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Review

Key roles of aquaporins in tumor biology☆

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ABSTRACT

Aquaporins are protein channels that facilitate the flow of water across plasma cell membranes in response to osmotic gradients. This review summarizes the evidence that aquaporins play key roles in tumor biology including tumor-associated edema, tumor cell migration, tumor proliferation and tumor angiogenesis. Aquaporin inhibitors may thus be a novel class of anti-tumor agents. However, attempts to produce small molecule aquaporin inhibitors have been largely unsuccessful. Recently, monoclonal human IgG antibodies against extracellular aquaporin-4 domains have become available and could be engineered to kill aquaporin-4 overexpressing cells in the malignant brain tumor glioblastoma. We conclude this review by discussing future directions in aquaporin tumor research. This article is part of a Special Issue entitled: Membrane channels and transporters in cancers.

Contents

1. Introduction

Aquaporins (AQPs) are a family of water channel proteins, which are found in the plasma cell membranes of various cells [1]. There are 14 AQPs in mammals, at least eight of which have been shown to transport water. AQP3, AQP7 and AQP9 also transport glycerol and are termed aquaglyceroporins [2]. Though some AQPs transport gases and ions in artificial systems, gas and ion transport are probably not relevant under physiological conditions [3,4]. To date, the key function of AQPs remains water transport.

AQPs assemble in cell membranes as homo-tetramers [5]. Each monomer is about 30 kDa and has its own water pore. In general, AQPs increase the water permeability of the plasma cell membrane 5–20 fold. AQP0 and AQP4 have unique properties; their tetramers assemble into higher order structures that form orthogonal arrays of particles. AQP4 exists as two isoforms, termed M1-AQP4 and M23-AQP4; M1 is the full-length protein with the sequence starting at methionine 1, whereas M23 lacks the first 22 amino acid sequence and starts at methionine 23. M23-AQP4 assembles in large orthogonal arrays, but

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M1-AQP4 exists as individual tetramers. M1 can hetero-tetramerize with M23 to form orthogonal arrays, the size of which increases with increasing M23:M1 ratio [6]. Though *in vitro* studies show that AQPs freely diffuse in the plasma cell membrane, *in vivo* AQPs may be anchored to parts of the plasma cell membrane [7,8]. For example, in the central nervous system AQP4 is concentrated in perivascular astrocyte endfeet [9]. Intracellular membrane proteins such as alpha syntrophin [10] and extracellular matrix proteins such as agrin may form part of the AQP4 anchoring mechanism [11], but further research is required to define the molecular anchor.

In this review we discuss the functions of AQPs in tumor cells and how elucidating these functions has identified novel therapeutic targets in cancer biology.

2. AQP expression

2.1. Normal tissue

AQPs are widely distributed in human tissues and are generally preserved in mammals including rodents and humans [1]. In some organs, such as the kidney, several AQPs are expressed and play a major role in normal function [1,12]. For example, in response to antidiuretic hormone (vasopressin), AQP2 (which is found in intracellular vesicles) becomes expressed in the apical plasma cell membrane of collecting duct epithelial cells and increases the reabsorption of urine by the kidney. Humans with AQP2 mutations have congenital nephrogenic non-X-linked diabetes insipidus thus confirming the key role of AQP2 in water reabsorption by the kidney. In other organs, such as the brain, AQPs do not appear to play a major role in normal function, but become important in pathological conditions [1]. In mice that lack AQP4, which is normally expressed in perivascular astrocyte foot processes, the brain is phenotypically normal at baseline. In cerebral ischemia, brain tumors, bacterial meningitis and other conditions AQP4 becomes upregulated in astrocytes and facilitates brain edema formation and elimination. Recently, however, AQP4 was proposed to play a role in the clearance of solutes from the interstitial fluid of normal brain through a paravascular pathway termed the glymphatic system [13]. In some locations, such as the stomach, AQPs do not seem to be important for normal functions or in pathological conditions. Although AQP4 is expressed in the basolateral plasma cell membrane of gastric parietal cells, which are responsible for secreting hydrochloric acid, AQP4 deletion in mice does not affect gastric acid secretion. Aquaglyceroporins are involved in cellular metabolism [1,2]. AQP3 is expressed in the stratum corneum layer of the skin. AQP3 deletion in mice impairs skin hydration, elasticity, barrier recovery and wound healing due to lack of glycerol in the cells. These deficiencies in AQP3 null mice can be reversed by glycerol administration. AQP7, expressed in adipocytes, controls glycerol movement into and out of the cell [1]. AQP7 deletion in mice is associated with adipocyte hypertrophy, likely due to impaired glycerol exit from the adipocytes.

