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REVIEW

Plant and animal aquaporins crosstalk: what can be revealed from distinct perspectives

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Abstract Aquaporins (AQPs) can be revisited from a distinct and complementary perspective: the outcome from analyzing them from both plant and animal studies. (1) *The approach in the study*. Diversity found in both kingdoms contrasts with the limited number of crystal structures determined within each group. While the structure of almost half of mammal AQPs was resolved, only a few were resolved in plants. Strikingly, the animal structures resolved are mainly derived from the AQP2-lineage, due to their important roles in water homeostasis regulation in humans. The difference could be attributed to the approach: relevance in animal research is emphasized on pathology and in consequence drug screening that can lead to potential inhibitors, enhancers and/or regulators. By contrast, studies on plants have been mainly focused on the physiological role that AQPs play in growth, development and stress tolerance. (2) *The transport capacity*. Besides the well-described AQPs with high water transport capacity, large amount of evidence confirms that certain plant AQPs can carry a large list of small solutes. So far, animal AQP list is more restricted. In both kingdoms, there is a great amount of evidence on gas transport, although there is still an unsolved controversy around gas translocation as well as the role of the central pore of the tetramer. (3) *More roles than expected*. We found it remarkable that the view of AQPs as specific channels has evolved first toward simple transporters to molecules that can experience conformational changes triggered by biochemical and/or mechanical signals, turning them also into signaling components and/or behave as osmosensor molecules.

Keywords Aquaporins · Diversity · Solutes · Gases · Osmosensor

Introduction

The discovery of aquaporins (AQPs) significantly changed the study of water, small solutes and gas transport in living organisms and broadened a newly unexplored field of scientific research. Extensive information is now available covering and integrating approaches such as phylogeny, structure and physiology, in particular transport studies or regulatory mechanisms to understand how the presence of these proteins makes a difference in cell physiology and how this can be extended to tissue/organ/individual levels. Here, we review knowledge on AQPs, conserved transport proteins that belong to the MIP superfamily of transmembrane proteins. Our perspective includes comparing information mainly on plants and animals and discussing current hypotheses and controversy on the role and function of AQPs. This revision is complemented with data from microorganisms and insects.

The first section is dedicated to the evolutive relationship between plant and animal AQPs. The number of identified members in each kingdom is discussed, and contrasted with the number of crystal structures determined. The second

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section is dedicated to the function and the relationship with physiology and pathology. Here, a difference is remarked on concerning the focus on research approaches in plants and animals. The third section is dedicated to comparing the transport capacities of plant and animal AQPs in terms of permeating molecules. The most outstanding difference is found here. While plant AQPs can transport a broad variety of solutes including non-metals and metals (urea, NH_3, boron, silice, arsenite, etc.), animal counterparts are more restricted, prevailing a limited list of small no charge solutes. Special attention is placed on the current discussion about the transport of gases and the role of the central pore of the tetramer. The fourth section reviews the regulatory mechanisms of AQPs. Although similarities exist on gating mechanisms and gas transport, some differences on trafficking can be observed. This section is divided into gating and trafficking events. The fifth section revisits the discussion on AQPs as osmosensors within the context of recent evidence. Conformational changes have been observed in AQPs gated by biochemical and mechanical signals, supporting the osmosensor hypothesis. Finally, the study of AQPs is discussed in perspective.

Does the number of AQPs count?

It is usually said that the diversity of aquaporins in plants is higher than in animals. This statement is supported on the fact that there are only 13 types of AQPs in mammals (Verkman et al. 2014) while in specific plant species, such as *Arabidopsis thaliana*, *Populus trichocarpa*, *Glycine max* or *Gossypium hirsutum*, there are 35, 55, 66 or 71 members, respectively (Johanson et al. 2001; Quigley et al. 2001; Gupta and Sankararamakrishnan 2009; Park et al. 2010; Maurel et al. 2015).

Diversity and evolution of plant and animal AQPs has been widely revisited (Abascal et al. 2014; Maurel et al. 2015; Finn and Cerdà 2015; Pérez Di Giorgio et al. 2014; Von Bülow and Beitz 2015; Song et al. 2014). Therefore, we highlight here some recent findings on this subject that are relevant to discuss our knowledge on the number of AQPs. This information is contrasted with the number of resolved crystal structures.

Classification of AQPs in higher plants describes seven subfamilies: the plasma membrane intrinsic proteins (PIPs), the tonoplast intrinsic proteins (TIPs), the nodulin 26-like intrinsic proteins (NIPs), the small basic intrinsic proteins (SIPs), the uncategorized (X) intrinsic proteins (XIPs) that are absent in some higher plant species, the hybrid intrinsic proteins (HIPs), and GlpF-like intrinsic proteins (GIPs) (Maurel et al. 2015). On the other hand, just four subfamilies are identified in animals: water-specific channels (AQP0, 1, 2, 4, 5, 6), aquaglyceroporins (AQP3, 7, 9, 10), water and ammonium aquaporins (AQP8), and unorthodox aquaporins (AQP11, 12) (Finn et al. 2014).

Besides separate classifications, plant and animal aquaporins are highly conserved and share common ancestors.

Phylogenetic analysis indicates that classical water channels or AQPs and glycerol transporters or aquaglyceroporins (GLPs) split from a common node of ancient membrane integral proteins (MIPs) (Abascal et al. 2014). Then, four ancestral subfamilies gave origin to the PIP-AQP1-like, TIP-AQP8-like, NIP-AQP3-like and SIP-AQP11-like branches, which supports the vertical transfer hypothesis (Soto et al. 2012; Pérez Di Giorgio et al. 2014). On the other hand, recent evidence suggests that horizontal gene transfer and genome fusion events would have given origin to other subfamilies. For example, NIP genes from plants would have originated from the nitrite-oxidizing class (AqpN) of Bacteria, before the evolution of Eukaryota (Finn and Cerdà 2015). Although there is no solid evidence to support the horizontal gene transfer hypothesis in general (Pérez Di Giorgio et al. 2014), the high diversity found in plant NIPs is thought to be associated with tandem duplication events as well as to the degree of polyploidy found in angiosperms (Finn and Cerdà 2015). The high genetic diversity found in plants also shows examples of loss events, such as GIPs in Dicotyledonae and XIPs in Monocotyledonae (Danielson and Johanson 2008; Finn and Cerdà 2015), a feature atributed to functional redundancy (Maurel et al. 2015). On the other hand, other events produced increments in the number of AQPs. For example, current PIPs are subdivided into PIP1 and PIP2 subfamilies, and current TIPs have five subfamilies in higher plants (Maurel et al. 2015), evidencing that PIPs have greater functional constraints than TIPs (Pérez Di Giorgio et al. 2014).

