Biochimica et Biophysica Acta 1840 (2014) 1507–1512

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagen

Review

The role of mammalian superaquaporins inside the cell ☆

Kenichi Ishibashi [a,*], Yasuko Tanaka [a], Yoshiyuki Morishita [b]

[a] Department of Medical Physiology, School of Pharmacy, Meiji Pharmaceutical University, Tokyo, Japan
[b] Department of Nephrology, Jichi Medical School, Tochigi, Japan

ARTICLE INFO

Article history:
Received 2 July 2013
Received in revised form 18 October 2013
Accepted 23 October 2013
Available online 1 November 2013

Keywords:
Superaquaporin
Vesicle fusion
Tissue recovery
Polycystic kidney
Pancreatitis

ABSTRACT

Background: The mammalian two superaquaporins, AQP11 and AQP12, are present inside the cell and their null phenotypes in mice suggest their unusual functions.
Scope of review: The surveyed literature on these superaquaporins and our unpublished data has been incorporated to speculate their roles.
Major conclusions: AQP11 and AQP12 have unique NPA boxes with a signature cysteine residue. Although some water permeability of AQP11 was demonstrated in liposomes and cultured cells, its permeability to glycerol is unknown. The function of AQP12 still remains to be clarified. AQP11 null mice develop polycystic kidneys following large intracellular vacuoles in the proximal tubule, which may be caused by ER stress or vesicle fusion failure. The role of AQP11 in the kidney and liver seems to alleviate the tissue damage and facilitate the recovery. Its expression in the sperm, thymus and brain suggests its potential roles in these organs in spite of the apparently normal null phenotype. Although AQP12 null mice appear normal, they suffer from severe pancreatitis, suggesting its role in the fusion of zymogen granules.
General significance: As many issues are unsolved, the clarification of the function and roles of the superaquaporin may lead to the identification of new roles of AQPs. This article is part of a Special Issue entitled Aquaporins.

1. Introduction

AQP family was initially divided into two subfamilies: classical AQPs (water-selective) and aquaglyceroporins (glycerol channel) from the functional and structural viewpoints [reviewed in [1]]. However, recent studies revealed that both subfamilies overlap functionally. For example, some plant AQPs, all classical AQPs in structure, transport glycerol and other small solutes as well as water. Thus the functional basis for the classification of AQPs appears dim.

Moreover, the structural basis for this dichotomy of AQPs was challenged by the discovery of a new group of AQPs highly deviated from the previous AQPs especially around the AQP signature sequence, NPA box [2–7]. This third subfamily was named superaquaporin after super-gene family of AQP family to indicate its very low homology with the previous two subfamilies (Fig. 1). Interestingly, this subfamily is absent in single cell organisms and the plant, while the plant has seven AQP subfamilies (GIP, PIP, TIP, NIP, SIP, XIP, HIP), all of which belong to classical AQPs [8].

Although superaquaporins are not much similar with each other, they have a perfectly conserved cystein residue downstream of the second NPA box (Fig. 2, arrowed) which is critical for function [9]. As the evolutional aspects of AQPs were reviewed previously [2], this review focuses on mammalian superaquaporins with their speculative roles.

2. The characteristics of superaquaporins

In the hour glass model of AQPs, NPA boxes are critical for the channel pore formation. As the superaquaporin has unusual NPA boxes, they may also function differently from the other subfamilies. However, the function of AQP11 was difficult to study as it is expressed intracellularly even in the *Xenopus* oocyte expression system [10]. To overcome this problem, AQP11 was reconstituted into liposomes to measure the water transport, which revealed a high water permeability [11], although it was later corrected to be lower by removing the detergent effect and it was shown to be mercury sensitive [12]. A recent cell volume measurement also indicated a high water transport activity of AQP11 in transfected cultured cells expressing some AQP11 at the plasma membrane [13]. The permeability of glycerol is still unknown. Similar to AQP11, AQP12 is also expressed inside the cell both in the *Xenopus* oocyte expression and transfected cell culture systems [14]. The function of AQP12 still remains to be clarified.

