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See related article, "MicroRNA-324-3p Promotes Renal Fibrosis and Is a Target of ACE Inhibition," on pages 1496–1505.

Aquaporin 2: Not Just for Moving Water

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Aquaporin 2 (AQP2) is widely recognized for its role in vasopressin-stimulated water transport across the collecting duct and hence in the production of concentrated urine.[1,2] AQP2 is primarily expressed in the apical plasma membrane and subapical vesicles of the collecting duct, although it has also been detected in the basolateral plasma membrane.[3] In response to vasopressin binding to the V_2-vasopressin receptor, AQP2 is trafficked from the subapical vesicles to the apical plasma membrane; AQP2 is endocytosed and recycled into subapical vesicles when the vasopressin stimulus ends.[1] Water exits collecting duct cells through AQP3 and APQ4, located in the basolateral plasma membrane, resulting in the transcellular reabsorption of water.[4]

In the current issue of *JASN*, Chen *et al.*[5] provide evidence for a novel role for AQP2 in promoting cell migration and epithelial morphogenesis. Their rationale for hypothesizing that AQP2 may do more than transport water merits explanation, as it is quite clever. They noted that the phenotype of AQP2-null and -transgenic mice includes the severe urine concentrating defect that one would anticipate, but also includes renal tubular abnormalities and neonatal mortality from renal failure.[6–8] Mice lacking AQP3 or AQP4 (or AQP1, which is not expressed in the collecting duct) also have a severe urine concentrating defect, but do not have the tubular abnormalities or neonatal mortality.[9] Thus, they reasoned the phenotype of the AQP2-null mouse was not simply the result of polyuria and a severe urine concentrating defect but must result from another, previously unrecognized, function of AQP2.

Insight into what this novel role may be came from Chen *et al.* identifying a potential integrin-binding site in AQP2, which is not present in other aquaporins. In addition, Tamma *et al.*[10] recently showed that integrin signaling modulates AQP2 trafficking. This suggested to Chen *et al.* that an interaction between AQP2 and an integrin at this site may contribute to the tubular abnormalities seen in AQP2-null mice.

What are integrins? Integrins are a large family of cell surface adhesion receptors that transduce signals coordinately with growth factors and the extracellular matrix.[11] Integrins are expressed in the collecting duct and play an important role in kidney development and repair.[12] More specifically, one of the integrins, integrin β1, plays an important role in collecting duct development and the maintenance of tubular integrity.[13,14] Thus, Chen *et al.* explored whether the potential integrin-binding site in AQP2 could play a role in the abnormalities found in AQP2-null mice.

In their study, Chen *et al.* confirmed that AQP2-null mice have tubular defects that were apparent as early as postnatal 7 days of age. They also found abnormal subcellular distribution of integrin β1 in the AQP2-null mice, with integrin β1 being expressed primarily at the basolateral plasma membrane. These *in vivo* studies are important for establishing a potential physiologic role for an AQP2–β1 integrin interaction.

To further explore the functional significance of an AQP2–β1 integrin interaction, Chen *et al.* proceeded to study cultured cells. They showed that AQP2 interacts with integrins through the integrin-binding site in AQP2, Arg-Gly-Asp (RGD), which is the same motif identified by Tamma *et al.*[10] They then observed that AQP2 promotes epithelial cell migration, which is an important mechanism of tissue repair following injury, in both MDCK and LLC-PK1 cells, and that promigration effects requires both AQP2 and β1 integrin. Finally, they proceeded to show that AQP2 promotes epithelial cell migration by facilitating the turnover of β1 integrin in the focal adhesions.

In the present study, Chen *et al.* elucidate a novel role for AQP2 in modulating β1 integrin trafficking and surface expression, and turnover at the focal adhesions. This mechanism

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allows AQP2 to contribute to cell motility and epithelial morphogenesis and may allow AQP2 to play an important role in the development and maintenance of tubular structure. These findings may also explain why AQP2-null mice have abnormal tubule development and neonatal mortality, in contrast to other AQP-null mice. The piecing together of the uniquely abnormal phenotype of AQP2-null mice and the integrin binding site, and then demonstrating the functional consequences of the AQP2–β1 integrin interaction, provides a significant advance in our understanding of AQP2 biology and suggests a previously unrecognized role for AQP2 in tubule development.

Although AQP2-null mice demonstrate neonatal mortality, there are humans with AQP2 mutations who do survive to adulthood. At first glance, this may suggest that the abnormalities in the AQP2-null mice do not occur in people. However, there is an important difference between AQP2-null mice and humans with AQP2 mutations: the mice completely lack AQP2, whereas the humans have a mutated form of AQP2 that does not transport water. Because the RGD motif that binds β1 integrin is located in the second extracellular loop of AQP2,[5,10] one wonders whether the mutant AQP2 proteins present in humans maintain this newly identified role of AQP2 in regulating epithelial cell migration through interaction with β1 integrin, even if they cannot transport water? It would be interesting to test whether known disease-causing AQP2 mutations interact with β1 integrin and maintain a promigratory effect on epithelial cell mobility.

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DISCLOSURES

None.

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See related article, "Aquaporin 2 Promotes Cell Migration and Epithelial Morphogenesis," on pages 1506–1517.

Lifetime Risk of ESRD: A Meaningful Concept?

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Turin and colleagues[1] present some fascinating estimates of both the lifetime and short-term risks of ESRD in this issue of *JASN*, exploiting the excellent epidemiologic database in Alberta, Canada. Based on a total population of nearly 2.9 million persons with nearly 26 million person-years of follow-up, they have been able to calculate actual lifetime event rates of ESRD (2.6% and 1.8% for men and women, respectively) rather than the synthetic estimates based on observed incidence rates applied to hypothetical populations.[2]

The advantage of this approach is not so much in increased accuracy of the estimate as in the ability to array the predictions

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