In insects, recent findings indicate that the *glp* genes (which encodes for aquaglyceroporins) disappeared in Holometabolus and Hemipterea (Finn et al. 2015; Van Ekert et al. 2016). In these lineages, glycerol transporters would have evolved by duplication of the *eglp* genes that encodes entomoglyceroporins, which are glycerol-transporting proteins that can also transport water, urea, and other polyols. These glycerol transporters evolved by mutation of the conserved His in the ar/R selectivity filter of water-selective channels and are phylogenetically more closely related to the classical aquaporin 4-type channels than to the GLPs (Finn et al. 2015).

In tetrapods, the lineage of water-specific channels would have evolved from AQP4, which appeared very early, in basal Deuterostomia, during pre-cambric, a period with an unexpected diversity of AQPs (Finn et al. 2014). This study also revealed unknown subfamilies of water channels in Vertebrata: AQP14, −15 and −16. These lineages disappeared along tetrapods evolution and are absent in current vertebrates (Finn et al. 2014). The lineage of AQP2–5 is absent in Actinopterygian fishes, and appeared later by positive selection in basal Sarcopterygii. This lineage constitutes a genomic apomorphy and its appearance highlights the pivotal role that AQPs played for terrestrial adaptation (Finn et al. 2014; Finn and Cerdà 2015).

Altogether, these evidences indicate that evolution of plant AQPs was less constricted than in animals, which could be related to terrestrial forms of life.

To date, the crystal structure of AQPs from ten different subfamilies has been resolved: AQP0 (Gonen et al. 2004; Palanivelu et al. 2006; Hite et al. 2010; Reichow et al. 2013), AQP1 (Murata et al. 2000; Sui et al. 2001; Ren et al. 2000; de Groot et al. 2001; Ruiz Carrillo et al. 2014), AQP2 (Frick et al. 2014), AQP4 (Hiroaki et al. 2006; Ho et al. 2009; Tani et al. 2009; Mitsuma et al. 2010), AQP5 (Horsefield et al. 2008; Kitchen et al. 2015a), AQPM from *Methanothermobacter marburgensis* (Lee et al. 2005), GlpF (Fu et al. 2000; Tajkhorshid et al. 2002), AQPZ from *Escherichia coli* (Jiang et al. 2006; Savage et al. 2003), *Pf*AQP from *Plasmodium falciparum* (Newby et al. 2008), Aqy1 from *Pichia pastoris* (Fischer et al. 2009; Kosinska Eriksson et al. 2013), *So*PIP2;1 from *Spinacia oleracea* (Törnroth-Horsefield et al. 2006; Nyblom et al. 2009; Frick et al. 2013), and *At*TIP 2;1 from *Arabidopsis thaliana* (Kirscht et al. 2016).

Although current AQPs show higher diversity in plants than in animals, recent evidence has revealed that the latter groups showed originally a high diversity in earlier mammals. It should be emphasized that structural studies predominate in animals. While the structure of almost 50% of mammal AQPs have been resolved, the structure of only two AQPs has been resolved in plants. Strikingly, these structures correspond to AQPs derived from the AQP2-lineage, which play important roles in water homeostasis regulation. This difference in the number of structural studies could be related to the different approach that drives research on each subfamily. While relevance of research in animal AQPs is put on pathology and the associated search for drugs that can act as inhibitors and regulators (Verkman et al. 2014), studies on plants are focused on the physiological role that AQPs play in the whole plant (Maurel et al. 2015).

It is evident that structural studies are needed in plant AQPs. Structural determinations already performed allowed seeing the same AQP in different conformations (for example *So*PIP2;1), evidencing the possibility of a gating mechanism. Furthermore, the structural resolution of the pore supported the needed information to perform molecular dynamics simulations. These in silico experiments confirmed the single file hypothesis and, at the same time predict the invertion of the water molecule when translocating through the channel (de Groot and Grubmüller 2001).

Thus, these approaches will also lead to valuable information on, for example, structural clues about the function of other AQPs as metalloporins.

Physiology versus pathology

Almost at the same time as the discovery of the first aquaporin in animal cells (Preston et al. 1992), there was evidence of a protein highly expressed in seeds structurally related to the bacterial glycerol facilitator GlpF (Johnson et al. 1989, 1990). A few years later, the activity of the first tonoplast water channel was described (Maurel et al. 1993).

Since water movements occur through biological membranes by simple diffusion, the discovery of water channels offered a novel pathway, which increases the membrane water permeability from 10 to 100 times more than in their absence. But the real impact of AQPs was their regulatory capacity at different levels, which is more restricted for the lipid bilayer (Calamita 2005). Therefore, the main approach in plants was to study the water transport capacity of tissues/organs where AQPs are highly expressed, focusing on the relationship between the function of water channels and a specific physiological process. Some of these processes, such as seed germination, water transport in roots and leaves, stomatal closure and other processes associated with circadian rhythms and stress conditions, are summarized in this section.

In animals, the most studied AQPs are the 13 members identified in mammals, which have tissue- and organ-specific expression (for a recent review, see Day et al. 2014). Although their role in physiological processes has been widely studied, the approach was generally driven by interest on human diseases, with a substantial number of articles using aquaporin-KO transgenic mice and analyzing the possible function due to the lack of a particular water channel. Since detailed reviews on mammal AQPs exist (Noda et al. 2010; Rutkovskiy et al. 2013; Sasaki et al. 2014; Ribatti et al. 2014; Nagaraju et al. 2016), we briefly summarize here the pathology-associated role of water-specific channels and aquaglyceroporins in organs such as heart, brain, liver, kidney, skin and eye.

The physiological focus in plants

Seed germination requires a rapid water uptake to the imbibition of tissues. Water entry is also required for the development of the embryo. Experiments with pea showed that water channels may participate in the first water-uptake events (Veselova et al. 2003), whereas AQPs in *Arabidopsis thaliana* or *Vicia faba* would contribute to growth of the embryo (Vander Willigen et al. 2006; Novikova et al. 2014).

In roots, aquaporin expression was investigated in different species, such as *Arabidopsis*, maize, rice and barley, showing specific patterns for different isoforms (Javot et al. 2003; Gattolin et al. 2009; Hachez et al. 2006; Sakurai et al. 2008; Knipfer and Fricke 2011). The contribution of AQPs to water transport in roots was studied using mercury chloride as inhibitor. These results showed that hydraulic conductivity (L_{pr}) can be reduced by up to 47% and 64% in *Populus* and *Arabidopsis*, respectively (Wan and Zwiazek 1999; Sutka et al. 2011).