The mechanism for the intracellular localization of AQP11 is intriguing. The change of NPC to NPA in AQP11 did not alter the subcellular localization but reduced the oligomerization and the water permeability [13]. Conversely, the change of NPA to NPC in AQP4 did not affect the subcellular localization, i.e., at the plasma membrane [15]. Therefore, NPA sequence itself may not be responsible for intracellular targeting,

☆ This article is part of a Special Issue entitled Aquaporins.

* Corresponding author at: Dept. of Pathophysiology School of Pharmacy, Meiji Pharm Univ 2-522-1 Noshio, Kiyose, Tokyo, 204–8588, Japan Tel./fax: +81 42 495 8502.
E-mail address: kishiba@my-pharm.ac.jp (K. Ishibashi).

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http://dx.doi.org/10.1016/j.bbagen.2013.10.039

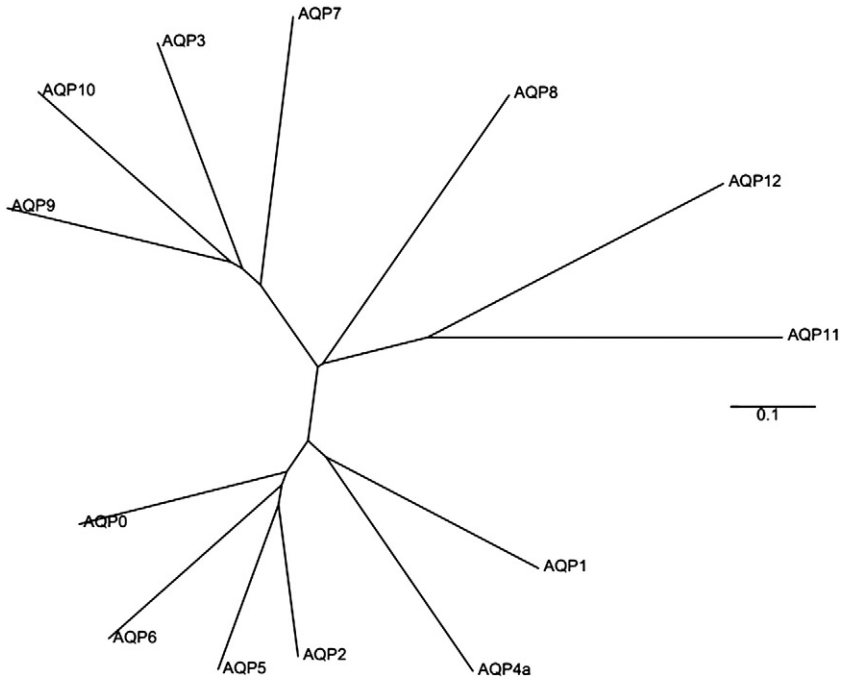

Fig. 1. The phylogenetic tree of human aquaporins. The classical AQP (AQP0, AQP1, AQP2, AQP4, AQP5, AQP6, AQP8); the aquaglyceroprin (AQP3, AQP7, AQP9, AQP10); the superaquaporin (AQP11, AQP12) The phylogenetic tree is drawn by Phylodendron, which is available at http://iubio.bio.indiana.edu/treeapp/treeprint-form.html.

and the intracellular localization of AQP11 may not be due to a defective mutation of NPA to NPC. It is still possible that some other mutations or even a cellular stimulation may drive the intracellular AQP11 to the plasma membrane. We tested the dehydration of mice but it did not affect the subcellular localization of AQP11 in the proximal tubule (Ishibashi, unpublished observation).

Fig. 2. The sequence alignment of human aquaporins around two NPA boxes. Human AQP0-AQP12 are aligned by Clustal X, which is available at ftp://ftp.ebi.ac.uk/pub/software/clustalw2/ The two NPA sequences are underlined and a signature cysteine residue for the superaquaporin is arrowed. The exceptional residues are in the white letter.

