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Review

Regulation of aquaporin-2 trafficking and its binding protein complex

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Abstract

Trafficking of water channel aquaporin-2 (AQP2) to the apical membrane is critical to water reabsorption in renal collecting ducts and its regulation maintains body water homeostasis. However, exact molecular mechanisms which recruit AQP2 are unknown. Recent studies highlighted a key role for spatial and temporal regulation of actin dynamics in AQP2 trafficking. We have recently identified AQP2-binding proteins which directly regulate this trafficking: SPA-1, a GTPase-activating protein (GAP) for Rap1, and cytoskeletal protein actin. In addition, a multiprotein "force generator" complex which directly binds to AQP2 has been discovered. This review summarizes recent advances related to the mechanism for AQP2 trafficking.

Keywords: PKA phosphorylation; Channel protein; Rho; Cytoskeleton; Vasopressin

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Body water homeostasis is regulated by the renal collecting duct. Key components in the regulation of collecting duct water permeability are vasopressin receptor and water channel aquaporin-2 (AQP2) [1–4]. Upon vasopressin stimulation, AQP2 translocates from intracellular storage vesicles to the apical plasma membrane, rendering the cell water permeable, which in turn causes water reabsorption leading to urine concentration [5–7]. AQP2 mutations cause congenital nephrogenic diabetes insipidus (NDI), a disease characterized by a massive loss of water through the kidney [8–22]. In this review, we focus on the AQP2 trafficking and AQP2-binding proteins.

1. The cAMP-mediated effect of vasopressin on AQP2 trafficking

In response to an increase in serum osmolarity and a reduction in effective circulating blood volume, osmoreceptors located in the hypothalamus are activated and stimulate the secretion of antidiuretic hormone arginine vasopressin from the posterior pituitary [23,24]. After released systemically,

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vasopressin binds to vasopressin type 2 receptor (V2R) located on the baso lateral membrane of the renal collecting duct principal cells [25]. The V2R is coupled to adenylate cyclase by the heterotrimeric G-protein, Gs. Gs is a guanosine triphosphate (GTP)-binding protein which consists of three subunits: α, β, and γ. The binding of vasopressin to its receptor causes the α subunit to release guanosine diphosphate (GDP), bind to GTP, and dissociate from the β and γ subunits. This G α–GTP complex, in turn, activates adenylate cyclase which catalyzes the conversion of ATP to cyclic adenosine monophosphate (cAMP). The subsequent activation of protein kinase A (PKA) leads to phosphorylation of AQP2 at serine 256 [26–30]. This phosphorylation event is required for AQP2 translocation from intracellular storage vesicles to the apical membrane which causes an increase in water permeability of renal principal cells. The increase in permeability allows water to flow from the tubule lumen to the hypertonic medullary interstitium. This then leads to the formation of concentrated urine. Withdrawal of vasopressin triggers the endocytosis of AQP2-containing vesicles and restores the water-impermeable state of the apical membrane. In this process, AQP2 on the plasma membrane is first retrieved to EEA1-positive early endosomes, and then transferred to Rab11-positive storage vesicles [31].

AQP2 forms homotetramer and for a plasma membrane localization at least three out of four monomers in an AQP2 tetramer have to be phosphorylated [19,32,33].

PKA phosphorylation of AQP2 at serine 256 is important for AQP2 trafficking as described above. In addition, it is reported that cAMP-dependent phosphorylation of AQP2 increased membrane water permeability (Pf) of oocytes expressing wild-type AQP2 but did not increased Pf of oocytes expressing the nonphosphorylatable mutant AQP2-S256A, whereas the amounts of wild and mutant AQP2 expression on the oocyte membrane were similar [34]. This finding indicates that PKA phosphorylation increases water permeability of AQP2 protein. On the contrary, using AQP2-containing endosomes derived from inner medullary collecting duct (IMCD), it is shown that PKA phosphorylation does not alter Pf of the AQP2-containing endosomes [35]. The effect of PKA phosphorylation of AQP2 on permeability of AQP2 water channel protein remains to be investigated directly.