Concerning leaves, AQPs were detected in guard cells of many species, such as *Helianthus annuus* (Sarda et al. 1997), *Vicia faba* (Sun et al. 2001), *Nicotiana glauca* (Smart et al. 2001), *Picea abies* (Oliviusson et al. 2001), *Arabidopsis thaliana* (Leonhardt et al. 2004; Prasch et al. 2015), *Spinacia oleracea* (Fraysse et al. 2005) and *Zea mays* (Heinen et al. 2014). AQPs were also detected in other tissues in the elongating zone of leaves, in the vascular bundles and in the mesophyll (Besse et al. 2011; Hachez et al. 2008; Prado et al. 2013).

Functional studies involved AQPs in leaf hydraulics (Postaire et al. 2010; Prado et al. 2013). Recently, it was reported that *At*PIP2;1 participates in stomatal closure (Grondin et al. 2015). The authors of this work proposed a model where the ABA-triggered phosphorylation of PIP2;1 at Ser-121 increases the water permeability of the guard cells inducing stomatal closure (Grondin et al. 2015; Maurel et al. 2016).

Contributions have also been made to show how water channels might participate in the shoot–root relationship. It has been reported that transpiratory demand can regulate both the expression of root AQPs and the root hydraulic conductivity (Laur and Hacke 2013; Vandeleur et al. 2014).

In addition, the role of AQPs on plant physiology was studied in association with circadian rhythms. For instance, the regulation of L_{pr} oscillations that occur during the day was studied in some plant species (Lopez et al. 2003; Vandeleur et al. 2009). In *Mimosa pudica*, an increased expression of a γ-TIP was correlated with pulvinar movements (Fleurat-Lessard et al. 1997), and in motor cells from *Samanea saman*, the expression pattern of the gene that codifies for *Ss*AQP2 showed the same diurnal rhythm as pulvinar movements (Moshelion et al. 2002).

Other physiological processes that implicate water and solute movements, and where AQPs play a relevant role includes color development in some flowers (Negishi et al. 2012), nutrient soil absorption (Ma et al. 2006; Takano et al. 2006), rhizobium–legume symbiosis (Rivers et al. 1997; Hwang et al. 2010) and mycorrizhae (Ruiz-Lozano et al. 2009; Barzana et al. 2014).

Besides analyzing plant growth and development, the contribution of water channels under stress conditions has also been extensively investigated. As an example, in trees species it has been demostrated that in winter or under drought, air bubbles may form within the vascular system (embolism) and some reports suggest that AQPs can contribute to embolism refilling in trees (Sakr et al. 2003; Secchi and Zwieniecki 2010). For a recent review on plant AQPs and stress, see Sade and Moshelion (2017).

The pathological focus in animals

As most mammal water channels, AQP1 is expressed in many organs. For example, AQP1 was found in kidney (Nielsen et al. 1993; Ishibashi et al. 1994), skin (Sougrat et al. 2002), liver (Marinelli and LaRusso 1997), pancreas (Hurley et al. 2001), brain (Shields et al. 2007; Arcienega et al. 2010), heart (Butler et al. 2006), and vascular endothelial cells, where it is the most expressed AQP (Verkman 2002).

High expression of AQP1 was early reported in tumor of microvessels (Endo et al. 1999). Following studies showed that deletion of AQP1 reduces the growth and vascularity of implanted tumors (Saadoun et al. 2005), and that water channels expressed in tumor cells improve their capacity to extravasate across blood vessels and to invade locally neighbor tissues (Hu and Verkman 2006). Over the years, other AQPs have been reported to be involved in many types of cancer, with implications in tumor edema formation and angiogenesis. Since information about the pivotal role that AQPs play in cancer is very extensive, we do not dedicate more than this brief mention to this subject as the topic has been previously reviewed in detail (Verkman et al. 2008; Verkman 2011; Ribatti et al. 2014; Nagaraju et al. 2016).

Water transport and AQPs function has been extensively studied in kidney where several water channels are expressed (AQP1, AQP2, AQP3 and AQP4). Most water reabsorption occurs in the proximal tubule through AQP1, whereas AQP2 is key in the fine regulation of water permeability in the apical membrane of principal cells of the collecting duct (Fushimi et al. 1993). Regulation of AQP2 expression in the apical membrane is mediated by the arginine vasopressin hormone, through its receptor located in the basolateral membrane (Marples et al. 1995; Yui et al. 2012). AQP3 and AQP4, which are constitutively expressed in the basolateral membrane of principal cells, facilitate the outflow of water to the blood. The regulation mechanism of AQP2 is one of the best known. For a detailed description, see Noda et al. (2010) and Sasaki et al. (2014).

While AQP1 knock-out mice showed defective fluid absorption (Schnermann et al. 1998), AQP2 mutations in humans cause nephrogenic diabetes insipidus (Deen et al. 1994), which results in urinary hypo-osmolality. Moreover, a polycystic kidney phenotype is observed in AQP11-deficient mice (Morishita et al. 2005).

In the brain, AQP4 is highly expressed in the plasma membrane of astrocytes, which are the most abundant glial cells (He and Sun 2007). In astrocytes, AQP4 is involved in the water exchange mechanism of the blood–brain barrier, and its absence produces decreased water uptake in mice brain (Haj-Yasein et al. 2011).

An interesting pathology concerns the role of AQP4 is neuromyelitis optica. As recently reviewed, this autoimmune disease is characterized by specific recognition of AQP4 by an autoantibody with preferential affinity for the M1 isoform (Pittock and Lucchinetti 2016).

The role of both AQP1 and AQP4 is now been studied in edema developmental events in brain and heart. AQP4 is a bidirectional water channel that facilitates both the water accumulation in brains that suffer cytotoxic edema (as ischemic stroke and bacterial meningitis) (Manley et al. 2000; Papadopoulos and Verkman 2005,) and the clearance of excess brain water in vasogenic edema (as obstructive hydrocephalus) (Bloch et al. 2006).

AQP1, -4, and -6 seem to play distinct roles in myocardial infarction (MI) in mouse hearts. While the time-dependent pattern of the observed up-regulated expression of AQP4 in MI coincides with that of myocardial edema (ME) and cardiac dysfunction, the expression of AQP1 and AQP6 persistently increases (Zhang et al. 2013).