Several studies report regulation of AQP expression [1]. Though AQPs become upregulated or downregulated in response to different pathologies, it is impossible to determine from these descriptive studies the roles of AQP in these pathological conditions.

2.2. Tumors

Several authors have suggested a role for AQPs in cancer [14–20]. Table 1 summarizes AQP expression in different tumors. In general, tumor cells overexpress AQPs including AQPs that are normally found in their cell of origin as well as AQPs not present in the originating cell. In tumor cells, AQPs are expressed in the plasma cell membrane as well as the cytoplasm. There is often a strong correlation between the level of AQP expression and tumor grade. An example is diffuse astrocytoma, which is an infiltrating brain tumor that arises from astrocytes. Diffuse astrocytomas are histologically classified as grades II, III or IV, with the most malignant grade IV also termed glioblastoma. Astrocytes normally express AQP4 in their perivascular foot processes. Normal astrocytes express AQP4, but little or no AQP1 and AQP9. We initially reported, using immunohistochemistry, strong AQP4 [21] and AQP1 [22] expression in diffuse astrocytomas with the level of expression positively correlating with tumor grade. There is now substantial evidence from different investigators that AQP1, AQP4 and AQP9 are strongly expressed in human astrocytomas [21–33]. Another example of human tumors that strongly express AQPs is epithelial ovarian tumors. By immunoblot there is substantially higher AQP7 and AQP9 protein expression in malignant and borderline tumors compared with benign tumors and normal ovarian tissue with AQP9 expression level positively correlating with tumor grade [34]. Though some tumor types show reduced AQP expression compared with their cell of origin, this is only seen for individual AQPs; when considering several AQPs, there appears to be increased overall AQP expression in all tumors listed in Table 1. In some cases there is correlation between increased AQP expression in the tumor and patient prognosis. Potential caveats of these studies include reporting bias for positive studies, failure to distinguish tumor cells from other cell types found within the tumor (e.g. reactive astrocytes, fibroblasts or leukocytes) and the poor specificity of some antibodies used for immunostaining e.g. anti-AQP9. Notwithstanding these caveats, the large number of tumor AQP expression studies raises the intriguing hypothesis that AQPs contribute to carcinogenesis in a range of tumor types.

Table 1
AQP expression in human tumors.

Tumor type	Aquaporins	AQP level	References
Astrocytoma	AQP1, 4, ?8, 9	high	[21–32]
Breast cancer	AQP5	high	[77–79]
	AQP1	high	[79]
	AQP4	low	[79]
Cholangiocarcinoma	AQP1	low	[80]
	AQP1	high	[81]
Colorectal cancer	AQP1, 3, 5	high	[60,82–85]
	AQP8	low	[85,86]
Cervical cancer	AQP1, 3	high	[87]
	AQP5	high	[88]
Choroid plexus tumor	AQP1	high	[89]
Hemangioblastoma	AQP1	high	[90]
Laryngeal cancer	AQP1	high	[91]
Leukaemia	AQP5	high (CML)	[92]
Liver cancer	AQP3, 5	high	[93]
	AQP8, 9	low	[94]
Lung cancer	AQP1, 3, 5	high	[64,95,96]
	AQP1, 4	high	[97]
Meningioma	AQP4	high	[98,99]
Nasopharyngeal cancer	AQP1	high	[100]
Oesophageal cancer	AQP3, 5	high	[101,102]
Ovarian cancer	AQP1, 5, 9	high	[103,104]
Renal	AQP3	high	[105]
Skin, SCC	AQP3	high	[106]
Stomach cancer	AQP5	high	[107]
	AQP4	low	[108]
	AQP3	high	[109]
Thyroid cancer	AQP4	high (papillary)	[110]
	AQP3, 4	low (undifferentiated)	[110]
	AQP7	high	[111]
Tongue cancer	AQP3, 5	high (SCC)	[112]
Urinary bladder	AQP3	low	[113,114]

CML, chronic myelogenous leujaemia; SCC, squamous cell carcinoma; AQP level indicates level of AQP expression in the tumor compared with the normal tissue.