As PKA and many of its substrates are present throughout the cell, localization of PKA to specific sites is necessary for a timely and spatially effective activation of PKA. This process is mediated by protein kinase A anchoring proteins (AKAPs) which tether PKA to specific sites and limit its access to a subset of substrates [36–38]. Lande et al. found that AQP2-bearing vesicles contained PKA activity [35]. The anchoring of PKA to AKAPs was demonstrated to be a prerequisite for the AQP2 shuttle using the membrane-permeable anchoring inhibitor peptide S-Ht31 [39–41]. Henn et al. found that a new splice variant of AKAP18, AKAP18δ, was involved in this AQP2 shuttle [42].

However, the precise role of AQP2 phosphorylation in AQP2 trafficking still remains to be established. Recent work has demonstrated that the serine/threonine phosphatase inhibitor okadaic acid induces AQP2 translocation even in the presence of H89, a specific PKA inhibitor [43]. In addition, phosphorylation-deficient AQP2 mutant S256A accumulates at the plasma membrane by GTPase-deficient dynamin mutant or cholesterol-depleting agent [44]. Thus, AQP2 translocation may involve a mechanism which is independent of PKA phosphorylation in renal collecting-duct cells.

While PKA phosphorylation is required for the vasopressin-induced cell-surface accumulation of AQP2, dephosphorylation of AQP2 is not necessary for its subsequent internalization. Prostaglandin E_2 stimulates removal of AQP2 from the surface of principal cells when added after vasopressin treatment but does not alter the phosphorylated state of AQP2 [30]. In addition, it is reported that both Prostaglandin E_2 and dopamine induce internalization of AQP2 independently of AQP2 dephosphorylation in MDCK cells transfected with AQP2 [45].

2. Role of calcium in AQP2 trafficking

Several studies have provided evidences for a role of intracellular Ca^{2+} mobilization in vasopressin-mediated AQP-2 trafficking. In addition to increasing cAMP levels in collecting duct principal cells, vasopressin binding to the V_2 receptor was also demonstrated to trigger a rapid increase of intracellular Ca^{2+}, followed by sustained oscillations [46–50]. Pre-incubating the isolated IMCD cells with an intracellular Ca^{2+} chelator prevented vasopressin-induced intracellular Ca^{2+} mobilization, apical exocytosis, and increase of osmotic water permeability. Both ryanodine and calmodulin inhibitors were shown to block vasopressin-stimulated translocation of AQP-2 to the plasma membrane [51,52]. Removal of extracellular Ca^{2+} in perfused IMCD did not prevent the initial rise of intracellular Ca^{2+} induced by vasopressin but inhibited the sustained oscillations [50]. These findings suggest that the vasopressin-induced Ca^{2+} increase and oscillations are important for AQP2 translocation to the apical membrane, and involve intracellular Ca^{2+} released from ryanodine-sensitive stores and the influx of extracellular Ca^{2+}.

In contrast with the findings as described above, Lorenz et al. showed that intracellular Ca^{2+} was not able to promote or evoke the AQP2 shuttle in primary cultured IMCD cells [53]. AQP2 trafficking was not promoted by increasing intracellular Ca^{2+} concentrations. Vasopressin-induced AQP2 redistribution to the plasma membrane was fully preserved even in the cases that intracellular Ca^{2+} concentrations were clamped at both 50 nM and 150 nM. Only clamping at 25 nM abolished the AQP2 trafficking, indicating a requirement of Ca^{2+} at a very low level. An intracellular Ca^{2+} chelator did not reduce forskolin-elicited Pf increment.

The discrepancy in the effect of intracellular Ca^{2+} on AQP2 trafficking may be caused by the different kinds of experimental systems. Further studies are required for clarifying the role of intracellular Ca^{2+} mobilization in AQP2 trafficking.