Analysis of evidence from rat (Page et al. 1998), mice (Montiel et al. 2014) and goats (Ding et al. 2013; Yan et al. 2013) suggests that AQP1, which colocalizes with Caveolin-1, would play a key role on the regulation of Connexin 43 during ME. On the other hand, a study with AQP1 knock-out mice reported microcardia (decreased myocyte dimensions) and low blood pressure (Montiel et al. 2014). The abnormalities caused by AQP4 knock-out on calcium-modulating proteins is associated with exacerbation of risk for cardiac arrhythmias and failure in mice heart (Cheng et al. 2012). A recent review on myocardial AQPs suggests that AQP4 is involved in calcium handling and may constitute an osmosensory apparatus in heart muscle (Rutkovskiy et al. 2013).

AQP0 show particular features within the water-transporting channels. In the eye, lens fiber cells are specialized to form a tightly transparent layer that minimizes the amount of incident light to support the function of the eye. Expression of AQP0 was reported in these cells (Kumari et al. 2011), where they assemble into large arrays forming functional microdomains that dynamically associate and dissociate (Scheuring et al. 2007). Mutations of AQP0 cause congenital cataracts in humans and mice by a mechanism that would involve loss of the cell packing required to minimize light scattering (Berry et al. 2000; Chepelinsky 2009).

Aquaglyceroporins have been well studied in adipocytes, skin and liver. In adipocytes. AQP7 modulates the glycerol membrane permeability and controls the fat cell size mediated by triglyceride accumulation (Hara-Chikuma et al. 2005; Duncan et al. 2007). AQP9 has been proposed as an important pivot for hepatic glycerol uptake (Carbrey et al. 2003). From analyses of this evidence arose the suggestion that both the fat-specific AQP7 and the liver-specific AQP9 act as key coordinated regulators in diabetes and obesity (Maeda et al. 2009). Interestingly, AQP7-null mice show lower levels of glycerol and ATP in heart, and accelerated hypertrophy following aortic constriction (Hibuse et al. 2009), indicating that AQP7 could play a key role in metabolism in heart (Gladka et al. 2009).

In skin, AQP3 mediates the glycerol transport determining the hydration status of the epidermis and the stratum corneum (Ma et al. 2002).

Besides studies in plants and animals that have been separately presented, there are features that can be compared, such as those described in the reproductive systems. In plants, specific pollen AQPs have been reported, such as TIP1;3, TIP5;1, NIP4;1 and NIP4;2 (Soto et al. 2008; Pérez Di Giorgio et al. 2016a, 2016b). These reproduction-associated AQPs showed low water permeability but the capacity to transport glycerol and urea, and have been suggested to be involved in the nitrogen metabolic pathway during pollen tube growth (Soto et al. 2008, 2010; Pérez Di Giorgio et al. 2016a, b).

In the human reproductive system, AQP3 and AQP7 have been identified in sperm (Chen and Duan 2011; Ishibashi et al. 1997) and AQP9 in epididymis (Tsukaguchi et al. 1998). Like in plants, transepithelial solute fluxes have been described. In particular, glycerol, urea, mannitol and sorbitol are mediated by these aquaglyceroporins (Pastor-Soler et al. 2002). Even, a recent report highlights the importance of AQP7 to protect mouse oocytes from hyperosmotic stress during cryopreservation by vitrification (Tan et al. 2015). This evidence confirms that AQPs as solute transporters play important physiological roles associated with the transport of glycerol, urea and other small solutes in the reproductive systems of both plants and animals.

Water, solute and now… gases

The diversity of AQPs shows that the classification is not simple. Moreover, experimental evidence has been adding increasing amounts of information indicating that AQPs are not only water channels. Now, it is known that AQPs can transport water, small solutes and also gases. There are recent and detailed reviews on this issue (Bienert et al. 2008; Verkman 2011; Rambow et al. 2014; Verdoucq et al. 2014; Kitchen et al. 2015b; Maurel et al. 2015). Therefore, we will focus on some features that open the discussion about the physiological role of AQPs.

In previous years, intense controversy was maintained concerning the possibility of ions translocation through animal AQPs. Contradictory evidence led to the publication of brief letters written by referent researchers in the same number of science magazine (Agre et al. 1997). Evidence on this subject, as well as the mechanism of proton exclusion, can be found in many reviews (Ozu et al. 2013; Kreida and Törnroth-Horsefield 2015). While animal AQPs do not transport ions, an increase amount of evidence shows that plant counterparts can also transport metals. In particular, NIPs mediate the transport of boron, silicon and selenium that are beneficial for plant growth, or arsenic and antimony that are toxic metalloids (Bienert et al. 2008; Zhao et al. 2010). The

role of *At*NIP1;1 in the sensitivity of *Arabidopsis* to arsenite was tested by expressing mutants in *Xenopus* oocytes (Kamiya et al. 2009). Other works have shown that arsenite and silicon translocate through the same pathway in *Os*NIP2;1, which was associated with the high capacity of rice to accumulate arsenite (Ma et al. 2008). In addition, *Os*NIP2;1 mediates selenium uptake in rice (Zhao et al. 2010), and XIPs are also permeable to metalloids (Bienert et al. 2011). This evidence not only indicates that NIPs would be involved in plant health and food quality (Maurel et al. 2015) but also highlights the great differences between plant and animal AQPs in their transport capacities.

The fact that animal AQP1 is expressed in tissues involved in gas but not water exchange, like the pulmonary capillaries, epithelium, vascular smooth muscle, and red blood cells (Effros et al. 1997; Preston and Agre 1991; Shanahan et al. 1999; Verkman 2006), supported the hypothesis that AQP1 could function as a gas channel. The first experimental evidence indicating that AQP1 could act as a gas channel was obtained studying the CO_2 transport in *Xenopus* oocytes expressing AQP1 (Nakhoul et al. 1998). Later works indicated that AQP1 could also increase the NO influx across cell membranes (Herrera et al. 2006), and that the relaxation of endothelial smooth muscle required AQP1-dependent transport of NO across cell membranes (Herrera and Garvin 2007). In addition, molecular dynamic simulations suggested that aquaporin-4 can also transport NO (Wang et al. 2007). However, the possibility that gases could cross membranes through AQPs was questioned by theoretical analysis (Missner and Pohl 2009). According to the authors, the experimental methods used to study CO_2, O_2 or NH_3 transport through AQPs are not always reliable. This analysis was in line with results from molecular dynamic simulations which concluded that CO_2 permeation through AQP1 can be expected only in membranes with low intrinsic CO_2 permeability, because the energetic barrier through the water channel can be higher than through the membrane, depending on the bilayer composition (Hub and de Groot 2006). Almost simultaneously, other molecular dynamic simulations showed that the free energy barrier for CO_2 and O_2 permeation through the central hydrophobic pore of the AQP1 is considerably smaller than the permeation barrier through the water pore of the monomer (Wang et al. 2007). The same group reported later that the central pore of the AQP4 tetramer can transport CO_2 and NO, which provides an energetically more favorable pathway than in AQP1 (Wang and Tajkhorshid 2010). Previous experimental results indicated that the pathway through the central pore of the tetramer could be regulated by interactions of cytoplasmic loops with cGMP (Yu et al. 2006). Other mammalian AQPs that could transport CO_2 would be AQP0, 5, 6 and 9 (Geyer et al. 2013).

