

Aquaporins: Navigating the channels of cellular hydration

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Abstract

Aquaporin's are water channel proteins found in all plasma membrane of various cells in all forms of life from bacteria to mammals. Around 17 mammalian aquaporin's have been identified till date, which are classified into 3 subcategories based on their permeability. In normal physiology, AQPs serve as essential modulators of fluid transport and homeostasis in multiple organs and tissues. Altered expression of aquaporin's is linked to numerous pathologies including fluid dysregulation, tumor metastasis and traumatic injury. Although some potential AQP modulators have been identified, challenges associated with the development of better modulators, include the suitability of the assay methods used to identify modulators and the drug ability of the target. The present review focus on aquaporin types and their altered conditions along with role of aquaporin's in cancer and other diseases.

Keywords: Water channel proteins; Aquaporin's; Traumatic injury; Cancer

1. Introduction

Aquaporin's (AQPs) are the major intrinsic protein (MIP) family, found in all forms of life from bacteria to mammals. These are a family of water channel proteins, which are found in the plasma cell membranes of various cells. It contains 6 membrane spanning, α -helical domains characterized by cytoplasmically aligned (-NH₂) terminal amino acid and (-COOH) terminal carboxyl groups. AQPs polypeptide structure is composed of a single chain containing around 270 amino acids. The six membrane regions are integrated by two intracellular and three extracellular loops. Two highly conserved sequences, comprising a short helix, are situated on opposing sides of the AQPs monomers and known as the NPA motif, composed of an Asparagine- Proline- Alanine sequence (Fig. 1A). The NPA motif forms the water channel by creating a specific "hourglass" shape, rendering the channel narrower in its middle, and wider at its ends. AQPs are assembled as homo-tetramers in cellular membranes (Fig.1B). with each AQP monomer behaving as a narrower water pore that weighs around 28 to 30 k Da and has a diameter of 2.8 Å. AQPs exhibit different protein sequences and sizes of the channels, thus allow the passage of various particle sizes and solvents (Parameswari Kasaet al.,2019) [1].

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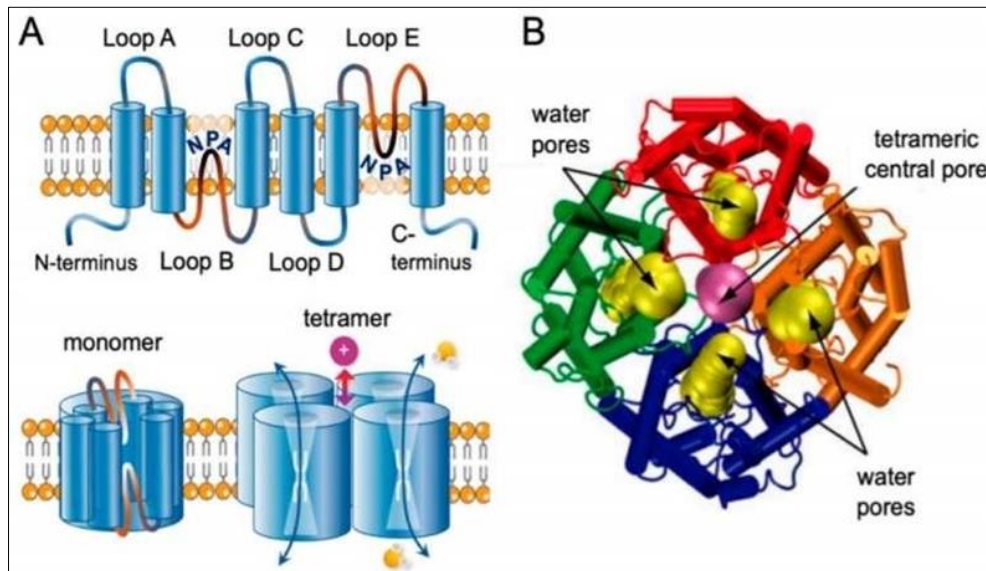


Figure 1 Structure of aquaporin

2. Aquaporin classification and distribution

Around 17 mammalian aquaporin's have been identified to date and AQP gene families are divided into 3 subgroups.

Aquaporin's that transport water alone are AQP0, AQP1, AQP2, AQP4, AQP5, AQP6 and AQP8.