Extracellular Ca^{2+} is also known to be involved in AQP2 regulation. Urinary AQP2 correlates with the severity of enuresis, a disease characterized by nocturnal polyuria and hypercalciuria [54]. Clinical amelioration demonstrated by a low calcium diet is accompanied by regulation of urine output

through remodulation of AQP2 expression/trafficking [55]. Drug-induced hypercalcemia/hypercalciuria causes polyuria and reduces AQP2 expression in rats [56]. Procino et al. showed that extracellular Ca^{2+} inhibited forskolin-induced AQP2 translocation to the apical membrane, possibly acting through calcium-sensing receptor signaling [57]. In this process, PKC activation, decrease in forskolin-elicited cAMP increment and increase in F-actin were observed.

3. Phosphorylation by the other kinases

Phosphorylation of AQP2 by not only PKA but the other kinases may potentially participate in regulation of AQP2 trafficking. Besides PKA sites, putative phosphorylation sites for PKG, PKC, and casein kinase II are also present in the AQP2 sequence. Serine 256 is also a substrate for Golgi casein kinase. It is reported that AQP2 transition in the Golgi apparatus is associated with a PKA-independent increase in AQP2 phosphorylation at serine 256, suggesting that phosphorylation by Golgi casein kinase may be required for Golgi transition [58]. In addition, activation of PKC pathway was shown to mediate endocytosis of AQP2 which was independent of the phosphorylation state of this water channel at serine 256 [26].

Phosphorylation of other cytoplasmic or vesicular regulatory proteins may also be involved. This issue remains to be investigated directly.

Other alternative (or parallel) trafficking pathways are also being uncovered. Bouley et al. have shown that nitric oxide and atrial natriuretic factor stimulate the insertion of AQP2 in renal epithelial cells via a cGMP-dependent pathway [59]. In addition, it is reported that cGMP phosphodiesterase inhibitor sildenafil citrate (Viagra) induced AQP2 membrane insertion [60]. It is not yet clear whether PKG directly phosphorylates AQP2 or whether the cGMP/PKG effect is ultimately mediated by activation of PKA.

4. Role of the cytoskeleton in AQP2 trafficking

The physiological properties within the cell differ significantly from conditions in aqueous solution. The large number of subcellular structures, organelles and macromolecules creates a crowded environment. In addition, cells contain significant mass percentages of protein, which sometimes exceed one quarter of their weight. The large proportion of proteins in the cytoplasm implies that their intracellular distribution more closely resembles a protein crystal than a protein solution [61]. Although diffusion can be the principal mechanism of molecular movement on a ~20 nm scale, movement over greater distances cannot occur simply through diffusion [62]. It has become clear that the microtubules and actin cytoskeletons act coordinately to regulate trafficking of many membrane proteins [63,64]. In the case of AQP2, the microtubules and actin cytoskeletons are also essential in its trafficking, and it has been generally believed that the coordinated and strictly regulated AQP2 trafficking therefore requires organized dynamics of the cytoskeleton and its associated proteins. Indeed, Proteomic analyses showed that both AQP2-bearing vesicles from IMCD and AQP2-containing exosomes isolated from urine contained cytoskeletal proteins and its associated proteins [65,66].

Even before the discovery of AQP2, several papers described that microtubular network was involved in regulation of water permeability of collecting tubules by vasopressin [67–69]. Microtubules are polar structures, arising from microtubule organizing centers (MTOCs), at which their minus ends are anchored, and with the plus ends growing into the cell. Dynein is shown to be present in the kidney and both dynein and dynactin, a protein complex believed to mediate the interaction of dynein with vesicles, associate with AQP2-bearing vesicles [70]. Both vanadate, an inhibitor of ATPases, and erythro-9-(2-hydroxy-3-nonyl) adenine (EHNA), an inhibitor of dynein, inhibit the antidiuretic response in toad bladder [71,72]. Thus, the microtubule-associated motor protein dynein and dynactin are important in vasopressin-regulated trafficking of AQP2-bearing vesicles.

