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Review

Aquaporin subfamily with unusual NPA boxes

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Abstract

Aquaporins have been identified based on highly conserved two asparagine–proline–alanine (NPA) boxes that are important for the formation of a water-permeating pore. Some aquaporin-like sequences, however, have less conserved NPA boxes. Although they have lower homology with conventional aquaporins, they should be included in aquaporin family based on their conserved six transmembrane domains and hydrophobic NPA box-like repeats. They are widely distributed in multicellular organisms. Only SIPs from plants and AQP11/12 from mammals were examined previously and found to be localized inside the cell. Intracellular localization will be a common feature of these aquaporin-like proteins since most of them have positively charged amino acid clusters at the carboxy-termini similar to di-lysine motif (–KKXX) for an endoplasmic reticulum retention signal. Accordingly, they are tentatively named subcellular-aquaporins in this review. Currently, studies on their functions and biological roles are limited. SIPs were shown to function as water channels and the disruption of AQP11 produced neonatally fatal polycystic kidneys. Further works on subcellular-aquaporins will reveal new insights into the roles of aquaporins.

Keywords: NPA box; Aquaporin; Subcellular; SIP; Polycystic kidney

Contents

1. Introduction

Although overall primary sequences are not well conserved (~30% identity with each other), all AQPs have two highly conserved hydrophobic asparagine–proline–alanine (NPA) repeats (NPA boxes), that form a pore for water and/or small molecules such as glycerol and urea. Remarkably, the upstream of the first NPA box and the downstream of the second NPA box are particularly conserved: SG(A/G)HXNPA and NPAR(S/D/A) as shown in the upper half in Table 1. In database, AQP-like sequences with less conserved NPA boxes are also present as shown in the lower half in Table 1. The first NPA box of these AQP-like sequences are highly deviated and diversified, while the second NPA boxes are relatively conserved, where the arginine (R) just after the second NPA is changed to valine (V) or alanine (A). NPA(V/A)A in the second NPA box seems be a clue to identify this new aquaporin subfamily as well as deviated NPA

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Table 1
Sequence alignments of aquaporins at the first and second NPA boxes and the carboxy-termini