3. AQP functions

In addition to the well-established role of AQPs in maintaining tissue water balance, other roles of AQPs include facilitating cell migration, cell proliferation and cell adhesion (Fig. 1). Under each section below, we first discuss the role of AQPs in normal cells, followed by their role in tumor cells. The functional data discussed here are largely derived

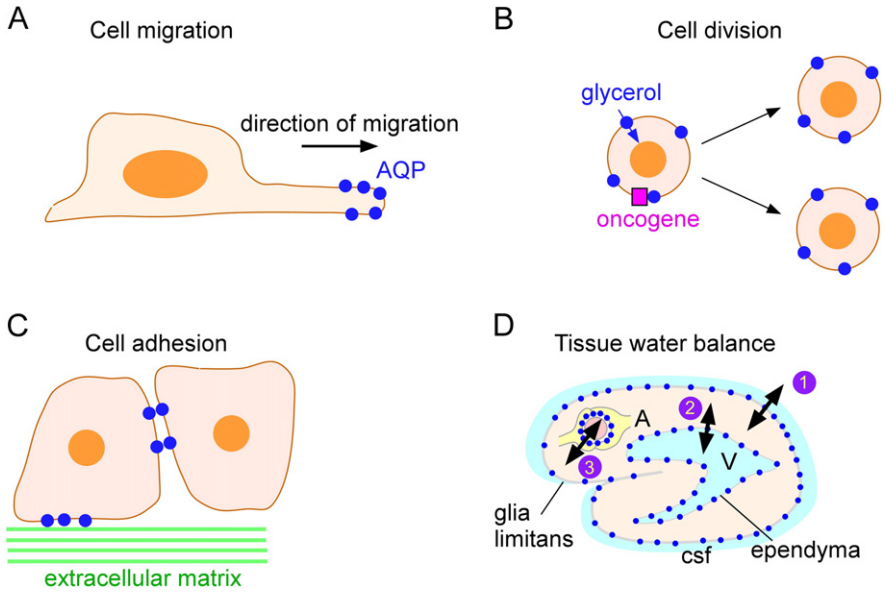

Fig. 1. Roles of AQPs in cancer. A. Cell migration. AQP polarizes to the leading end of the cell and facilitates formation of the lamellipodium. B. Cell proliferation. Aquaglyceroporin facilitates glycerol entry into the cell, which is essential for biosynthesis. AQP may directly interact with oncogenes. C. Cell adhesion. AQP0–AQP0 or AQP4–AQP4 binding increases cell–cell adhesion. AQP may increase adhesion of the cell to the extracellular matrix. D. Tissue water balance. Example of brain where AQP4 controls water flow between the brain and major fluid compartments: 1) glia limitans (brain–subarachnoid cerebrospinal fluid), 2) ependyma (brain–ventricular cerebrospinal fluid), 3) astrocyte foot processes (brain–blood). A, astrocyte; csf, cerebrospinal fluid; V, ventricle.

from experiments comparing wildtype vs. AQP null mice and should be interpreted with caution because of compensatory effects that may have developed in these mice as a result of longstanding AQP deletion. To minimize compensatory effects, some authors have created central nervous system specific AQP4 deletion in mice [35]. Ideally, conditionally inducible AQP knockout mice are required to eliminate the confounding effect of long-term adaptation to AQP deletion. Such mice are not currently available, but may provide more definitive information about AQP4 function. Another way to elucidate AQP function is to inhibit AQPs; this is not currently possible because of a lack of non-toxic, specific AQP inhibitors [36].