A reorganization of actin cytoskeleton has also been shown to be essential in the trafficking of AQP2-containing vesicles. It has been suggested that the actin cytoskeleton provides a network that anchors the AQP2-bearing vesicles in the unstimulated cell and that a reorganization of the apical actin network may be critical in promoting the trafficking of AQP2-bearing vesicles. Indeed, vasopressin has been shown to depolymerize apical F-actin in rat inner medullary collecting duct, resulting in the fusion of water channel-carrying vesicles with the apical membrane [73]. Both forskolin and okadaic acid stimulate AQP-2 translocation by inducing a reorganization of the apical actin network [43]. Recent studies showed that actin depolymerization was a prerequisite for cAMP-dependent translocation of AQP2 and inhibition of small GTPase Rho induced this translocation by causing actin depolymerization [74,75]. These data provide strong evidence for a major regulatory role of the actin depolymerization in the vasopressin-induced recycling of AQP2 between intracellular vesicles and the cell surface.

Furthermore, RhoA inhibition through PKA-mediated phosphorylation of RhoA is shown to be a key event for actin dynamics inducing AQP2 translocation [76]. In addition, Tamma et al. showed that stimulation of prostaglandin E3 receptors inhibited vasopressin-induced Rho inactivation, vasopressin-induced F-actin depolymerization, and vasopressin-, cAMP - and forskolin-induced AQP2 translocation [77]. Bradykinin is shown to increase Rho activity, resulting in cortical F-actin stabilization and impairment of AQP2 trafficking [78]. Ezrin/radixin/moesin (ERM) proteins cross-link actin filaments with the plasma membrane and it is reported that moesin is involved in AQP2 apical targeting by inducing actin depolymerization [79].

Actin depolymerization is shown to be important for AQP2 trafficking as described above. On the contrary, it is reported that actin-depolymerizing agent cytochalasin D did not enhance water permeability of the epithelium of toad urinary bladder [80]. The authors speculate that F-actin had at least two hypothetical pools: one is involved in the barrier function and the other pool is involved in migration of AQP2 from diverse regions of cytoplasm to the subapical region. In addition, it is

reported that vasopressin signaling induces myosin light chain phosphorylation which is known to result in an enhancement of myosin-actin filament interaction and the formation of actin fibers [81].

Tajika et al. showed that actin depolymerization caused by cytochalasin D or latrunculin B induced AQP2 accumulation in EEA1-positive early endosomes, indicating that actin filaments were required for the transfer of AQP2 from the early endosomes to Rab11-positive subapical storage vesicles [82]. The authors also showed that actin depolymerization induced the retrieval of AQP2 from the apical plasma membrane even in the presence of forskolin.

Cytoskeleton-modulating agents inevitably affect the overall cell architecture at least to a small extent which makes the experiments examining the role of actin in AQP2 trafficking difficult. It is speculated that in the process that the physiological trafficking of AQP2 occurs in vivo, the actin dynamics may change in a restricted narrow area around AQP2 molecule and may vary among different areas within the cell.

5. Fusion of AQP2 vesicles with the apical membrane

The molecular machinery for the docking and fusion of AQP2-containing vesicles with the apical membrane has some similarity to the process of synaptic vesicle fusion with the presynaptic membrane and involves vesicle (v) SNAREs (soluble NSF attachment protein receptors) and target membrane (t) SNAREs. vSNAREs such as VAMP-2 (vesicle-associated membrane polypeptide-2) are present in the collecting duct principal cells and colocalize with AQP2 in the same vesicles [83–85]. Treatment with tetanus toxin, which cleaves the SNARE protein VAMP-2/synaptobrevin, abolishes vasopressin-induced AQP2 translocation to the plasma membrane [86]. The tSNARE syntaxin 4 is present in the apical plasma membrane of collecting duct principal cells [87,88]. Another tSNARE, SNAP23 (soluble *N*-ethylmaleimide-associated protein), has also been found in collecting duct principal cells both in the apical membrane and in AQP2-bearing vesicles [89]. In-vitro studies have revealed that SNAP-23 bound to syntaxin-4 and VAMP-2 [90]. However, another study reported that the localization of SNAP-23 was different from AQP2 [91]. In addition to SNARE proteins, heterotrimeric GTP binding proteins of the G_i family are also involved in the AQP2 shuttling and/or fusion process [92].