	First NPA boxes	Second NPA boxes	Carboxy-termini
AQPZ	–VGHISGGHFNPAVTIGLWAG–	–SIPVTNTSVNPARSTAVAIFQG–	–GGLIYRTLLEKRD
GlpF	–TAGVSGAHLNPAVTIALWLF–	–MGPLTGFAMNPARDFGPKVFAW–	–KETTTPSEQKASL
Chlam	–VGHISGGKLNPAVSIGVLIG–	–GGGLTGAAMNPARAFGPALVSG–	–MLKDLTTLSTPSV
Ustil	–CATTSGGQFHPAFTIAQVVF–	–CFSSSNVVANSARDIGARLVCS–	–QKQRTNLGVKNF
A.nid	–YLATPSPACNPAISIIMALI–	–LGWQTGYAINPARDFGPRLFSA–	–DKAADRNGELRLD
A.fumig	–FYRVTGGLFNPVVSPTHELQ–	–GDYYTGGSLNPARSLGPDVINR–	–NRPVSGAEQV
Tryp1	–FGYISGGHFNPAVTMAVFLV–	–VGRISGGAFNPAAATGLQLALC–	–SAANGVAPVQ
Tryp2	–FGYISGAHFNPAITFATFIN–	–VGGFTGGAFNPAVATGTQLVGC–	–DRVAPIELSGQVF
Leish	–FGYISSSHFNPAVSIAVFLV–	–AGRISGGAFNPAAASGLQVAMC–	–ATTSWEGPTFNRR
TIP1.1	–GANISGGHVNPAVTFGAFIG–	–GGAFSGASMNPAVAFGPAVVSW–	–INTTHEQLPTTDY
PIP2.6	–TAGISGGHINPAVTFGLFLA–	–TIPITGTGINPARSFGAAVIYN–	–YGSVRSQLHELHA
NIP1.2	–LGHISGAHFNPAVTIAFASC–	–AGPVSGASMNPGRSLGPAMVYS–	–GSFLKTVRNGSSR
AQP1	–VGHISGAHLNPAVTLGLLLS–	–AIDYTGCGINPARSFGSAVLTR–	–NSRVEMKPK
AQP3	–AGQVSGAHLNPAVTFAMCFL–	–MGFNSGYAVNPARDFGPRLFTA–	–VKLAHMKHKEQI
AQP8	–LGNISGGHFNPAVSLAVTVI–	–GGSISGACMNPARAFGPAVMAG–	–DEKTRLILKSR
SIP1.1	–TVIFGSASFNPTGSAAFYVA–	–GSKYTGPAMNPAIAFGWAYMYS–	–KKQKKA
SIP1.2	–GNVLGGASFNPCGNAAFYTA–	–GSKFTRPFMNPAIAFGWAYIYK–	–KKQKKA
SIP2.1	–QQATKGGLYNPLTALAAGVS–	–GSDLTGGCMNPAAVMGWAYARG–	–PKAKSE
CeAQP9	–IEFQRDAVAHPCPLVTNCYR–	–GINYTGMYANPIVAWACTFNCL–	–EESEEQEKDTKKKE
CeAQP10	–NIFNRGAMTNCAPIFEQFVF–	–LYVVGVPGLNPIVATARLYGCR–	–KAEKKAKAAAKKSD
CeAQP11	–ALCNRTAFCSPLAPIEQYLF–	–VTFVGDQALDPLVASTLFFGCR–	–KEKKAEKKRAKKNE
Brigg9	–CYFQRDAVAHPCPLVTNCYR–	–GINYTGMYANPIVAWACTFNCL–	–EEQTESQKESKKTD
Brigg10	–GIFNRDAWTNCAPIFEQFIF–	–LYIVGVPGLNPIVATARLYGCQ–	–KKEKKAAAAAKKSD
Brigg11	–ALCNRTAFCSPLAPIEHYLF–	–VTFVGDQALDPLVASTLFYGCR–	–KEKKAEKKRAKKSE
Dros.me	–GRVWGDASACPYTHMEDVVE–	–AFNFSGGYFNPVLATALKWGCR–	–EGAASKSKQE
Dros.ps	–GKVWGDASACPYTHMEDVLE–	–AFNFSGGYFNPVLATALKWGCR–	–KLPIVRRFLLGE
Anoph	–GRNWGSATACPYTYMEQIVE–	–AFNYSGGYFNPVLATALKWGCA–	–FLTDTKTKSE
Urch1	–LTFDGDSTANTCMIWQSMLK–	–GLEWTGMMFNPALAAGITLNCG–	–NRPTPAVPPTKED
Urch2	–NEELSNAGDAPLGQAVQVQP–	–GLEYTGAPMNPILGFASGWGCK–	–NEVNGWVTSV
ZF1	–GFSFRGAICNPTGALELLSR–	–GGRLTGAVFNPALAFSIQFPCP–	–QQLNSNGLKKKKMK
ZF2	–TAVMQDVSGNPAVTLLRLLQ–	–ANNYTSGYVNPALAYAVTLTCP–	–RLPKGKTNDEKSS
Xeno	–GFTFNKASGNSAVSLQDFLL–	–AGSYTGAFFNPTLAAALTFQCS–	–RKAATLPAQKRSS
Chic11	–GLTLPGSTCNPCGTLQPLWG–	–GGNLTGAIFNPALAFSLHPHCF–	–KSFLGHQKTLKSQL
Chic12	–AACANGAASNPTVSLQEFLL–	–AAPATGAFFNPALATASTFLCA–	–QKGKGEKSNPAPRA
AQP11	–GLTLVGTSSNPCGVMMQMML–	–GGSLTGAVFNPALALSLHFMCF–	–WLHNNQMTNKKE
AQP12	–GVTLDGASANPTVSLQEFLM–	–AGPFTSAFFNPALAASVTFACS–	–SPGSVDAKMHKGE