3.1. Tissue water balance

There is now substantial evidence that AQPs play a major role in maintaining water balance in several tissues. One of the first organs to be investigated following the discovery of AQPs was the kidney, in which multiple AQPs (AQP1, AQP2, AQP3 and AQP4) are responsible for water absorption and elimination [12]. Key roles for AQPs have also been defined in the central nervous system, with AQP4 playing a central role in edema fluid accumulation and elimination, and AQP1 in cerebrospinal fluid production [37]. The mechanisms of AQP4 involvement in brain edema are discussed in detail elsewhere [37]. In the salivary gland, AQP5 is found in the apical plasma cell membrane of acinar epithelial cells and plays a role in osmotic water transport across the cells into the sweat duct [38]. In some tissues, loss of AQP expression in mice does not influence function, e.g. deletion of AQP1, AQP3, AQP4, and AQP5 in mouse lacrimal glands does not affect tear secretion, probably due to the low level of transepithelial water transport rates in these tissues [39]. In general, AQPs facilitate water flow across cells in response to osmotic gradients produced by salt transport.

A major role for aquaporins in tumor edema was first postulated by Saadoun et al. who showed that astrocytomas express high levels of AQP1 [22] and AQP4 [21] with the level of AQP expression positively correlating with the presence of brain tumor edema on computed tomography. The most malignant astrocytomas also express AQP9 [23,28,29]. AQP4 is expressed by astrocytoma cells, but also by reactive astrocytes in and around the tumor [21]. Subsequent experiments showed that AQP4 deletion in mice increases edema around B16F10 brain melanoma [40]. In this mouse model there is prominent reactive gliosis around the melanoma. These findings suggest that the increased AQP4 expression by reactive astrocytes in and around the tumor facilitate elimination of brain edema fluid. Whether AQP4 expressed in tumor cells also plays a role in brain edema remains unknown and could be defined by implanting AQP4-expressing and non-expressing tumor cells in mice and quantifying the water content of the tumor and brain. Because the brain is surrounded by the non-distensible skull, brain tumor edema is a major clinical problem that causes increased intracranial pressure, brain ischemia, herniation and, ultimately, brain death. To date, a role for AQPs in tissue edema associated with tumors outside the central nervous system has not been investigated.

3.2. Cell migration

An unanticipated role for AQPs in facilitating cell migration was first suggested by Loitto et al. who studied AQP9 in neutrophils [41]. Subsequently, Saadoun et al. showed that several AQPs facilitate cell migration in different cell types including AQP1 in aortic endothelial cells [42] and AQP4 in astrocytes [43]. The overall conclusion from several studies *in vitro* and *in vivo* is that AQP expression enhances cell migration towards a chemotactic stimulus [41–47]. The exact mechanism remains unclear, but may involve targeted water entry into the leading edge of a migrating cell, which enhances formation of the lamellipodium (a flattened protrusion at the leading end of a migrating cell, which is essential for cell motility) [48]. The idea that AQPs facilitate formation of the lamellipodium is consistent with the polarization of AQPs to the leading end of migrating cells. It has been suggested that AQPs also facilitate the rapid changes in cell shape that take place as a migrating cell squeezes through the tortuous extracellular space [14]. Such changes in cell volume are likely to require rapid flow of water into and out of the cell. Some authors have recently suggested that cells may utilize directed water permeation mediated by AQPs to create a net inflow of water and ions at the cell leading edge and a net outflow of water and ions at the trailing edge leading to net cell displacement [49]. This mechanism, termed the osmotic engine model, may allow cell migration through confined micro-spaces without the need for actin depolymerization–polymerization or myosin II-mediated contractility. It is important to note that lack of AQPs does not entirely inhibit cell migration, but renders

migration towards a chemotactic stimulus less efficient. This may explain why AQP-null mice develop normally *in utero* even though cell migration is an important component of embryogenesis.