6. Endocytosis

During the endocytotic process of AQP2 recycling pathway, AQP2 accumulates in clathrin-coated pits and is internalized via a clathrin-mediated process [93–96]. Recent studies showed that AQP2 accumulated on the plasma membrane in a vasopressin-independent manner when clathrin-mediated endocytosis was inhibited by dominant-negative, GTPase-deficient K44A dynamin [96]. Dynamin is a GTPase that is involved in the formation and pinching off of clathrin-coated pits to form clathrin-coated vesicles [97–99]. The dominant-negative form has a point mutation, K44A, that renders the protein GTPase deficient and arrests clathrin-mediated endocytosis [99–101]. Phosphorylation-deficient mutant AQP2-S256A accumulates at the plasma membrane by the GTPase-deficient dynamin mutant K44A or methyl-β-cyclodextrin [44]. This drug depletes membranes of cholesterol and results in a rapid inhibition of endocytosis. An extensive accumulation of AQP2 at the cell surface has been accomplished within 15 min after inhibition of endocytosis by treatment with methyl-β-cyclodextrin. These data indicate that AQP2 recycles constitutively and rapidly between intracellular stores and the cell surface and the constitutive trafficking process is not dependent on phosphorylation of AQP2 at serine 256.

7. Impaired trafficking of mutant AQP2 causes nephrogenic diabetes insipidus

Mutations in AQP2 cause congenital nephrogenic diabetes insipidus (NDI), a disease characterized by an inability to concentrate urine despite normal or elevated plasma concentrations of vasopressin, resulting in a massive loss of water through the kidney. AQP2 mutant proteins are misrouted and cannot be localized at the luminal membrane. To date, 35 mutations in AQP2 have been reported. There are two inheritance types: most common autosomal-recessive type and less common autosomal-dominant type. Recessive mutations cause misfolding of the protein and retention in the endoplasmic reticulum (ER) [8–16]. Dominant mutations cause retention of AQP2 in the Golgi complex, late endosomes/lysosomes, or basolateral membrane [17–22]. These mutants, in contrast to recessive mutants, are able to heterotetramerize with normal AQP2 protein. The resulting complex is hindered in its transport to the apical membrane. This process explains the dominant-negative effect of these mutations. Recently, Mattia et al. found AQP2-R254L mutation in one allele of a family with dominant NDI [102]. R254L mutation lacks vasopressin-mediated phosphorylation of AQP2 at Ser256, resulting in its impaired transport to the cell surface.

The molecular mechanism that impaired AQP2 trafficking causes NDI suggests a pharmacological strategy for correction of the sorting in NDI using chemical chaperones [103,104]. However, much work remains to be done before such methods are available clinically.

Degradation pathway of wild type AQP2 involves both the proteasomal and lysosomal pathways [105]. Hirano et al. investigated aspects of the biosynthesis and degradation of the ER-retained mutant AQP2-T126M and the Golgi apparatus-retained mutant AQP2-E258K [106]. AQP2-T126M was synthesized as a glycosylated 32-kDa as well as a nonglycosylated 29-kDa form, both of which were rapidly degraded by the proteasome, albeit a different kinetics. AQP2-E258K was not exclusively retained in the Golgi apparatus but became misrouted to late endosomes/lysosomes and its degradation involved both proteasomes and lysosomes. The final degradative pathway is different among AQP2 mutants.

Recently, a high prevalence of V168M mutation, which caused a partial defect in exit from the ER and resulted in partial NDI, was found in a town in Mexico by the genetic

epidemiologic study [107]. This finding provides evidence for an important health care problem in the village.