There is no other superaquaporin than AQP11 and AQP12 in mammals, although a nematode, *C.elegans*, has three members [5]. It should be noted that these three AQPs have extremely unusual NPA boxes and low homology with each other. Remarkably, the sequence of NPA has been changed to HPC, NCA, SPL, NPI, or DPL, whereas the mammalian superaquaporins have NPC, NPT and NPA (Fig. 2). The superaquaporins with such highly deviated NPA may have lost in mammals through evolution because NPA sequence was so critical that small changes may have jeopardized the function and such animals could not survive for generations. However, the correction of NPC to NPA in AQP11 unexpectedly disrupted the water permeability [13]. Furthermore, an NPA-null AQP1 mutant was shown to function as an efficient water channel [16], suggesting NPA itself may not be crucial for the channel formation. Therefore, even the deviated NPA can form a pore to function as a channel in the nematode. Although the functions of some AQPs in *C.elegans* were reported, those of the superaquaporins remain to be examined [17]. The functions and roles of superaquaporins in lower animals will help to elucidate those of mammalian superaquaporins.

3. AQP11

Although most of the null phenotypes of mouse AQPs are mild, AQP11 null mice suffer from a fatal kidney failure due to polycystic kidneys and die around one month after birth [18]. Unlike the other disease models of polycystic kidneys, the proximal tubule of AQP11 null mice contains many huge intracellular vacuoles before developing the cysts. The vacuoles originate mostly from the endoplasmic reticulum (ER) membrane with attached ribosomes. These vacuoles may represent cellular damage, autophagy or apoptosis. Indeed, microarray analysis of the AQP11 null mouse kidney showed the presence of apoptosis with enhanced expression of ER stress genes [19].

Such vacuoles may also be produced by accumulation of osmotic substances in the vesicle to attract the excessive water into the vesicle. Sudan-black B staining failed to stain the vacuole (Ishibashi, unpublished observation) speaking against the lipid accumulation. The protein expression array was employed to identify a putative accumulated protein induced by AQP11 absence, which revealed two upregulated proteins: Hspa5 78 kDa (glucose-regulated protein) and Mups3 (major urinary protein3) (Ishibashi, unpublished observation). Hspa5 is a heat shock protein inducible by the ER stress, while Mup3 is normally synthesized by the liver and excreted in the urine but accumulated in the cysts of jck polycystic kidney mice. The result suggests the absence of accumulated specific proteins. They are probably induced by the cell damage and their relationship to cystogenesis is unclear.

Alternatively, the numerous vacuoles may indicate a problem with exocytosis or endocytosis. Recently, osmotic regulation of seamless tube growth has been reported in *C.elegans* [20–22]. The expanding luminal membrane is supported by a reservoir of intracellular vesicles which have an intracellular aquaglyceroporin, AQP8. Hypertonicity stimulated the fusion of these vesicles to the luminal plasma membrane to expand the luminal diameter and length of a homolog of lymphatic canal. Interestingly, AQP8 was not detected at the luminal membrane even after the fusion induced by the osmotic stress, suggesting that AQP8 functions intracellularly to facilitate the vesicle fusion. Similarly, AQP11 may facilitate vesicle fusion to expand and lengthen the proximal tubule after birth. Its absence will lead to fusion failure, resulting in the accumulation of intracellular vacuoles and the premature development of the proximal tubule. A few survived tubules may regenerate to form cysts, leading to the development of polycystic kidneys.

In the event of tubular injury, a similar mechanism may operate to regenerate the proximal tubule, where the upregulation of AQP11 may enhance the recovery of the proximal tubule after damage. Conversely, the decrease of AQP11 expression may aggravate the proximal tubular damage by delaying the recovery. In fact, the kidney damage by a glucose through oxygen-radical production was enhanced in AQP11 heterozygote mice expressing only a half amount of AQP11 [23]. Therefore, intervention to increase AQP11 expression in the kidney will alleviate the kidney damage and facilitate its recovery.

