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Review The role of mammalian superaquaporins inside the cell $\stackrel{\mbox{\tiny\scale}}{\rightarrow}$



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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Scope of review: The surveyed literature on these superaquaporins and our unpublished data has been incorporated to speculate their roles.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. © 2013 Elsevier B.V. All rights reserved.

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

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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,

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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).

	: * * * :
AQP9	S AVAMAI VAG VSGGHINPAVSLAMCLFGRMKWFKLPFYVGAQFLGAFVGA
AQP10	SLAVTIAI VGGNVSGAHLNPA SLAMCIVGRLPWVKLPIYIL QLL AF A
AQP3	G AVTLGILIAGQVSGAHLNPAVTFAMC LAR PWIKLPIY LAQTLGAFLGA
AQP7	G GVTMGVHVAGRISGAHMN AVTFANC LGRVPWRKFPVYVL QFLG FLAA
AQP2	GLGIGTRVQALGHISGAHINPAVTVACLVGHVSVLRAAFYVAAQLLGAVAGA
AQP5	GLAIGTL QALGPVSGGHINPA TLALLVGNQISLLRAFFYVAAQL GAIAGA
AQP6	NLV AMAVQVT K SGAH NPAVTLAFLVGSHISLPRAVAYVAAQL GATVGA
AQP0	${\tt GLALATLVQSVGHISGAHVNPAVTFAFLVGSQMSLLRAFCYMAAQLLGAVAGA}$
AQP1	GLSIATL QSVGHISGAHLNPAVTL LLLS QISIFRALMYIIAQC GAIVA
AQP4a	GLSIATMVQ FGHISGGHINPAVTVAMV TRKISIAKSVFYIAAQCLGAIIGA
AQP8	GLALGLVIATLGNISGGH NPAVSLAAMLIG LNLV LLPY V QLLG MLGA
AQP12	$\textbf{TLL} : \textbf{LLFLA} : \textbf{G} \lor \textbf{T} \sqcup \cup \textbf{GA} \cong $
AQP11	TLV FFSLV G TLVGTSSNPCGVM QMMLG MSPE GAVELLAQLVSALCSE
	· data · · ·
	. :
AQP9	. :
AQP9 AQP10	. :
AQP9 AQP10 AQP3	. :
AQP9 AQP10 AQP3 AQP7	. :
AQP9 AQP10 AQP3 AQP7 AQP2	. :
AQP9 AQP10 AQP3 AQP7 AQP2 AQP5	GLV VIG S GEN G AVNPARDLSPRLFTALAGWG EVF AGNNFWW V GML LGLS GAN G PLNPARDLGPRLFTYVAGWGPEVFSAGNGWWW V GLVV VIG S GFN G AVNPARDFGPRLFTALAGWGSAVFTTGQ WWWV V GILV IIGVS GMNTG AINP RDL PRIFT IAGWGK VFS GENWWWV V GFSVALGHLLGIHYTGCSMNPARSLAPAVVTGKFDDHWVFW GLSVTLGHLVGIYFTGCSMNPARSFGPAVVMNRFSAHWVFWV
AQP9 AQP10 AQP3 AQP7 AQP2 AQP5 AQP6	GLUV VIG S GEN GCAMNPARDLSPRLFTALAGWG EVF AGNNFWW PV GML LGLS GAN G PLNPARDLGPRLFTYVAGWGPEVFSAGNGWWV V GLVV VIG S GFN G AVNPARDFGPRLFTALAGWGSAVFTTGQ WWW V GILV IIGVS GMNTG AINP RDL PRIFT IAGWGK VFS GENWWV V GFSVALGHLLGIHYTGCSMNPARSLAPAVVTGKFDDHWVFW GLSVTLGHLVGIYFTGCSMNPARSFGPAVVMNRFSAHWVFWV GISVALGHLIGIHFTGCSMNPARSFGPAIIIGKFTVHWVFWV