Aquaglyceroporins, which transport glycerol, water, organic compounds, alternative little solutes, including AQP3, AQP7, AQP9 and AQP10.

Super aquaporin's or sub cellular- AQPs belonging to a novel subfamily expressed in the cytoplasm AQP11 and AQP12.

3. Functional mechanism and physiological role of aquaporins

Table 1 Classification and functions of various types of AQPs

Type of Aquaporin	PDB ID	Function/Role	Location	Reference	Altered conditions
AQP0	2B6P	*Fluid balance with the lens *Osmotic protection	Eye: Lens fibrecells Red blood cells	Sindhu SKumari et al.,2014 [2]	severe lenscataract
AQP1	1FQY 1IH5	*Concentration of urine *production of aqueous humor *production of cerebrospinal fluid *Alveolar hydration state	Kidney: Proximal tubule Eye: Ciliary epithelium Brain: Choroid plexus Lung: Alveolar epithelial cells	Daniel Seeliger et al., 2012 [3]	oedema in the brain, lung and heart, glaucoma, cancer, renal dysfunction.
AQP2	4NEF	*Mediate antidiuretic hormone Activity	Kidney: Collecting ducts	Bo Qiu, et al., 2014 [4]	Traumatic brain injury (TBI),
AQP3	-	*Reabsorption of water into blood, skin hydration and	Kidney: collecting ducts Epidermal keratinocytes Trachea:	Ana Paula Martins, et al., 2012 [5]	skin tumorigenesis melanoma

		Epidermal proliferation. *Secretion of water into Trachea	epithelial cells		
AQP4	3GD8 2ZZ9	*Reabsorption of water *Osmosensing function *Water permeability *Bronchial fluid secretion *CSF fluid balance	Kidney: collecting ducts Brain: hypothalamus Brain: astrocytes Lungs: bronchial epithelium Brain: ependymal cells	Marios Papadopoulos et al., 2013 [6]	C Brain oedema, cancers Neuromyelitis optica
AQP5	3D9S	*Production of saliva *production of tears	Salivary gland Lacrimal glands	Takata, K et al., 2004 [7]	Sjogren's syndrome
AQP6	1S5E	*Very low water permeability	Kidney	Mohammed Abir-Awan et al., 2019 [8]	Unknown
AQP7	6QZI 6KXW	*Transport glycerol out of Adipocytes	Fat cells	Agre, P et al., 2003 [9]	Adipocytes hypertrophy
AQP8	_	*Colonic water adsorption *hepatocyte-bile formation	Colon, pancreas, liver, Other	Nilofarkhanal., 2015 [10]	Unknown
AQP9	_	*Transports energy substrates	Brain, leukocytes	Ishibashi, K et al., 1998 [11]	Osteoporosis
AQP10	6F7H	*Permeate neutral solutes such as glycerol and urea	Epithelial organs	Mohammed Abir-Awan et al., 2019 [8]	Unknown
AQP11	_	*Physiological role not clear	Brain, kidney, Heart, endoplasmic reticulum	Yakata, K et al., 2011 [12]	Polycystic kidneys
AQP12	_	*Secretion of digestive enzyme and fluids	Pancreatic acinar cells	Nilofarkhanal., 2015 [10]	Unknown

4. Aquaporin's in pathophysiology

4.1. Role of AQP's in cancer

In normal physiology, AQP's serve as essential modulators of fluid transport and homeostasis in multiple organs and tissues. In pathological cancer conditions, aquaporin's are implicated in the growth, migration, invasion, and angiogenesis, contributing to cancer progression and the life-threatening process of metastasis and expressed in more than twenty types of cancer cells (Fig 2A-D). In cerebral ischemia, brain tumors, bacterial meningitis and other conditions AQP4 becomes up regulated in astrocytes and correlated with more prominent brain edema.