The development of polycystic kidneys in AQP11 null mice was unexpected and could be a secondary effect of AQP11 absence. For example, the expression of PKD-related genes can be affected by AQP11 loss. A microarray analysis of the AQP11 null kidney indicated that the expression of PKD-related genes was normal (Table 1) [19]. Therefore, the possibility of the secondary effect on cystogenic genes will be small although the effect on their protein levels and trafficking to the plasma membrane can not be ruled out.

Alternatively, the cyst formation may be a reaction to the early damage on the developing proximal tubule. A mouse study with conditional knockout of PKD1 revealed the presence a critical period to produce polycystic kidneys after birth. Inactivation of PKD1 before postnatal day 13 resulted in severe polycystic kidneys within 3 weeks, while its inactivation at postnatal day 14 and later resulted in the development of mild cysts only after 5 months [24]. The proximal tubule of AQP11 null mice accumulated intracellular vacuoles at a week after birth, probably due to ER stress as revealed by a microarray study [19]. Therefore, the cyst formation can be a response to the early cellular damage with unknown cystogenic gene dysfunction just before the critical developmental switch at day 12 postulated by the above study. Hopefully, the conditional knockout of AQP11 will resolve this issue.

AQP11 is also expressed in the liver and its knockout produced intracellular vacuoles in the hepatocyte around portal area, which was more pronounced by fasting in the liver specific AQP11 knockout mice [25]. Similar to the kidney [18], these vacuoles were derived from the ER membrane, which was enhanced by feeding after fasting, especially with amino acid administration [25]. The vacuoles were also associated with the induction of ER stress similar to the kidney [19,23]. As blood transaminase levels stayed normal, the liver damage induced by AQP11 defect seems to be small and the mice grew and survived normally [25]. Speculatively, as in the kidney, the enhanced expression of liver AQP11 may alleviate the liver damage by ER stress which causes many liver diseases. Interestingly, AQP11 was transiently expressed in the regenerating rat liver, suggesting that AQP11 may also facilitate the growth of the hepatocyte [26].

Such intracellular vacuoles are also observed in the epithelial cell of the intestine, which is present at the tip of the villi but absent at the crypt, suggesting that the vacuole formation is more related to the solute absorption than secretion (Fig. 3, upper). As described above, only the hepatocyte around portal area was vacuolated which also actively absorbs nutrients. Therefore, vacuoles seem to be produced in absorbing cells: the proximal tubule, the hepatocyte around portal area and the epithelium of intestinal villi. Alternatively, AQP11 can be selectively expressed at the vacuolated cells and absent in nonvacuolated cells. The smaller body size of AQP11 null mice may be caused by poor absorption of nutrients rather than the effect of uremic toxins to inhibit growth hormone secretion with renal failure [18].

AQP11 is most abundantly expressed in the testis, specifically at the residual cytoplasm of elongated spermatids and the distal tail of

Table 1
The expression pattern of cystogenic genes in AQP11 null kidney (KO) at 3 days after birth through microarray analysis.

Gene symbol	Gene	P value	Ratio (KO/WT)
Pkd1	polycystic kidney disease 1 homolog	0.40	0.89
Pkd2	polycystic kidney disease 2	0.44	0.94
Pkhd1	Polycystic kidney and hepatic disease 1	0.34	0.91
Nphp1	nephronophthisis 1 homolog	0.52	1.07
Inv	inversin	0.54	1.08
Nphp4	nephronophthisis 4 homolog	0.96	0.99
Iqcb1	IQ calmodulin-binding motif containing 1	0.46	1.07
Cep290	centrosomal protein 290	0.31	0.91