8. Critical region of AQP2 for its trafficking

Phosphorylation of serine 256 in the cytoplasmic C-terminal region of AQP2 is important for an apical localization of AQP2 as described above. In addition, mutations located in the C terminus of AQP2, which are encoded in dominant NDI, cause AQP2 missorting [17–21]. These findings have shown the importance of the AQP2 C-terminus for its trafficking. Furthermore, van Balkom et al. showed that region N220-S229, which was the proximal region of the C terminus of AQP2, was essential for localization of AQP2 in the apical membrane and that the N and C termini of AQP2 were essential for trafficking of AQP2 to intracellular vesicles and its shuttling to and from the apical membrane [108]. In addition, the sixth transmembrane domain of AQP2, including a dileucine motif, is involved in regulated trafficking of this water channel [109]. These data suggest the existence of the proteins which interact with these regions and directly regulate AQP2 trafficking.

9. AQP2-binding protein complex which directly regulate AQP2 trafficking

Controlled apical positioning of AQP2 suggests the existence of proteins that recruit AQP2 by binding directly. To date, several proteins which are localized in AQP2-bearing vesicles and supposed to mediate its sorting have been reported as described above, however, proteins that directly interact with AQP2 and provide specificity in AQP2 sorting have not been identified. Recently, we have identified for the first time the AQP2 binding proteins: actin and SPA-1 [110,111]. SPA-1 is a specific GTPase-activating protein (GAP) for Rap1 and the GAP activity of SPA-1 is shown to be required for AQP2 trafficking to the apical membrane. These findings are the first report of direct binding of a channel protein to a GAP and a cytoskeletal protein actin. In addition, these findings show a novel role of Rap1GAP family in the regulation of channel protein sorting.

Rap1 is a Ras-related small GTPase. Rap1 is known to be implicated in many cellular processes including regulation of Ras/extracellular-signal-regulated kinase (ERK) signaling pathway, cell morphogenesis, and cell differentiation [112–114]. Rap1 is also required for cell adhesion and cytoskeletal organization [115]. In addition, Spine-associated RapGAP (SPAR), which is homologous to SPA-1, has actin-reorganizing activity and regulates dendritic spine morphology of neurons via its GAP and actin-interacting domains [116]. Recently, it is reported that SPA-1 interacts with an actin-binding protein alpha-actinin [117]. These findings indicate the involvement of Rap1/SPA-1 signaling in actin cytoskeleton.

It is also reported that Rap1 is involved in cytoskeletal organization through the crosstalk with other small GTPases including Ral and Rho. Active form of Rap1 (Rap1GTP) binds to Ral guanine nucleotide exchange factors (RalGEFs) [118–120] that can activate Ral GTPase. RalBP1, one of Ral GTP-binding proteins, is shown to be a GAP for Rho family GTPases [121], which participate in the cytoskeletal organization. Moreover, it is reported that in budding yeast the Rap1 orthologue Bud1 acts upstream of Rho signaling pathway [122]. Hogan et al. show that activation of Cdc42, a member of Rho family, rescues the inhibitory effect of RapGAP on the formation of E-cadherin-based cell–cell contacts and that overexpression of RapGAP suppresses the activation of Cdc42, suggesting that Cdc42 functions downstream of Rap1 [123].

Furthermore, recent growing evidence indicates the involvement of Rap1 in trafficking of membrane proteins [123–128]. These findings support the novel mechanism that SPA-1, a GAP for Rap1, is involved in membrane protein sorting.