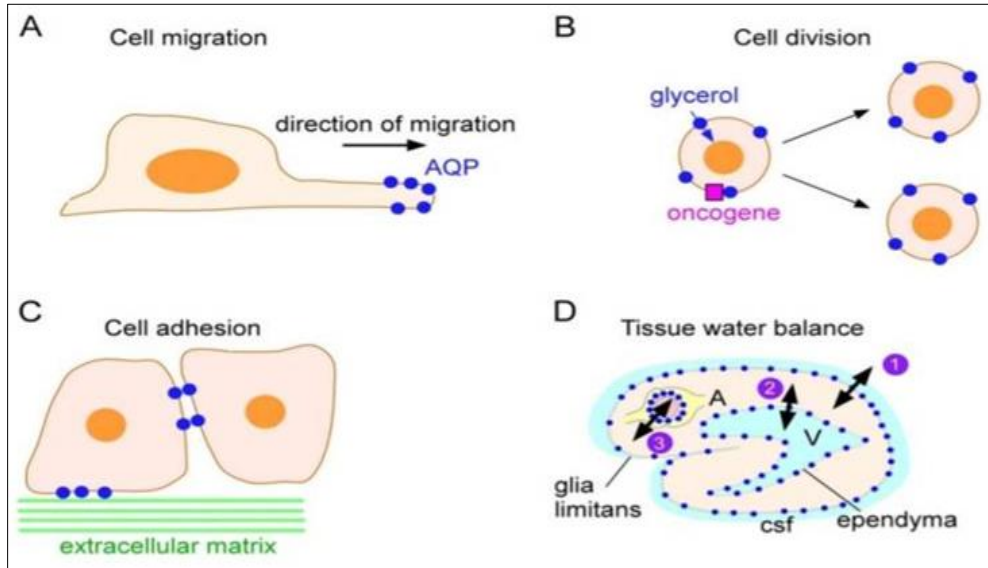


Figure 2 Roles of AQP in cancer

Table 2 Role of AQP in various cancers

Type of cancer	AQPs Involved	Role	References
BREASTCANCER	AQP1AQP3 AQP5	*Cancer is induced by stimulating endothelial cells by AQP1 through oestrogen receptors. *AQP3 represented a vital and crucial factor in the cancer cell migration elicited by fibroblast growth factor-2 (FGF-2).	Yin et al., 2008[13] Trigueros-Motos et al.,2012[15] Parameswari Kasa et al.,2019[1]
OVARIAN CANCER	AQP5	*AQP5 is proposed to modulate the proliferation as well as migration of ovarian tumour cells. *AQP7 was mainly localized in plasma membrane of ovarian cells, were as in borderline and malignant tumour cells, it was selectively stained in the nuclear membrane. *AQP9 n was detected at a low level in normal ovarian epithelium, was mainly located in the basolateral membranes of benign and borderline tumour cells, and was distributed throughout the plasma membranes of malignant cells	Yang et al.,2011b[14] Prameswari Kasa et al., 2019 [1]
CERVICAL CANCER	AQP1 AQP3 AQP5	*exact role is undefined. Over expression of AQP's in this cancer may increase tumour cell permeability and modify the shape and volume of these cells and could promote Metastasis in cervical cancer.	Parameswari Kasa et al., 2019 [1]
ENDOMETRIAL OR UTERIAN CANCER	AQP2AQP5	*AQP2 expression levels low in early stages of disease. *AQP5 expression levels were high during the late stage	Jiang Wang et al., 2015[17] Parameswari Kasa et al., 2019 [1]
COLORECTAL CANCER	AQP1AQP3 AQP5AQP9	*AQP1 increased the plasma membrane water permeability and migration ability. *AQP5 induce tumour proliferation by the activation of RAS-MAPK pathway, Cyclin D1/CDK4 complexes and then	Kang SK et al.,2008 [16]