In the last years, increasing evidences for the putative role of AQPs as gas channels have been accumulating in all kingdoms. The transport of CO_2 through AQPs has also been reported in microorganisms (Nehls and Dietz 2014). *Tc*AQP1 from *Terfezia claveryi* facilitates water and CO_2 diffusion (Navarro-Ródenas et al. 2011).

In plants, members of the PIP1 and PIP2 subfamilies show different CO_2 transport capacity. The CO_2 transport properties of PIP2 from *Hordeum vulgare L.*, tested in *Xenopus* oocytes, show that *Hv*PIP2;1, *Hv*PIP2;2, *Hv*PIP2;3 and *Hv*PIP2;5 facilitated CO_2 transport but *Hv*PIP2;4 did not. This latter member of the PIP2 subfamily in barley has a methionine in position 254 instead of the conserved isoleucine present in the other members. This conserved isoleucine is fundamental for CO_2 selectivity (Mori et al. 2014). Interestingly, the CO_2 transport capacity of monomeric and tetrameric arrangements has also been investigated in plants. Experiments performed in yeast expressing PIP1 from *Nicotiana tabacum* (*Nt*AQP1) showed that tetramers exhibit higher CO_2 transport rates than monomers, supporting the hypothesis that CO_2 permeates through the central pore of the tetramer (Otto et al. 2010). CO_2 permeation was also demonstrated with *At*PIP1;2, but not with *At*PIP2;3 (Heckwolf et al. 2011).

As well as CO_2, both in animals and plants, AQPs can transport reactive oxygen species, which make them important players in redox signaling and detoxification. Specific aquaporin isoforms facilitate the passive diffusion of hydrogen peroxide (H_2O_2) across biological membranes and control H_2O_2 signaling in living organisms (Bienert and Chaumont 2014).

Molecular dynamic simulations show that both mammalian and plant aquaporin models may transport not only H_2O_2 but also highly reactive hydroxyl radicals (HO) and the protonated form of superoxide radicals (HO_2) that can reach the pore interior and oxidize amino acids responsible for channel selectivity (Cordeiro 2015).

In teleost fishes, AQP8b, an orthologue of human aquaporin-8, is phosphorylated and inserted into the inner mitochondrial membrane of activated spermatozoa. AQP8b facilitates H_2O_2 efflux from the mithocondria, in an important detoxification mechanism for the maintenance of flagellar motility (Chauvigné et al. 2015).

H_2O_2 translocation through AQPs is an important signal for the onset of immunological responses in animals and plants. In mammals, the transport of H_2O_2 through AQP3 contributes to the intracellular signaling in response to epidermal growth factor (Miller et al. 2010), and mediates the signal transduction that triggers the inflammatory response against the intestinal pathogen *Citrobacter rodentium* in the colonic epithelium (Thiagarajah et al. 2017).

In *Arabidopsis thaliana*, evidence supports that H_2O_2 transport through *At*PIP1;4 is necessary for the cytosolic import of apoplastic H_2O_2 induced by bacterial pathogens, indicating that the function of *At*PIP1;4 as a H_2O_2 channel is involved in the apo-cytosolic signal transduction in immunity pathways (Tian et al. 2016).

Other studies in plants highlight the key role that AQPs play for tolerance under stress conditions. Transgenic tobacco overexpressing a wheat PIP2 homolog (*Ta*AQP7) showed enhanced tolerance to drought stress by reducing ROS accumulation (Zhou et al. 2012). Other recent works show that transcript levels of specific PIPs increase under stress by hypoxia (*Nt*PIP1;3) (Zwiazek et al. 2017) or boron (*Os*PIP1;3 and *Os*PIP2;6) (Mosa et al. 2016). Other PIPs, NIPs, and also TIPs have been previously involved in boron uptake or tolerance in *Arabidopsis*, barley, rice, and maize (Takano et al. 2006; Tanaka et al. 2008; Schnurbusch et al. 2010; Bogacki et al. 2013; Pang et al. 2010; Dordas and Brown 2001; Fitzpatrick and Reid 2009; Kumar et al. 2014).

By means of quantitative phenotypic assay, H_2O_2 permeability of both the human aquaammoniaporin AQP8 and the prototypical orthodox water channel AQP1 from rat have been confirmed. Correlation of H_2O_2 permeability with water permeability and with pore diameter (rAQP1, hAQP8 and *Pf*AQP from malaria parasite *Plasmodium falciparum*) suggests that all water-permeable AQPs are H_2O_2 channels, and that H_2O_2 permeability varies with the isoform (Almasalmeh et al. 2014).

As revealed by the great amount of evidence on gas transport through AQPs, research on this subject is comparable in both plants and animals. In plants, relevance is related to the role of CO_2 associated with gas exchange and signal transduction. In animals, relevance is related to the physiological processes of gas exchange in lungs and detoxification mechanisms.

Conserved versus particular/specific regulatory mechanisms

Many regulatory mechanisms are known in AQPs. Since recent detailed reviews have been dedicated to them (Törnroth-Horsefield et al. 2010; Verdoucq et al. 2014; Kreida and Törnroth-Horsefield 2015; Chevalier and Chaumont 2015), we mention here the most relevant features for comparison between plants and animals.

Gating

It has been reported that aquaporin activities can be regulated by phosphorylation, pH and calcium. In plants, a gating mechanism induced by acidic pH was observed in PIPs (Tournaire-Roux et al. 2003; Alleva et al. 2006; Bellati et al. 2010). It was described that protonation of a highly-conserved residue of *loop D* (His197) was responsible of gating in *So*PIP2;1. A molecular mechanism was proposed based on high-resolution structures of the water channel in open and close states (Törnroth-Horsefield et al. 2006). At low pH, protonation of His193 from *loop D* produces a conformational change of this intracellular loop, which in consequence caps the channel from the cytosol and occludes the pore. His193 interacts with Asp28, Glu31 and Ser115 from *loop B*, to stabilize *loop D* in a closed pore conformation (Törnroth-Horsefield et al. 2006; Frick et al. 2013).