As described in "4. Role of the cytoskeleton in AQP2 trafficking", RhoGTP prevents cAMP-dependent translocation of AQP2 to the apical membrane by stimulating F-actin polymerization [74,75]. It is speculated that the increase in F-actin polymerization functions as a barrier for AQP2 sorting to the apical membrane. Using SPA-1 mutant lacking GAP activity (LIG-SPA-1) and constitutively active Rap1 mutant (Rap1V12), we have shown that increase in active form of Rap1 blocks the apical delivery of AQP2 and GAP activity of SPA-1 is necessary for the AQP2 trafficking [110]. In addition, dominant negative Rap1 mutant (Rap1N17), which suppresses the endogenous Rap1 activity, increases the AQP2 trafficking to the apical membrane. We are tempting to speculate that Rap1 affects the assembly of F-actin that functions as a barrier for the AQP2 trafficking between the apical membrane and the intracellular compartments through the crosstalk with Rho family GTPases. Thus, SPA-1 binding to AQP2 may decrease the levels of Rap1 GTP that trigger F-actin disassembly in a

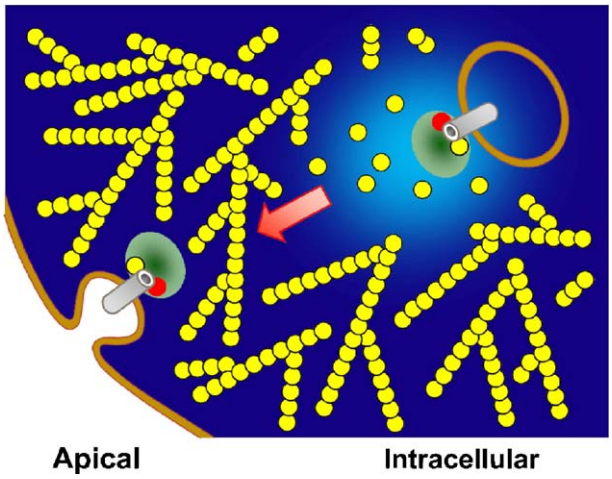

Fig. 1. Schematic representation of the postulated mechanisms for regulation of AQP2 trafficking by its binding proteins. AQP2 directly binds to SPA-1, actin, and the other 11 proteins. Gray column, AQP2; red circle, SPA-1; yellow circle, G-actin; yellow circles linked, F-actin; green oval, AQP2 binding protein complex. The depth of blue color in the background indicates the levels of Rap1GTP: deep blue color indicates relatively high levels of Rap1 GTP, and light blue color indicates the area where Rap1GTP is decreased. It is speculated that SPA-1 binding to AQP2 reduces the levels of Rap1GTP that may trigger F-actin disassembly in a restricted narrow area around AQP2, resulting in the promotion of the AQP2 sorting. The other 11 proteins which also bind to AQP2 may provide the machinery of driving AQP2 movement.

restricted area around AQP2 molecule, resulting in the promotion of the recycling of AQP2 (Fig. 1).

Based on these findings, we have speculated the existence of a multiprotein complex which includes AQP2, SPA-1 and actin, for providing the mechanism which generates force and motion in AQP2 trafficking. We have therefore tried to clarify the proteins comprising the complex. To isolate a large amount of proteins which directly bound to AQP2, 100 mg of protein which was completely solubilized by detergent from the extract of rat kidney papilla was applied to immunoaffinity column coupled with anti-AQP2 antibody [129]. The isolated proteins were analyzed by matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI-TOF MS). In addition to SPA-1 and actin, 11 proteins were identified using this method: ionized calcium binding adapter molecule 2, myosin regulatory light chain smooth muscle isoforms 2-A and 2-B, alpha-tropo myosin 5b, annexin A2 and A6, scinderin, gelsolin, alpha-actinin 4, alpha-II spectrin, and myosin heavy chain nonmuscle type A. These proteins have actin binding ability. It is therefore speculated that each interaction of these proteins in the complex may be dynamic and this dynamic assembly acts as a key point for the regulation of the AQP2 trafficking.

These findings are the first report that a multiprotein "force generator" complex directly binds to a channel protein. This multiprotein complex may provide the machinery of driving AQP2 movement. Further studies are required for clarifying the detail.

Considerable progress has been obtained on the mechanism of AQP2 trafficking over the past few years. Continued analyses will reveal detailed molecular insight into the fundamental physiology of water balance homeostasis and pathophysiology of water balance disorders.

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