		phosphorylated retinoblastoma protein in nucleus and caused transcription of genes related with cell proliferation.	
CHOLANGIO CARCINOMA	AQP1	*AQP1 increased the plasma membrane water permeability and migration ability.	Jiang Wang et al.,2015. [17]
LIVER CANCER	AQP3 AQP5 AQP8,9	*Co-expression of AQP3 and 5 in Hepatocellular carcinoma has a significant association with serum AFP, tumour stage and grade.	Guo et al.,2013[18] Jian Wang et al.,2015[17]
ASTROCYTOMA	AQP1AQP4 AQP8AQP9	*AQP1 can combine with carbonic anhydrases to shut H ⁺ from intercellular to extracellular compartment. The acid extracellular compartment promoted glioma cells to release Cathepsin B, a proteolytic enzyme involved in tumour. * AQP4 was involved in the control of glioblastoma cell migration and invasion through cytoskeleton rearrangement and cell adhesion regulation	Hayashi et al.,2007[19]
LUNG CANCER	AQP1AQP3 AQP4AQP5	*AQP1 regulate lung cancer cell invasion and migration in lung adenocarcinoma (ADC) and bronchoalveolar carcinoma (BAC). *AQP3 involved in initiative of angiogenesis in lung cancer through HIF-2 α -VEGF pathway, cancer cell invasion partly by the AKT-MMPS pathway, cellular glycerol uptake or mitochondrial ATP formation. AQP3 over expressed in non-small cell carcinoma (NSCLC). *AQP5 facilitates lung cancer cell growth and invasion through the activation of the EGFR /ERK/P ³⁸ MAPK pathway. Phosphorylation at serine 156 in PKA consensus site in AQP5 was demonstrated as a key role in tumour proliferation and invasion by ser156 mutants in lung cancer cells.	Xie et al.,2012 [20]
ORAL CANCER	AQP3AQP5	*Higher levels of AQP3 in human oesophageal and lingual cancer tissues.	Mamatha G. S. Reddy et al.,2017 [21]
MENINGIOMAS	AQP4	*AQP4 is involved in peritumoral brain edema formation in meningiomas and also related to the expression of vascular endothelial growth factor (VEGF)	P. Wang et al.,2011 [22]
ESOPHAGEAL CANCER	AQP3 AQP5	*High expression of AQP3 and AQP5 were both correlated with advanced invasion depth, aggressive lymph node status and positive distant metastasis in oesophageal squamous cell carcinoma.	Sulin Liue et al.,2013 [23]
THYROID CANCER	AQP3 AQP4	*AQP3, AQP4 may reflect the biological nature of normal, hyperplastic, neoplastic thyroid cells and additionally have some value for diagnosing thyroid tumors.	Dongfeng Niu et al., 2012 [24]

4.2. Role of AQPs in other diseases

AQP4 is involved in the pathologies of edema, epilepsy, schizophrenia, and possibly abnormal cytoskeletal morphology. Modulators of this protein might be useful as therapeutic agents for any of these diseases.

Table 3 Role of Aquaporin's in diseases other than cancer

Disease	Aquaporin involved	Expression	Role	Reference
Pseudophakic			*Increased AQP3 is associated with the process of scarring or tissue remodelling but not with chronic edema.	Grayson,1983 [25]M.Cristian Kenney et al.,2004[26]
Bullous				
keratopathy	AQP1	Low	*AQP1 decrease leads to delayed recovery of corneal transparency and increased thickness to 600-850µm from 550µm after treatment	
(Corneal edema after Cataract surgery)	AQP3	High		
	AQP4	High		

4.3. Future Directions and Challenges of Aquaporin's

Future directions in aquaporin research involve elucidating their intricate roles in complex biological systems, expanding the scope of investigation beyond water transport, and advancing therapeutic targeting for various disorders. Engineering aquaporin's for biotechnological applications, enhancing imaging techniques, and exploring their function in unconventional environments are pivotal. Addressing knowledge gaps, technical challenges, and understanding aquaporin involvement in disease progression are critical for clinical translation. Collaborative, interdisciplinary approaches and consideration of ethical and societal implications will be paramount in guiding future aquaporin research toward innovative solutions and responsible implementation.

5. Conclusion

In conclusion, aquaporin's stand as remarkable molecular channels crucial for maintaining cellular homeostasis and physiological balance through their unparalleled water transport capabilities. Their diverse roles extend beyond mere hydration, influencing numerous biological processes and pathways across various organisms. While significant strides have been made in understanding their structure, function, and regulation, many avenues remain unexplored, presenting opportunities for further investigation and technological innovation. Leveraging this knowledge holds promise for advancing biomedical research, facilitating the development of novel therapeutic interventions, and addressing pressing global challenges related to water management, health, and environmental sustainability. As we continue to delve deeper into the intricacies of aquaporin biology, collaborative efforts across disciplines will be essential in realizing their full potential and harnessing their benefits for the betterment of humanity.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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