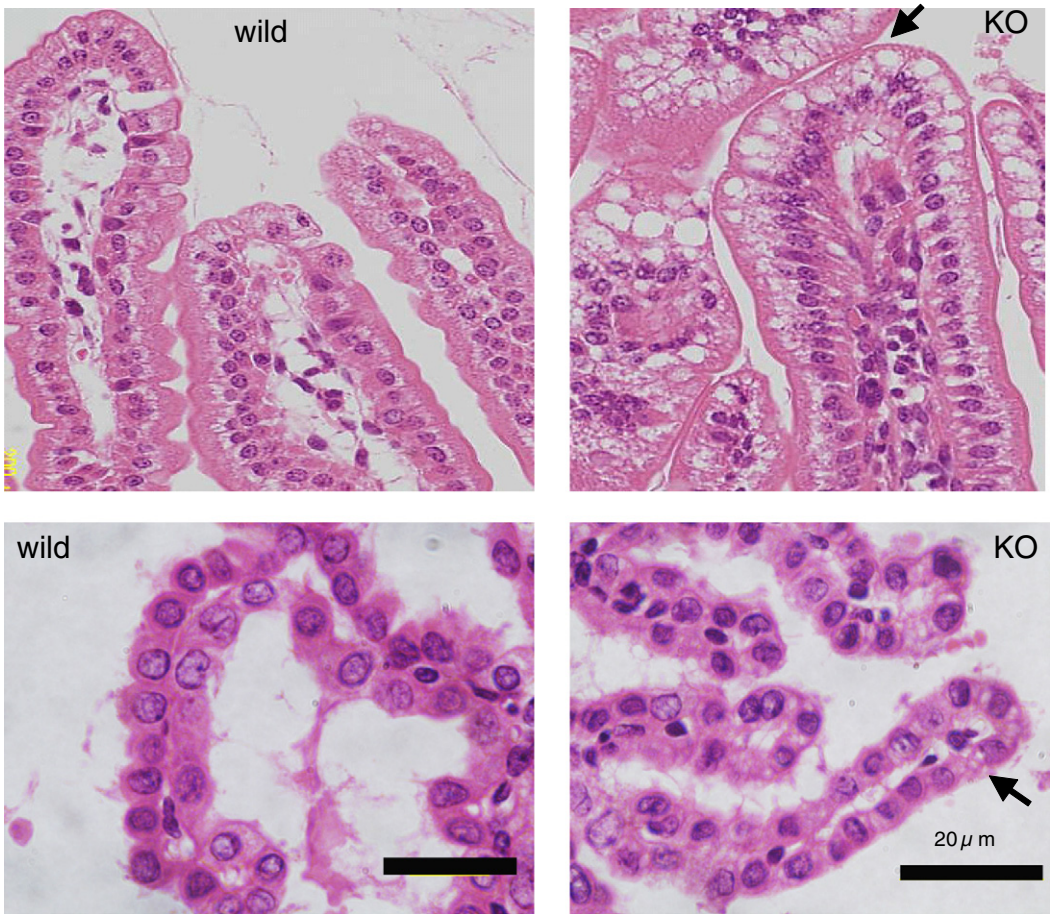

Fig. 3. Intracellular vacuole formation of AQP11 null mice in the jejunum and the choroid plexus. Upper pictures:jejunum, Lower pictures: choroid plexus (a bar indicates 0.2 micrometer) Left pictures: wild type mice, Right pictures: AQP11 null mice (KO). Vacuoles are indicated by the arrow in the pictures of AQP11 null mice. Hematoxylin and Eosin Staining.

spermatozoa [27]. As AQP11 null mice die around one month after birth just when AQP11 starts to appear in the testis, it is difficult to identify the role of AQP11 in the testis with AQP11 null mice. Rare long-lived AQP11 null mice will be useful. However, such mice also have an advanced renal failure which will be toxic to the testis. Moreover, other AQPs in the testis (AQP7 and AQP8) may compensate for the loss of AQP11.

Another highly AQP11 expressing tissue is the thymus. The morphological phenotype of AQP11 null mice is a smaller thymus although its functional phenotype is unclear (Ishibashi, unpublished observation). AQP11 is also expressed at human amniotic membranes and equine endometrium, whose roles are also unclear [28,29].