In *Fragaria ananassa*, *Fa*PIP2;1-*Fa*PIP1;1 heterotetramers modify both the water permeability and the pH sensitivity by combining subunits with different transport properties. While *Fa*PIP2;1 homotetramers reach the plasma membrane and are inhibited at low pH, *Fa*PIP1;1 homotetramers do not reach the plasma membrane (Yaneff et al. 2014, 2016). Interestingly, heterotetramers promote a change in sensing cytosolic by shifting the EC50 value (Yaneff et al. 2014).

There have also been reports of inhibition by acidic pH in TIPs (Soto et al. 2010; Leitaõ et al. 2012). Although a His residue localized in the intravacuolar *loop C* was demonstrated to be involved, the mechanism in TIPs is unknown.

While the known mechanism of pH regulation seems to be highly conserved among plant PIPs (Tournaire-Roux et al. 2003; Alleva et al. 2006; Frick et al. 2013), the scenario seems to be more variable in animal water channels, where pH regulatory effects have been observed but in contrasting ways. While water and glycerol permeability in oocytes expressing AQP3 was inhibited at acidic pH (Zeuthen and Klaerke 1999), low pH increased the water permeability of AQP6 (Yasui et al. 1999) and AQP0 (Németh-Cahalan and Hall 2000). Németh-Cahalan showed that mutations on His40 from *loop A* produces loss of pH sensitivity in AQP0, suggesting a key role of this amino acid in facilitating the regulation of water permeability. A later study comparing pH effects on water permeability of different AQPs (bAQP0, MIPfun, hAQP1 and rAQP4) indicated that the position of external histidines from *loops A* and *C* can modify the pH dependence (Németh-Cahalan et al. 2004), for example, alkaline pH increases the rAQP4 water permeability.

The electron diffraction structure of AQP0 has been reported with different resolutions (Harries et al. 2004; Gonen et al. 2004, 2005) and the comparison showed different conformations of the extracellular *loop A*, with small movements of some residues that make the water pore narrower near the ar/R constriction site.

Thus, the mechanism proposed for aquaporin gating by pH in animals depends on slight movements of some residues that reduce the pore size restricting the passage of water. This is quite different from what it is proposed in plant PIPs.

Water transport through plasma membrane can also be regulated by divalent cations (Gerbeau et al. 2002; Alleva et al. 2006). Besides calcium, evidence for direct gating of PIPs by cadmium and manganese has been reported (Verdoucq et al. 2008). Identified residues located at the N-terminal (Glu31 and Asp28) are involved in both divalent cation- and H^+-

mediated gating. The mechanism of gating by cations would be the same as that proposed for pH, where *loop D* rearrangement, together with a few residues located at the N-terminal, occludes the pore (Törnroth-Horsefield et al. 2006, 2010). A second site between *loop D* and the C-terminal has been described in *So*PIP2;1, reflecting a stabilizing role of the C-terminal in the folding of *loop D* (Frick et al. 2013).

In animal AQPs, a decrease of calcium concentration increased AQP0 water permeability, and a residue located in *loop A* (His40) is required for sensitivity to cations (Németh-Cahalan and Hall 2000). These authors suggested that calcium acts through calmodulin on an internal site of the aquaporin. Co-expression of AQP0 with a mutant of calmodulin showed that sensitivity to calcium was lost but sensitivity to pH was maintained, demonstrating that both modulations are separated and occur at opposite sides of the membrane (Németh-Cahalan et al. 2004). In contrast to plants, the sites for Ca^{2+} and pH inhibition are differentiated in animals. Moreover, both regulation mechanisms seem to be completely separate.

Structure-function studies performed with members of some groups of plant AQPs (TIPs, PIPs, y NIPs) showed that some residues exposed to cytosol can be phosphorylated and modulate water transport (Maurel et al. 1995; Johansson et al. 1998, Guenther et al. 2003). Structural models based on purified crystals of AQPs showed that phosphorylation of different serine residues modifies the channel width and closes the pore together with modifications of the C-terminal end of the protein (Törnroth-Horsefield et al. 2006).

Other studies using mass spectrometry allowed identifying multiple sites of phosphorylation in plasma membrane AQPs, some of which could be linked to the aquaporin function in vivo (Prak et al. 2008). In the same way, several works have identified phosphorylation sites in plant AQPs through mass spectrometry and amino acid sequencing (See Santoni 2017).

Among animal AQPs, phosphorylation of AQP1 (Han and Patil 2000), AQP2 (Deen et al. 1994), AQP5 (Yang et al. 2003) and AQP8 (Garcia et al. 2001) has been reported. In all these AQPs, phosphorylation is involved in protein trafficking (Conner et al. 2010; Noda and Sasaki 2005; Kosugi-Tanaka et al. 2006, Garcia et al. 2001). On the other hand, the activation of a protein kinase C significantly decreased the membrane permeability of kidney cells that express AQP4. But in this case, experiments whit GFP-AQP4 revealed that phosphorylation of Ser180 is involved in gating but not in trafficking (Zelenina et al. 2002).

In plants, other co- and post-translational modifications, such as methylation, deamidation, NH_2-terminal acetylation, ubiquitination and *N*-glycosylation, has been described (Casado-Vela et al. 2010; Kim et al. 2013; Santoni et al. 2006; Lee et al. 2009; Vera-Estrella et al. 2004). In animals, deamination in AQP0 and ubiquitination in AQP2 have been described (Wenke et al. 2015).

The effect of membrane-tension changes had been hypothesized as a possible regulatory mechanism for some AQPs from *Saccharomyces cerevisiae*, *Zea mayz*, *Chara corallina*, human and *Vitis vinifera* (Soveral et al. 2008; Wan et al. 2004; Ye et al. 2004; Ozu et al. 2011; Leitão et al. 2014). These and other experimental evidence (Niemietz and Tyerman 1997) suggested that cell volume or pressure could be directly involved in the regulation of AQPs under hyper- and hypo-osmotic conditions. Recently, mechanical gating has been probed as a possible mechanism in hAQP1 (Ozu et al. 2013) and *Vv*TIP2;1 (Leitão et al. 2014), and experimentally probed for *Bv*TIP2;1 (Goldman et al. 2017). This gating mechanism would be cooperative, maybe involving the four monomers of the tetramer (Ozu et al. 2013). In addition, sensitivity differences could exist between PIPs and TIPs (Goldman et al. 2017). Taken together, this evidence suggests that this mechanism would have existed before divergence of PIP-AQP1-like and TIP-AQP8-like AQPs. Additional emerging questions are whether this mechanism was present in ancestral AQPs and if this could have been an early sense, allowing the first cells to face osmotic changes of environmental medium (already proposed for mechanosensitive ion channels; Booth and Blount 2012).