The sequences above the line are conventional aquaporins (water selective aquaporins and aquaglyceroporins); the sequences below the line are subcellular-aquaporins. Highly conserved NPAs (asparagine–proline–alanine) are underlined. Except for SIPs, the second NPA boxes are conserved in subcellular-aquaporins: NPA(L/V/A/I)AXXXXXXC. Most of the carboxy-termini of subcellular-aquaporins are lysine (K)-rich, especially in nematodes, *C. elegans* and *C. briggsae*.
AQPZ and GlpF are from bacteria, *Escherichia coli* (NP_415396, NP_418362). Chlam is from a chlamydia (*parachlamydia* sp. UWE25; CAF23520). The next three are from fungi, Ustil (*Ustilago maydis* 521; XP_758316.1), A. nid (*Aspergillus nidulans* FGSC A4; XP_658434.1), and A. fumig (*Aspergillus fumigatus* Af293; EAL84488). The next three are from the protozoa, Tryp1/2 (*Trypanosoma cruzi*; XP_815990, AF31269.1) and Leish (*Leishmania major*; CAJ08765.1). TIP1.1 (tonoplast intrinsic protein), PIP2.6 (plasma membrane intrinsic protein), NIP1.2 (NOD26-like intrinsic proteins) are from a plant (*Arabidopsos thaliana*; P25818, Q9ZV07, Q8LFP7). AQP1/3/8 are from mice (NP_031498, NP_057898, NP_031500). SIP1.1, 1.2, 2.1 are from a plant (*Arabidopsos thaliana*; Q9M8W5, Q9FK43, Q9M1K3). CeAQPs and Briggs are from nematodes (*C. elegans*; NP_001021552.1, NP_496105.1, NP_499821.2, *C. briggsae*; CAE57975.1, CAE60164.1, CAE71341.1). The next three are from insects, Dros. me (*Drosophila melanogaster*; AAF58409.2), Dros. ps (*Drosophila pseudoodscura*; EAL25342) and Anoph (*Anopheles gambiae*; Xp_309823.2). Urch1/2 are from purple sea urchin (*Strongylocentrotus purpuratus*; XP_780933.1, XP_787329.1). ZF1/2 are from zebrafish (*Danio rerio*; AAH95775.1, AAH95564.1); Xeno from a frog (*Xenopus laevis*; AAH82904.1). Chic11/12 are from chickens (*Gallus gallus*; XP_424343.1, NP_001030011.1). AQP11/12 are from mice (NP_780314, NP_808255).

boxes. Furthermore, cysteine (C) at the downstream of the second NPA is also highly conserved except for plant SIPs (Small basic Intrinsic Proteins) [1]. In the literature, only SIPs and mammalian AQP11/12 have been reported. SIPs function as water channels and are localized subcellularly to the endoplasmic reticulum (ER) [2]. AQP11/12 are also localized inside the cell [3,4]. Accordingly, these aquaporin-like proteins with less conserved NPA boxes are tentatively named 'subcellular-aquaporins' in this review.

This review will be focused on the classification of a new aquaporin-like subfamily: subcellular-aquaporin family. The criteria for subcellular-aquaporins is the presence of less conserved sequences around 'both' NPA boxes. Thus, an aquaporin-like sequence with only one deviated NPA box should not be included and will be classified on the basis of the conserved NPA box. Although such a sequence is very rare, it may be an intermediate or transitional form between conventional AQPs and subcellular-aquaporins and merits future classification. Currently, this classification solely depends on the primary sequences. However, in the near future subcellular-aquaporins will be reclassified on the basis of their functions and/or cellular localizations.

2. Absence of subcellular-aquaporins in unicellular organisms

Curiously, no subcellular-aquaporins are found in bacteria, which suggests that there is no prototype of subcellular-aquaporins in bacteria and that subcellular-aquaporins first appeared in eukaryotes with accumulated mutations around NPA boxes. Alternatively, bacteria may have lost subcellular-aquaporins in their course of evolution. Vigorous searches for homologs or transitional forms of subcellular-aquaporins in bacterial genomes are needed.

Similarly, the absence of subcellular-aquaporins in fungi and protozoa is also noteworthy [5,6]. Exceptionally, an aquaporin-like sequence of *Aspergillus nidulans* has deviated sequence at the first NPA box: PSPACNPA (A. nid in Table 1). However, its second NPA box (NPARDFG) is highly similar to aquaglyceroporins and downstream cysteine (C) is absent. Accordingly, it should be classified as an aquaglyceroporin. Its functional study will confirm this classification. Its deviated upstream sequence of the first NPA seems to be produced by the deletion rather than accumulation of mutations [6]. Similarly, an aquaporin-like sequence of a fungus, *Ustilago maydis* has HPA in the first NPA box (Ustil in Table 1). However, its second NPA box (NSARDIG) is similar to aquaglyceroporin and will be classified as such. Interestingly, it has a downstream cysteine (C) that is conserved in subcellular-aquaporins. Therefore, it could be a transitional form between conventional aquaporins and subcellular-aquaporins. Taken together, subcellular-aquaporins seem to appear first in multi-cellular organisms. Another vigorous search for subcellular-aquaporins in the genomes of fungi and protozoa is necessary.

