increased acid load and do not have enhanced urinary Ca^{2+} losses or nephrocalcinosis.

Surprisingly, the authors found that these animals have an impaired ability to adapt to a low-NaCl diet. Normally, transition to a low-NaCl diet is accompanied by enhanced Na^+ reabsorption in the nephron and reduced urinary Na^+ excretion. Studies of cortical collecting ducts isolated from mice lacking the vacuolar H^+-ATPase B1 subunit revealed that both Na^+ and Cl^- absorption were suppressed, as were transporters responsible for Na^+ and Cl^- absorption (ENaC α and γ subunits and pendrin) in this nephron segment. The impaired Na^+ reabsorption was not due to reductions in the renin-angiotensin-aldosterone system, which is known to activate Na^+ transporters in the distal nephron. These findings raised the possibility that there are other factors responsible for blunting NaCl absorption in the distal nephron.

The authors found increased urinary excretion of PGE_2 and ATP in mice lacking the vacuolar H^+-ATPase B1 subunit. β-intercalated cells have a key role in the release of PGE_2, as blocking vacuolar H^+-ATPase in β-intercalated cells within isolated cortical collecting ducts was associated with enhanced PGE_2 release. This prostanoid is a known inhibitor of ENaC (17). Extracellular ATP has a role in this process, as PGE_2 release was dependent on ATP-dependent signaling via purinergic receptors. Extracellular ATP, released by connexin hemichannels and signaling through purinergic receptors, is also a known ENaC inhibitor that reduces channel open probability (18, 19).

In addition to the changes in renal Na^+ handling, mice lacking expression of the vacuolar H^+-ATPase B1 subunit had a urinary concentrating defect, reflecting reduced aquaporin 2 expression. When fed a low-Na^+ diet, these mice also exhibited enhanced renal K^+ loss, which appeared to be due to increased BK channel expression and increased urinary flow.

A cooperative future

In summary, the work presented by Gueutin and colleagues (14) introduces a new paradigm of crosstalk between principal and intercalated cells and provides further evidence that both cell types are important in maintaining Na^+ balance and thus blood pressure. This work also raises a number of questions that we hope will be addressed in future studies. While inhibition of basolateral vacuolar H^+-ATPase in β-intercalated cells was necessary to see the crosstalk between intercalated and principal cells, we do not know whether this regulatory interaction is also seen when β-intercalated cell vacuolar H^+-ATPase activity is reduced by endogenous regulatory factors, such as increased acid load associated with a "typical" Western diet. Do inhibitors of prostaglandin synthesis (e.g., indomethacin and other nonsteroidal antiinflammatory drugs) have a role in preventing urinary loss of Na^+ in individuals with congenital or acquired distal renal tubular acidosis, with the caveat that long-term use of the drugs may damage the kidney? What are the cellular mechanisms that lead to increased ATP release when vacuolar H^+-ATPase in β-intercalated cells is inhibited? Are impairments in different components of this paracrine signaling pathway involved in the pathogenesis of salt-sensitive hypertension? The answers to these questions should provide useful information by which to understand the interaction between principal and intercalated cells, and also direct development of therapeutics for renal disease. On a final note, the authors' observations raise the possibility that other mechanisms of crosstalk exist between these cells to facilitate the coordinated regulation of transporters between intercalated and principal cells.

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