AQP dynamics: Trafficking and localization

Several recent works on plant and animal AQPs have focused on trafficking mechanisms, which have been reviewed in detail (Luu and Maurel 2013; Verdoucq et al. 2014; Conner et al. 2013; Chevalier and Chaumont 2015; Hachez et al. 2013; Kitchen et al. 2015b; Noda et al. 2010).

In plants, the most studied group is that of PIPs, in which trafficking is closely associated with heterotetramerization. Increasing amounts of evidence demonstrate that different types of PIPs form heterotetramers in the membrane and that the interaction between monomers of different types modifies the final destination of one of them, as well as the permeability properties of the other. Examples of this have been described in *Zea mays*, *Fragaria ananassa* and *Beta vulgaris* (Bienert et al. 2012; Yaneff et al. 2014; Jozefkowicz et al. 2016). In these cases, homotetrameres of the PIP1 isoform do not reach the plasma membrane while homotetramers of the PIP2 isoform can. Interestingly, coinjection of both subtype isoforms produces heterotetramers with different stoichiometry in the membrane (Zelazny et al. 2007; Bienert et al. 2012; Yaneff et al. 2014, 2016; Jozefkowicz et al. 2016).

The study of structural features indicates that loop A would not be involved in interactions between PIP1 and PIP2 monomers (Bienert et al. 2012; Jozefkowicz et al. 2013). On the contray, point mutations on the *Zm*PIP1;2 and *Zm*PIP2;5 maize isoforms demonstrated that the single P220A mutation in the transmembrane domain 5 activates the water channel

activity of *Zm*PIP1;2 at the same time that it inactivates *Zm*PIP2;5 within a heterotetramer (Berny et al. 2016). On the other hand, a diacidic motif (DXE) found at the N-terminus of some maize and *Arabidopsis* PIP2s (Zelazny et al. 2009) was shown to act as an endoplasmic reticulum (ER) export signal. By keeping the diacidic property in the sequence of *At*PIP2;1, it was shown that a strict DXE motif instead of a generic diacidic motif is required for proper trafficking (Sorieul et al. 2011). This suggests that oligomerization likely happens at the ER membrane during PIP biogenesis and that ER-sorting would act as a regulatory checkpoint after homotetramer or heterotetramer formation (Verdoucq et al. 2014). Furthermore, two SNARE proteins of *Arabidopsis*, *At*SYP61 and *At*SYP121, were recently shown to form a complex that modulates the *At*PIP2;7 post-Golgi trafficking (Hachez et al. 2014). In maize, the homolog *Zm*SYP121 was shown to physically interact with *Zm*PIP2;5, favoring its targeting to the plasma membrane (Besserer et al. 2012).

Trafficking studies in animal AQPs have a little different focus. Most of the AQPs studied in this subject belong to the water transport subgroup: AQP1, AQP2, AQP4, and AQP5. And their trafficking mechanisms show common features (Noda et al. 2010; Sasaki et al. 2014; Kitchen et al. 2015b). Phosphorylation events of certain serines are induced by osmolality changes and mediate the trafficking of these AQPs to the plasma membrane. In astrocytes and AQP4-transfected HEK293 cells, phosphorylation of S276, via PKA, is associated with calcium influx and calmodulin activation (Kitchen et al. 2015a). In AQP5-transfected HEK293 cells, phosphorylations of S156 and PKA are involved, but a conformational change of the C-terminal end was discarded (Kitchen et al. 2015c). In astrocytes and AQP1-transfected HEK293 cells, the hypotonic stimulus produces increments of the intracellular calcium concentration, calmodulin activation and phosphorylation of AQP1 by PKC (but not PKA) at T157 and T239 simultaneously (Conner et al. 2012). Moreover, this type of trafficking mechanism seems to be mediated by microtubules but not the actin network, as was previously reported for AQP1-transfected HEK293 cells (Conner et al. 2010) and AQP5 MDCK cells (Karabasil et al. 2009). Another recent work shows that activation of muscarinic acethylcholine receptors (mAChR) induces the reversible translocation of AQP5 from the cytoplasm to the nucleus and the apical and basolateral membranes of parotid acinar cells (Cho et al. 2015).

Regarding structural features, loss of tetramerization does not affect the single channel permeability of AQP1, AQP4 and the aquaglyceroporin AQP3. These observations support the hypothesis that loop D-mediated inter-monomer interactions may control the formation of the signature quaternary structure of the family, but seems not to be necessary for trafficking to the plasma membrane (Kitchen et al. 2016).

AQP4 exists in more than one isoform in mammals: M1-AQP4, M23-AQP4 and Mz-AQP4. Recent evidence shows that M1 and M23 have distinct aggregation properties that produce differences in their cellular localization and functions (Smith et al. 2014). While M1-homotetramers can diffuse along the plasma membrane and incorporate to lamellipodia regions in migrating astrocytes, M23-arrays are unable to diffuse rapidly enough to enter lamellipodia, being excluded from the leading edge of migrating astrocytes, and at the same time stabilizing the binding to adhesion complexes in vivo. Both the differencial diffusion capacity and function of M1 and M23 isoforms are associated with the capacity of M23 to form orthogonal arrays (OAPs) (Jin et al. 2011), which can be constituted by more than 100 tetramers. Like the cases of PIPs from plants, M1 and M23 can form heterotetramers, which exhibit a variable capacity to diffuse and bind to adhesion complexes (Smith et al. 2014).

Trafficking research in AQPs show differences between plants and animals. While in plants the focus has been put on structural determinants, in animals it has been put on signal transduction and the role of the cytoskeleton. To our knowledge, studies on signal transduction-associated trafficking constitutes an open field for both research areas. In particular, expression of different plant PIP subgrups in the same membrane justifies the study of heterotetramerization. This type of study in animals is performed with AQP4 isoforms. Studies on both PIPs and AQP4 indicate that intra- and extra-cellular loops (A and D, respectively) would not be involved in tetramer stabilization and trafficking. Future works will elucidate important details of these two different mechanisms observed in plant PIPs and AQP4 from animals.

