Paracellular Channels!

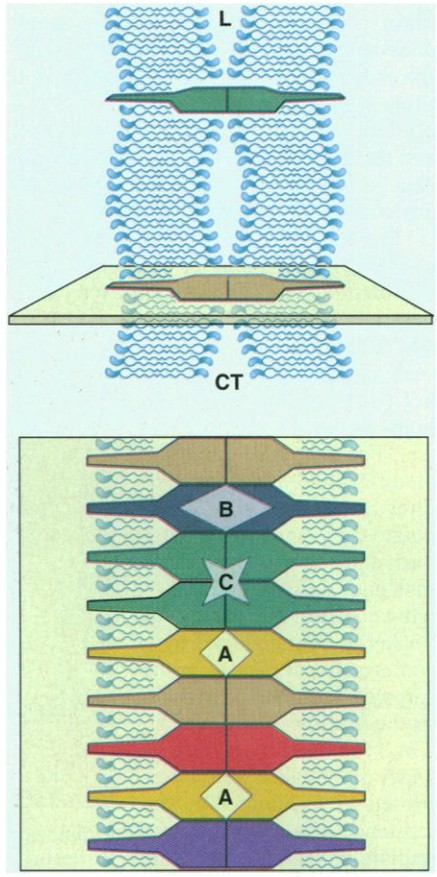
Vivian Wong and Daniel A. Goodenough

Each human kidney contains about 1.3 million minute tubules lined by a continuous layer of epithelial cells. Fluid that is forced out of the blood from specialized capillaries enters these tubules at their origins and exits into the ureter leading to the urinary bladder. Molecules and ions that the body needs are resorbed back across the epithelial layer of the tubules into the blood. Resorption depends on two separate routes: a transcellular pathway (through the cell cytoplasm via selective pumps and cotransporters on epithelial cell plasma membranes) and a paracellular pathway (through the intercellular space between cells). The paracellular pathway is regulated by tight junctions, intercellular structures in which the plasma membranes of adjacent epithelial cells come into very close contact (see figure, top). Tight junctions circumscribe the entire apical boundary of each cell and can be visualized by freeze-fracture as linear arrays of membrane proteins (*1*), which include occludin (*2*) and members of the claudin protein family (*3*). On page 103 of this issue, Simon *et al.* (*4*) now report that a new member of the claudin protein family, paracellin-1, regulates the paracellular transport of magnesium ions (Mg^{2+}) in the kidney tubule. This is the first report of a tight junction protein that is involved in paracellular ion conductance.

The resistance of the electrical seal of the tight junction can be assessed by the flow of ions through the paracellular pathway. Epithelial cells from different parts of the body form tight junctions that range from "leaky" (with a high ionic flow rate) to "tight" (with a low ionic flow rate) (*5, 6*). Several characteristics are shared by tight junctional channels and conventional ion channels, which regulate ion flow across plasma membranes. First, both types of channel can be blocked by large, positively charged ions. Second, they both have estimated pore diameters of the same order of magnitude. Third, tight junctions are selective for cations over anions, resembling certain semiselective cation channels such as the acetylcholine receptor. A notable difference between the two types of channels is that junctional channels are oriented parallel to the plane of the membrane, whereas conventional channels are oriented perpendicular to the plane of the membrane. Thus, tight junctional channels do not cross the membrane lipid bilayer. There has been no direct evidence, however, for the formation of a paracellular channel by any of the known tight junction proteins.

In a lovely dance between clinical and basic science, the report by Simon *et al.* (*4*) now reveals that paracellin-1 regulates the resorption of Mg^{2+} through paracellular channels in the kidney tubule. Unlike other ions such as Na^+, K^+, and Ca^{2+}, which depend on active resorption, Mg^{2+} is resorbed largely by transport through the paracellular pathway, driven by an electrochemical gradient across the tubule epithelium (*7*). By analyzing 12 families with hypomagnesemia—a wasting syndrome characterized by excessive loss of Mg^{2+} and Ca^{2+} and kidney failure—Simon and co-workers positionally cloned the gene encoding paracellin-1. This novel protein is found exclusively in the tight junctions of the thick ascending limb of the kidney tubule, the region that is responsible for Mg^{2+} resorption.

The disease mutations documented in paracellin-1 may result in an increase in the resistance of the electrical seal of tight junctions, with a concomitant decrease in epithelial ionic permeability. Thus, owing to the exclusive location of paracellin-1 in the tubule's thick ascending limb, Mg^{2+} resorption through tight junctions would be selectively impeded. Alternatively, the results of the Simon study could indicate that paracellin-1 forms a highly selective Mg^{2+}/Ca^{2+} channel. Indeed, their data support an attractive hypothesis suggesting that each member of the claudin family (and possibly also occludin) constitutes a distinct channel that possesses selective permeability (see figure, bottom). The expression of different claudins would provide a flexible mix-and-match system for regulating the paracellular pathway. The heterogeneity of the claudin family would permit channels with differing permeabilities to reside side-by-side within the same tight junction. Oligomeric assemblies could create other channel topologies (see figure, bottom). Moreover, interchangeable subunits offer a mechanism to modulate paracellular permeability within the tubule epithelia without reconstructing the entire structure of the tight junctions. The elegant study of Simon *et al.* introduces new avenues for research that should improve our understanding of the paracellular pathway of ion transport and its regulation by tight junctions.



Tight squeeze. The lipid bilayers of two apposed epithelial cells interact to form a tight junction (**top**). Integral membrane proteins (such as occludin or a member of the claudin protein family) interact at discrete points of contact, occluding the extracellular space, thus providing a seal between lumenal (L) and connective tissue (CT) compartments. (The different colors indicate the heterogeneity of protein composition.) The protein-protein interactions must be continuous around the perimeter of each cell such that in a perpendicular section at one point of contact (**bottom**), the proteins are arrayed with tight lateral interactions, in addition to head-to-head interactions. Heterogeneity in this protein array offers the possibility of different types of channels (A, B, and C) composed of pairs of proteins (A and B) or oligomers of proteins (C).

The authors are in the Department of Cell Biology, Harvard Medical School, Boston, MA 02115, USA. E-mail: daniel_goodenough@hms.harvard.edu

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