3. Subcellular-aquaporins in lower animals

It is noteworthy that a nematode, *Caenorhabditis elegans* has three subcellular-aquaporins out of eleven aquaporins (CeAQP9-11 in Table 1). Moreover, their NPA boxes are highly deviated from conventional AQPs especially at the first NPA boxes. There seems to be no homology even among three subcellular-aquaporins at their NPA boxes. The fact that the NPA boxes are different even among subcellular-aquaporins suggests that each subcellular-aquaporin has been produced independently. After careful inspection, however, these subcellular-aquaporins are conserved at the second NPA box: NPXVA, where valine (V) will be a signature sequence for subcellular-aquaporins as it is arginine (R) in most of the conventional AQPs. Similar three subcellular-aquaporins are also present in another nematode *C. briggae* (Brigg9–11 in Table 1). Notably, these nematode subcellular-aquaporins are particularly rich in basic amino acids at the carboxy-termini (Table 1).

A fruit fly, *Drosophila melanogaster* has only one subcellular-aquaporin out of eight aquaporins (Dros. me in Table 1). A previous report on AQPs of *Drosophila* did not include this subcellular-aquaporin [7]. In fact, the first NPA sequence, CPY, is so different that one would hesitate to include it as a member of aquaporins. However, it definitely belongs to AQPs from its primary structure. We previously deposited it in GenBank (Accession #AB036345) and similar genes are also present in other insects (Dros. ps and Anoph in Table 1).

Two subcellular-aquaporins are also found in sea urchin (Urch1/2 in Table 1). Again, their NPA boxes are highly deviated. The functions of these subcellular-aquaporins in lower animals are particularly intriguing due to their highly deviated first NPA boxes, which may form unusual pores.

4. Subcellular-aquaporins in plants

The plant subcellular-aquaporins were previously named SIP (short basic intrinsic proteins) because of their shorter sequences and abundant positively charged amino acids [1]. They are most similar to conventional AQPs among subcellular-aquaporins. They lack the downstream cysteine (C) in the second NPA boxes which is completely conserved in other subcellular-aquaporins (lower half of Table 1). Recently, the function and subcellular localization of SIPs have been reported [2]. All three SIPs are localized inside the cell. The tissue subcellular fractionation showed their localization at the ER. GFP-tagged SIPs were also targeted to the ER, especially to the rough ER where protein synthesis is conducted. It is noteworthy that most subcellular-aquaporins have highly basic carboxy-termini like SIPs (lower half of Table 1). Di-lysine motif (–KKXX) is known for an ER localizing signal [8]. The ER-localization may be a common feature of subcellular-aquaporins.

Structurally, SIPs can be divided into two subgroups: (SIP1.1, SIP1.2) vs. SIP2.1. The former is highly homologous with each other (70% identity) and both are indeed water channels when expressed in yeast vesicles. On the other hand, SIP2.1 (25% identity with SIP1s) is functionally not a water channel. Water channel function may not be the sole function of SIPs and absence water channel activity with SIP2 suggests it has other functions. Since cellular and subcellular distributions of SIP1 and SIP2 are similar, they may also form a heterotetramer. Such heteromerization may stabilize the proteins and affect channel activities. Alternatively, SIP2 may be closed unless a ligand or other regulatory molecule is present.

SIP1s are widely expressed except for dry seeds in tissue- and cell-specific manners [2]. SIP2 is expressed in 2-week-old roots and flowers. SIPs are expressed in the germinating seeds by the induction from dry seeds. SIPs are also accumulated in suspension-cultured cells, suggesting their induction in moist environment. In the root, SIPs are highly expressed in differentiated and elongating regions including a central cylinder which is a main water pathway. In the flowers, SIPs are expressed in the stigma of the carpel and pollen, suggesting their roles in seed maturation and fertilization. Taken together, all inductions and expressions of SIPs seem to be associated with water movement.