What are AQPs for

Since the first water channel report (Preston et al. 1992), the discovery of AQPs had a significant impact on the study of water and solute transport. However, the view of AQPs as specific water channels has been changing due to large amount of evidence showing that some AQPs carry small solutes or gases, and others are expressed in tissues where water flow dynamics appear to be less relevant (Bienert et al. 2008; Kitchen et al. 2015b; Pérez Di Giorgio et al. 2016a, 2016b).

As was reviewed by Hill et al. (2004), the first studies with knock-out mice performed by Alan Verkman's laboratory revealed negligible effects upon AQPs deletion; for example: AQP5 in Type-1 pneumatocytes (Ma et al. 2000), AQP1 in the epithelium secreting bile (Mennone et al. 2002), AQP1, 3, 4 or 5 on the rates of tear fluid production (Moore et al. 2000), AQP1 on the rates of fluid equilibration in endothelial cells (Verkman 2002), AQP4 on the stimulated secretion of parietal cells from gastric glands (Wang et al. 2000), and AQP1 on water movements across the corneal epithelium (Kuang et al. 2004). This evidence suggested that AQPs could have a regulating role in transepithelial water transport rather than just

being the water pathway (Fischbarg 2010). In line with this, the fact that transepithelial water transport can occur against the osmotic gradient generated doubts about the role of AQPs (Zeuthen 2010), since AQPs are just channels where water translocation is driven by passive forces and occurs by a stochastic mechanism (Zeuthen et al. 2013). Furthermore, it has recently been demonstrated that significant water fluxes are maintained by cotransport with sodium and glucose, through the sodium glucose cotransporter SGLT1 of the brush border membrane of the mouse small intestine, where orthodox AQPs are absent but the SGLT1 is abundant (Zeuthen et al. 2016). This recent report adds to the water-solute cotransport evidence extensively described before (Zeuthen 2010).

The body of evidence obtained by animal physiologists led to the hypothesis that AQPs would be osmosensors (Hill et al. 2004), acting as both sensors and signal transducers (Hill and Shachar-Hill 2006). According to this hypothesis, each monomer could have two reversible states (open and closed) that can be reached by conformational changes induced by osmotic pressure differences. In addition, the conformational changes in a tetramer would occur by a cooperative mechanism involving the four monomers (Hill et al. 2004; Hill and Shachar-Hill 2015).

The role of an osmosensor was satisfactorily tested by mathematical modeling and simulation for isotonic fluid transport across animal epithelia (Hill and Shachar-Hill 2006). In animal epithelia, the AQP would function like a thermostat by sensing the transepithelial gradient and regulating-via a cell signaling system-the magnitude of the paracellular flow to approach an osmotic set point (Hill and Shachar-Hill 2006). In addition, a model combining mechanical parameters with osmotic dynamics developed for growing pollen tubes suggests the existence of a molecule acting as an osmosensor (Hill et al. 2012). The following experimental evidence suggested that AQPs could be an osmosensor located in the plasma membrane of growing pollen tubes of *Lilium longiflorum* (Shachar-Hill et al. 2013). In *Arabidosis thaliana*, the most expressed AQPs in pollen are non-orthodox and seem not to be involved in water transport (Pérez Di Giorgio et al. 2016a, 2016b). So far, their role is more complex and needs to be elucidated.

As we have seen in previous sections, increasing evidence is emerging on regulatory mechanisms in plant and animal AQPs supporting the assumptions of the osmosensor hypothesis. For example, interactions between monomers can modify the transport properties of the tetramer (Bienert et al. 2012; Yaneff et al. 2014; Jozefkowicz et al. 2016), which opens the possibility for cooperative interaction between subunits. Moreover, cooperative regulation mechanisms have been both predicted for closure of hAQP1 mediated by membrane tension increments (Ozu et al. 2013) and proposed for closure of the cytoplasmic gate of AQP0 mediated by the binding of calmodulin (CaM) to the C-terminal domain (Reichow et al. 2013).

The case of AQP0 is interesting for several reasons. Each monomer forms a channel with very low water permeability (comparable to lipid bilayer) and can be gated by acidification (Németh-Cahalan and Hall 2000). AQP0 also forms gap junctions, and monomers in these arrays exhibit a closed conformation that do not transport water because two tyrosines (T23 and T149) occlude the water path (Gonen et al. 2004). Management of forces between the protein and the surrounding lipids could also be part of a signaling mechanism. A very recent work has shown that the hydrophobic mismatch between the protein and the lipid bilayer is compensated by stretching of the annular layer of lipids around the surface of AQP0 (Briones et al. 2017). In addition, this compensation induces specific fluid- and gel-phase prone areas, allowing the speculation that these areas might guide the AQP0 lipid sorting interactions with other membrane components (Briones et al. 2017).

Evidence from parasitic and free-living microorganisms highlights the role of AQPs in osmoregulation (Von Bülow and Beitz 2015). For example, the recently cloned aquaglyceroporin *Sj*AQP from *Schistosoma japonicum* plays a fundamental role in osmoregulation, especially during cercariae transformation, when this human parasite faces extreme osmolality changes because of its living cycle stage in fresh water (Huang et al. 2016). In other parasitic organisms, AQPs are located in the membranes of the complex of flagelo, so it has been proposed that they are involved in the mechanisms of osmotaxis, as well as in osmoregulation (Von Bülow and Beitz 2015).

Perspectives

The amount of accumulated information provides detailed descriptions on some features of AQPs. However, gaps still exist at the molecular level when addressing their function in both plant and animal subfamilies. More crystallographic studies are needed for a better understanding of plant APQs. These would provide subastantial information to comprehend distinctive isoforms as metalloporins. In addition, structural details are critical to test hypotheses related to conformational changes, and only by combining this information with experimental approaches can unsolved issues be properly unravelled. Open questions include whether AQPs are osmosensors, molecular features of the mechanical gating, and gas transport capacity.

Finally, deeper knowledge on molecular features, in combination with novel functional information, will provide important data to obtain more precise information regarding their complex diversity and evolutionary constraints.

Summary

Since its discovery, research interest on AQPs has experienced an exponential increase. Plant and animal AQPs are also probably the most studied channels due to their impact in terms of economical interests: growth, development and fitness when addressing the plant kingdom, and mainly human health and disease in the case of animal AQPs. However, diversity and phylogenetic approaches have broadened our perspective as a whole. We have summarized a crosstalk of the most notable features of plant and animal AQPs and compared the known information provided by phylogenetic, structural and functional studies. This revision reflects differences in research approaches as well as regulatory mechanisms. Current hypotheses about its cellular role as possible osmosensors have also been revisited.

Compliance with ethical standards

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