Tumor cell migration is a fundamental property of different cancers and contributes to tumor cell infiltration into surrounding tissue as well as the metastatic spread. B16F10 melanoma cells and 4T1 breast cancer cells transfected to express AQP1 were more likely to extravasate after tail vein injection in mice [50]. The resulting lung tumors were more diffusely infiltrating into the surrounding alveolar tissue compared with tumor cells lacking AQP1. AQP1 is important for endothelial cell migration that takes place during angiogenesis, which is vital to permit solid tumors to grow rapidly. Melanoma tumors produced by subcutaneous implantation of B16F10 cells grow faster in wildtype than AQP1 null mice [42]. Histological examination of these tumors revealed that AQP1 deficiency is associated with impaired tumor angiogenesis. Tumor vascular endothelial cells express AQP1, which plays a major role in tumor angiogenesis by facilitating endothelial cell migration. These findings are supported by several follow-on studies. One study found reduced proliferation of implanted melanoma cells in mice treated with AQP1 siRNA [51]. AQP1 deficiency in mice that spontaneously develop well-differentiated breast adenomas with lung metastases reduced total tumor mass and volume compared with wildtype mice, due to impaired angiogenesis in the AQP null mice [52]. A key role for AQP1 in enhancing angiogenesis has also been shown in several other non-tumor pathologies including liver cirrhosis [53,54] and hypoxia-inducible angiogenesis in the retina [55]. Together, these findings suggest that, by enhancing cell migration and angiogenesis, AQPs may facilitate tumor growth, local infiltration and metastasis.

Further work is required to define the role of AQPs in tumor cell infiltration. This could be achieved by mapping the location of AQP-expressing and non-expressing astrocytoma cells in human tumor specimens. If AQP expression increases tumor cell infiltration, then we hypothesize that the AQP-expressing cells will be located in infiltrative parts of the tumor whereas non-AQP expressing cells that should be mostly within the tumor core. A recent study reported AQP1 expression in astrocytoma cells in areas of tumor infiltration, distant from the necrotic tumor core, thus supporting this hypothesis [25]. Experiments are also required to investigate whether it is the water transport, or another, unknown AQP function that contributes to tumor cell infiltration and spread.

The mechanism by which AQPs facilitate cell migration remains unknown. Here we propose a novel hypothesis, that AQPs do not increase the speed of migrating cells, but by polarizing to the leading edge, AQPs ensure that the lamellipodium forms in the direction of the chemotactic gradient. This effect may enhance the directionality of migration i.e. cells expressing AQPs follow a less tortuous route towards their target compared with cells lacking AQPs (Fig. 2). A detailed description of the molecular basis of cell migration is beyond the scope of this paper and is the subject of other reviews [56,57]. A useful analogy for a migrating cell is a moving car. The wheels of the car are the integrins, which are transmembrane proteins that allow cell–cell and cell–extracellular matrix interaction during cell migration. The petrol in the car is the ATP that provides the energy for cell migration. The car engine is the actin cytoskeleton that forms the propulsion system for cell migration. The road is the extracellular space. A map is also needed, which is provided by several proteins that facilitate detection of the chemotactic gradient. Here we propose that the AQPs are the steering wheel, which ensures that the moving car heads towards its destination. Further experiments are required to test these ideas, by determining the effect of AQP expression on the speed, directionality and tortuosity of cells in migrating chemotactic chambers.

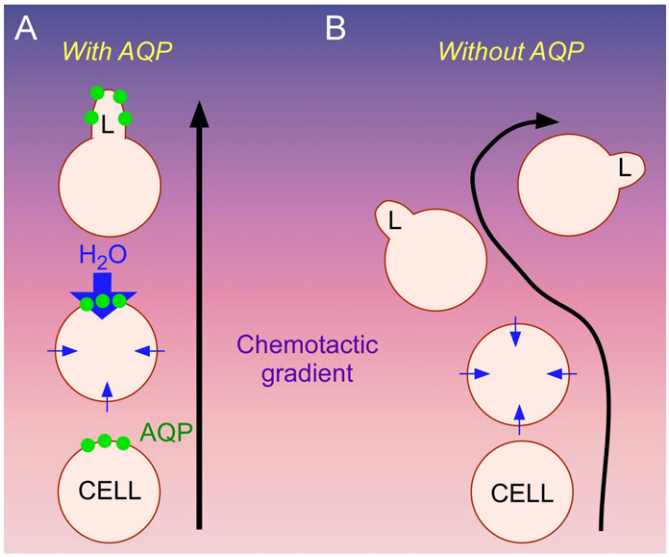

Fig. 2. Proposed role of AQP in increasing directionality of migrating cell. A. AQP polarizes to the leading end of the cell thus ensuring that the lamellipodium forms in the direction of the chemotactic gradient. The cell migrates toward the chemotactic gradient. B. Without AQP, the lamellipodium does not form in the direction of the chemotactic gradient and, therefore, the cell migrates in a more tortuous route.