The brain also expresses AQP11. Its exact localization, however, is unclear due to the poor quality of the antibodies. A previous report showed the expression of AQP11 at the Purkinje cell in the cerebellum [10]. Our preliminary observation indicated that AQP11 was expressed at the epithelium of the choroid plexus and the endothelium of the brain capillary (Ishibashi, unpublished observation). As in the kidney, intestine and liver, the epithelium in the choroid plexus of AQP11 null mice contains intracellular vacuoles (Fig. 3, lower) although no other apparent brain phenotype was observed including normal cerebral ventricles (Ishibashi, unpublished observation). AQP11 was previously identified as a gene specifically expressed in the brain endothelium and not in the endothelium of the other organs [30]. The brain capillary is important for the formation of the blood brain barrier (BBB) and its disruption will lead to brain edema. AQP11 expression was examined under hyper- and hypo-tonic conditions of animals. Both maneuvers decreased the expression of AQP11 in the brain (Ishibashi, unpublished observation) suggesting that AQP11 may protect the brain through reducing its expression to limit water transport when osmotically challenged.

Finally, the structural analysis of AQP11 protein is noteworthy. Since AQP11 has less conserved NPA boxes, its 3D structure by using homology modeling may not be feasible, which may predict the permeating substances [31]. A homology modeling of mouse AQP11 indicated that the critical cysteine residue downstream of the second NPA box is located at the extracellular surface but away from the pore, suggesting its role for 3D structure formation rather than for the pore formation [12]. In fact, mutations at this cysteine residue disrupted the AQP11 oligomerization as well as its function [13]. Obviously, the confirmation of this model awaits a crystallographic analysis of the protein.

4. AQP12

AQP12 is selectively expressed intracellularly at the acinar cell of the pancreas [32]. However, a recent survey on the gene expression studies revealed that AQP12 was also expressed at the retina, mostly at the pigmented epithelium, as was also the case with AQP11 [33–35]. However, the eye phenotype of AQP11 or AQP12 null mice was not vigorously examined.

The pancreas of AQP12 null mice showed enhanced response to a CCK-analog stimulation (caerulein), leading to a severe acute pancreatitis, but otherwise normal [32]. AQP12 at the zymogen granule seems to be important for the membrane fusion at stimulated states. Osmotic swelling of the granule induced by a coupled influx of water and ions into the granule will initiate exocytosis. A decreased water flow at the

granule may delay or even inhibit exocytosis, leading to the accumulation and merging of the granule to form larger vacuoles.

AQP1 has also been reported to play a role in the secretion of the pancreatic zymogen granules [36] as well as AQP6 at the secretory granule in the salivary gland [37,38]. In these tissues, the secretory vesicle swelling facilitated by AQP1 or AQP6 was required for expelling the intravesicular content during secretion. However, the null phenotypes of AQP1, AQP6 and AQP12 in mice seem to be normal [32,39], suggesting the compensation of other AQPs. Alternatively, the results may speak against the significant role of AQP in the granular secretion at least under the normal condition. Further double or even triple KO mice will be necessary to resolve this issue.

Since both AQP11 and AQP12 share similar characteristics as a superaquaporin, it is intriguing that the phenotype of AQP12 null mice is almost normal comparing the fatal phenotype of AQP11 null mice. Possible compensation by the coexisting AQP1 and/or AQP8 at the acinar cell in the pancreas will be an explanation. As AQP12 is also highly expressed at the ER membrane, water permeability of the ER membrane of the pancreas from AQP12 null mice was examined. Surprisingly, there was no difference of the water permeability of pancreatic ER membrane between AQP12 null and wild mice [32]. Other AQPs may have masked the effect of AQP12. In fact, previous studies on AQP1 or AQP8 knockout mice also revealed only mild phenotypes [39] suggesting the presence of the compensation by other AQPs. Alternatively, AQP12 may not transport water much to be detectable *in vitro* assay.