AQP9 AQP10 AQP3 AQP7 AQP2 AQP5 AQP6 AQP0	GLL VIA S GLN GCAMNPARDLSPRLFTALAGWG EVF AGNNFWW PV GML LGLS GAN G PLNPARDLGPRLFTYVAGWGPEVFSAGNGWWV V GLVV VIG S GFN G AVNPARDFGPRLFTALAGWGSAVFTTGQ WWV V GILV IIGVS GMNTG AINP RDL PRIFT IAGWGK VFS GENWWV V GFSVALGHLLGIHYTGCSMNPARSLAPAVVTGKFDDHWVFW GLSVTLGHLVGIYFTGCSMNPARSFGPAVVMNRFSAHWVFWV GISVALGHLIGIHFTGCSMNPARSFGPAIIIGKFTVHWVFWV GFS ALGHL GMYYTGAGMNPARSFAPAILTGNFTNHWVYWV
AQP9 AQP10 AQP3 AQP7 AQP2 AQP5 AQP6 AQP0 AQP1	GLL VIA S GLN GCAMNPARDLSPRLFTALAGWG EVF AGNNFWW PV GML LGLS GAN G PLNPARDLGPRLFTYVAGWGPEVFSAGNGWWV V GLVV VIG S GFN G AVNPARDFGPRLFTALAGWGSAVFTTGQ WWV V GILV IIGVS GMNTG AINP RDL PRIFT IAGWGK VFS GENWWV V GFSVALGHLLGIHYTGCSMNPARSLAPAVVTGKFD
AQP9 AQP10 AQP3 AQP7 AQP2 AQP5 AQP6 AQP6 AQP0 AQP1 AQP4a	GLI VIA S GLN GCAMNPARDLSPRLFTALAGWG EVF AGNNFWW PV GMLI LGLS GAN G PLNPARDLGPRLFTYVAGWGPEVFSAGNGWWV V GLVV VIG S GFN G AVNPARDFGPRLFTALAGWGSAVFTTGQ WWV V GILV IIGVS GMNTG AINP RDL PRIFT IAGWGK VFS GENWWV V GFSVALGHLLGIHYTGCSMNPARSLAPAVVTGKFDDHWVFW GLSVTLGHLVGIYFTGCSMNPARSFGPAVVMNRFSAHWVFWV GFS ALGHL GMYYTGAGMNPARSFGPAIIIGKFTNHWVFWV GLSVALGHLLAIDYTGCGINPARSFG AVITHNFSNHW FWV GFSVALGHLLAIDYTGCGINPARSFGPAVIMGNWENHW FWV
AQP9 AQP10 AQP3 AQP7 AQP2 AQP5 AQP6 AQP6 AQP0 AQP1 AQP4a AQP8	GLI VIA S GLN GCAMNPARDLSPRLFTALAGWG EVF AGNNFWW PV GMLI LGLS GAN G PLNPARDLGPRLFTYVAGWGPEVFSAGNGWWV V GLVV VIG S GFN G AVNPARDFGPRLFTALAGWGSAVFTTGQ WWV V GILV IIGVS GMNTG AINP RDL PRIFT IAGWGK VFS GENWWV V GFSVALGHLLGIHYTGCSMNPARSLAPAVVTGKFDDHWVFW GLSVTLGHLVGIYFTGCSMNPARSFGPAVVMNRFSAHWVFWV GISVALGHLIGIHFTGCSMNPARSFGPAIIIGKFT
AQP9 AQP10 AQP3 AQP7 AQP2 AQP5 AQP6 AQP6 AQP0 AQP1 AQP4a AQP4a AQP12	GLL VIA S GLN GCAMNPARDLSPRLFTALAGWG EVF AGNNFWW V GML LGLS GAN G PLNPARDLGPRLFTYVAGWGPEVFSAGNGWWV V GLVV VIG S GFN G AVNPARDFGPRLFTALAGWGSAVFTTGQ WWWV V GILV IIGVS GMNTG AINP RDL PRIFT IAGWGK VFS GENWWV V GFSVALGHLLGIHYTGCSMNPARSLAPAVVTGKFD
AQP9 AQP10 AQP3 AQP7 AQP2 AQP5 AQP6 AQP0 AQP1 AQP4a AQP4a AQP8 AQP12 AQP11	GLL VIA S GLN GCAMNPARDLSPRLFTALAGWG EVF AGNNFWW V GML LGLS GAN G PLNPARDLGPRLFTYVAGWGPEVFSAGNGWWV V GLVV VIG S GFN G AVNPARDFGPRLFTALAGWGSAVFTTGQ WWWV V GILV IIGVS GMNTG AINP RDL PRIFT IAGWGK VFS GENWWV V GFSVALGHLLGIHYTGCSMNPARSLAPAVVTGKFD

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. Download English Version:

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