3.3. Cell proliferation

AQP3, which is expressed in the epidermis, enhances the proliferation rate of basal keratinocytes [46]. AQP3 null mice have impaired wound healing, due to reduced glycerol and ATP content in the keratinocytes, which are required for biosynthesis [58,59]. Little is known about the role of aquaglyceroporins 7 and 9 in the proliferation of normal cells.

There is direct and indirect evidence that AQP3 and AQP5 play a role in tumor cell proliferation. AQP5 might interact with the Ras pathway in colon cancer [60]. Ras activation switches on other proteins that ultimately turn on genes involved in cell growth, differentiation and survival. Another study showed AQP5-facilitated lung cancer cell proliferation and migration, possibly through activation of the EGFR/ERK/p38 MAPK signaling pathway [61]. These AQP5–oncogene interactions may represent novel AQP functions, which are unrelated to water transport. AQP3 null mice are remarkably resistant to the development of skin tumors following exposure to the tumor initiator and promoter, phorbol ester [62]. Glycerol supplementation corrected the reduced proliferation in AQP3 deficiency, with cellular glycerol, ATP, and proliferative ability being closely correlated. There is, therefore, an established link between AQP3 expression in the epidermis and skin cancer. It is worth noting here that some moisturizing creams (such as Eucerin®, Be^{+}®, HydrAction®) are marketed to improve skin hydration by increasing AQP3 expression in keratinocytes. At least one investigator has cautioned the cosmetics industry that products that increase AQP3 expression in the skin might be carcinogenic [63]. AQP3 expression is high in non-small cell lung cancer [64] and, in a mouse model, AQP3 knockdown suppressed tumor growth and reduced angiogenesis in human non-small cell lung cancer xenografts [65].

Though a role for some AQPs in facilitating tumor cell proliferation seems likely, further studies are required to define the link between the expression level of some AQPs, notably AQP3 and AQP5, and tumor cell proliferation. This could be achieved in a variety of human tumors by doubly immunostaining for the AQP of interest and the cell proliferation marker Ki67. If AQP increases cell proliferation, then a greater proportion of AQP^{+} than AQP^{-} tumor cells should also be Ki67^{+}. It is unclear whether and how some AQPs directly interact with oncogenes or whether the increased proliferation in AQP expressing tumor cells is a secondary effect of increasing the glycerol content in the cell. It is also unclear whether the water transporting function of AQPs is necessary to increase cell proliferation.

3.4. Cell adhesion

A role for AQP0 in cell–cell adhesion is well established. AQP0 is expressed in lens fiber cells in the eye where it constitutes about 50% of the fiber cell membrane protein. Studies using AQP0 null mice revealed that AQP0 is important for maintaining the structure of interlocking protrusions that is critical to the integrity and transparency of the lens. A role for AQP4 in cell–cell adhesion was also proposed based on structural considerations [66]. AQP4 contains a short helix in an extracellular loop, which mediates weak interactions between AQP4 molecules in adjoining plasma cell membranes, in effect binding adjacent cells to each other. Expression of AQP4 in L-cells (which lack endogenous adhesion molecules) resulted in clustering of the cells thus supporting the idea that AQP4 may play a role in cell–cell adhesion. There is also evidence against a significant effect of AQP4 expression on adhesion in several different cell types, including L-cells [67]. Recent experiments show that during cell migration, M1-AQP4 isoforms (which exist as individual tetramers) polarize to the leading edge of the cell, to support cell migration [68]. However, the larger M23-AQP4 rich orthogonal arrays do not enter the lamellipodium, but become bound with adhesion complexes, suggesting a role for M23-AQP4 but not M1-AQP4 in cell adhesion to the extracellular matrix. We conclude that data regarding the role of AQP4 in cell adhesion are contradictory. It is thus unclear whether AQP4 plays any role in tumor cell adhesion.