AQP12 was also highly expressed in breast cancer cells together with other AQPs [40]. Such studies were mostly conducted at the transcription level and the poor quality of commercially available antibodies against AQP12 makes the interpretation difficult. In fact, the antibody against the shorter intracellular C-terminus of the mouse AQP12 did not work in the mouse tissue but was able to detect the rat AQP12 [32]. In fact, the roles of AQPs in tumor biology are a hot topic including proliferation and metastasis through regulation of cell volume and cellular metabolism [41]. The research will provide good biomarkers for tumors and targets for cancer therapy. Interventional studies with specific inhibitors will give more direct insights into the roles of AQPs in cancer biology.

5. Speculation and perspective

The structure and function of AQP11 and AQP12 are currently not well studied. Their roles are only speculated by the phenotypes of their null mutants. The defect of AQP11 induces a developmental defect of the kidney, polycystic kidneys, which limit the life span to a month, suggesting a critical role of AQP11 for the proximal tubular development. However, this phenotype is difficult to analyze and its relationship to the defect of water transport is not obvious. As high surface to volume ratios are present for the membrane of cell organelles, water channel may not be necessary inside the cell. Accordingly, the function of intracellular AQPs may be different from that of AQPs at the plasma membrane.

Unlike the mouse model, AQP11-deficient zebrafish displayed a curved tail which was rescued by human AQP11 [13]. This unexpected phenotype may be caused by the remodeling of extracellular matrix and its relationship to the water transport defect is again not apparent. It can be a secondary effect of AQP11 deficiency unrelated to water transport. The reason for the absence of renal cysts in AQP11-deficient zebrafish is that AQP11 is not expressed in zebrafish kidney [13].

The phenotype unexplained by the defect of water transport can be caused by mechanical dysfunction such as cell-to-cell adhesion as suggested by AQP2 in the collecting duct [42]. For example, correct tertiary structure of AQP11 may be crucial for keeping intracellular vesicles packed densely as stacks of the ER membrane, whose disruption will lead to the expansion of the contents to develop intracellular vacuoles. The developments of permeation defective mutants or specific channel inhibitors will be useful to examine this issue.

Alternatively, a putative interaction of intracellular AQPs with cytoskeletons will be important as shown with the trafficking of AQP2 in the principal cell [43]. The absence of such interactions will cause an organelle trafficking failure leading to exo/endocytosis defects and an eventual intracellular vacuole formation.

Still, the water transport through the superaquaporin inside the cell will be important for the cell organelle function. For example, the facilitated vesicle-to-plasma membrane fusion will be controlled by the water transport through vesicular AQPs as suggested by AQP12 null mice [32]. Such vesicle fusions may also be important for capillary morphogenesis and angiogenesis as suggested by the seamless tube growth in *C.elegans* [20–22]. AQP11 at the endothelium at the blood brain barrier may also facilitate capillary vessel tubule formation together with AQP1.

Finally, the application of the knowledge on the superaquaporin to human disease should be pursued. Human diseases with AQP11 or AQP12 defect have not been identified yet. Some infants born with polycystic kidneys (autosomal recessive polycystic kidney disease: ARPKD) may have AQP11 mutations. In fact, a previous survey of 90 ARPKD patients revealed that no mutation in the PKHD1 gene could be found in 20 patients [44], suggesting there can be another unidentified responsible gene for ARPKD. The AQP11 gene is a good candidate. Since the AQP11 gene is much shorter than the PKHD1gene, it may be easier to screen it first.

Both AQP11 and AQP12 can be a risk factor for a specific organ damage including the kidney, liver and pancreas. Such will be used to identify vulnerable patients to the organ damage. The recovery from the damage can be facilitated by increasing the expression of AQP11 or AQP12.

The research on the superaquaporin will reveal a novel role of AQPs.

Acknowledgments

This work was supported in part by grants from the High-Tech Research Center Project (S0801043) and JSPS KAKENHI (24591243).

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