5. Subcellular-aquaporins in the vertebrates

In zebrafish, two subcellular-aquaporins are present (ZF1/2 in Table 1). It is difficult to assign them to corresponding homologs of AQP11 and AQP12 due to their low homologies. There may be more subcellular-aquaporins in fish due to whole genome duplication in teleosts. Similarly, more subcellular-aquaporins

will be expected in frogs although only one was identified in the currently undergoing genome project (Xeno in Table 1). In chickens, two subcellular-aquaporins are present which are easily correlated to the mammalian homologs from their primary sequences (Chic11/12 in Table 1).

In mammals, two subcellular-aquaporins are present out of 13 aquaporins (AQP11/12 in Table 1) [9,10]. Northern blot analysis showed that AQP11 is expressed widely; highest in the testis, and moderate in the kidney and liver [3]. In contrast, AQP12 is selectively expressed at acinar cells of the pancreas [4]. Both AQP11 and 12 were expressed intracellularly when transfected into cultured cells. Moreover, AQP11 expression was co-localized with an ER marker. The failure of AQP11/12 to reach the plasma membrane in *Xenopus* oocytes when transfected precludes their functional studies with conventional methods. In the kidney, AQP11 is expressed in the cytoplasm of the proximal tubules. A previous membrane vesicle study revealed the presence of a functional water channel at the ER membrane [11]. AQP11 can be a responsible molecule.

6. Physiological roles of subcellular-aquaporins

Currently, no functional studies on subcellular-aquaporins have been reported except for SIPs, which, however, examined only the water permeability [2]. As they are not expressed at the plasma membrane, it is difficult to study their function. They used a yeast expression system and collected the microsome fractions to examine the water permeability by a stop-flow method. As SIPs function as water channels and their expressions seem to be associated with water transport, they may be important for water metabolism. However, these results may not be extrapolated to the functions of other subcellular-aquaporins since SIPs are more similar to conventional AQPs.

Gene disruption studies may reveal physiological significance without the knowledge of the function. AQP11-knockout (KO) mice appeared to be born normally but had vacuolated proximal tubules at birth. These tubules eventually form cysts to develop polycystic kidneys which are fatal [3]. To a lesser extent, vacuoles were also observed in other organs (the liver and the small intestine). The vacuoles are mostly originated from the ER. AQP11-KO mice may have intravesicular defects leading to the accumulation of unprocessed substances inside the vacuoles. The eventual intravesicular osmotic imbalance will accumulate water to produce vacuoles. These results suggest an important role of AQP11 in the intravesicular homeostasis. Indeed the primary cultured proximal tubules had a defect in endosomal pH regulation unrelated to Cl transport as endosomal Cl regulation was not affected [3]. Since pH of the ER compartment is normally not acidic, AQP11 may also have other roles than intravesicular pH regulation.

7. Intracellularly expressed aquaporins

Some conventional AQPs are also expressed in the cytoplasm. Interestingly, some of them share similar second NPA boxes with subcellular-aquaporins. The second NPA boxes of tonoplast intrinsic proteins (TIPs) are similar to those of subcellular-aquaporins: NPAVA (TIP1.1 in Table 1). TIPs are localized at the intracellular organelle (tonoplast). Protozoan AQPs also have similar second NPA boxes: NPA(V/A)A (Tryp1/2 and Leish in Table 1). Furthermore, a downstream cysteine (C) in the second NPA boxes is conserved although it is one-frame shifted. As these protozoa are parasitic to survive inside the host cells, their AQPs may virtually function as intracellular AQPs in the host cells [5]. In mammals, AQP8 also has similar second NPA boxes: NPARA (Table 1). Recent immunohistochemical and biochemical analyses have revealed that the inner mitochondrial membrane of rat hepatocytes contains AQP8, which may be involved in rapid expansion of mitochondria in cell division and apoptosis [12]. These results suggest that these conventional intracellular AQPs and subcellular-aquaporins may share a common ancestor.

The distributions and roles of intracellular AQPs should be clarified. They will play important roles as suggested by a fatal gamma-TIP KO plant [13]. The swelling of zymogen granules are shown to be regulated by AQP1 in the pancreas [14] and by AQP5 in the salivary gland [15]. The roles of AQP1 and AQP6 in synaptic vesicle swelling have also been speculated [16]. Unexpectedly, AQP10 has been shown to be expressed at intracellular granules of gastro-entero-pancreatic endocrine cells in the small intestine [17].

The researches on subcellular-aquaporins will stimulate the researches on intracellular AQPs. These studies will definitely expand the scope of AQPs.

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