4. AQP-based tumor therapeutics

If AQPs play a role in tumor cell infiltration, metastasis, proliferation and possibly cell adhesion, then AQP modulators may be useful anticancer agents. For effects that are dependent on the water transport property of AQPs such as tumor cell migration, inhibitors of AQP transport are required. For other effects that are independent of water transport through the AQP channel other drugs are required, e.g. disruptors of AQP-oncogene interaction to reduce cell proliferation.

To illustrate the therapeutic potential of AQP inhibitors, we consider glioblastoma, which is the most common primary brain tumor with fatal prognosis. The median survival from diagnosis is about a year even with aggressive treatment (radical surgery, radiotherapy and temozolomide chemotherapy) [69,70]. What makes glioblastoma so aggressive is its ability to infiltrate extensively into the brain, which renders the tumor impossible to excise surgically. Drugs that inhibit water flow through the AQP4 pore may reduce tumor cell infiltration thus converting a tumor that is not surgically excisable into a tumor with well-defined margins that can be surgically resected. Currently, chemotherapy and radiotherapy target the rapidly dividing cells. By eliminating the most infiltrative cells, AQP4 inhibitors would offer a novel therapeutic option, which targets the main cause of tumor malignancy in glioblastoma. Vascular endothelial cells within glioblastoma express AQP1 and, therefore, AQP1 inhibitors may reduce angiogenesis, which would secondarily inhibit glioblastoma growth.

A recent review has summarized attempts to develop AQP-based therapeutics and concluded that such attempts have been largely unsuccessful [36]. Heavy metals such as mercury inhibit AQP1 but are too toxic for clinical use. There are several reports of AQP4 inhibitors including acetazolamide, anti-epileptic drugs, bumetanide, sumatriptan and thiadiazole [71–73]. Unfortunately, follow-on studies on these compounds by other investigators using different assays have failed to confirm AQP4 inhibition. For a detailed discussion on the issues related to discovering AQP inhibitors please refer to the recent review by Verkman et al. [36]. One interesting development is the discovery of an autoantibody against AQP4 found in patients with an inflammatory demyelinating disease of the central nervous system termed neuromyelitis optica, termed AQP4-IgG or NMO-IgG [74]. AQP4-IgG is pathogenic, by binding AQP4 on astrocytes and causing complement-dependent astrocyte damage, followed by leukocyte infiltration into the lesion. Monoclonal AQP4-IgG can now be produced artificially [75]. AQP4-IgG linked to a toxin could be used for destroying AQP4-expressing glioblastoma cells, most of which express large amounts of AQP4. However, it is unclear whether eliminating the AQP4-expressing subpopulation of tumor cells will render the glioblastoma less aggressive. Local AQP4-IgG delivery in human glioblastoma is possible by using wafers positioned against the resection cavity wall or by convection-enhanced delivery. The side effect of AQP4-IgG treatment may be neuromyelitis optica type symptoms caused by AQP4-IgG-mediated damage to normal astrocytes. A more elegant approach is to link AQP4-IgG to a toxin that becomes activated when AQP4-IgG is internalized (Fig. 3). There is evidence that intact astrocytes (which express AQP4 in the perivascular foot processes) do not internalize AQP4-IgG, but cells that express AQP4 throughout the plasma cell membrane (such as glioblastoma) internalize AQP4-IgG [76]. This observation suggests that, compared with normal astrocytes, AQP4-expressing glioblastoma cells may be selectively vulnerable to damage by AQP4-IgG internalization, thus reducing the side effects of this treatment.

5. Future directions

Several roles of AQPs in tumor biology are beginning to emerge. There is a need to define further the molecular mechanisms responsible for AQP-mediated cell migration and cell proliferation. It is unclear whether the water transporting property of AQPs is important or whether there are as yet unidentified interactions between AQPs and oncogenes. Further research is also required to discover non-toxic AQP inhibitors, which can be used to define AQP functions and as novel cancer therapeutics. AQP inhibitors, which could target tumor infiltration, metastasis and angiogenesis, might be used in combination with current cancer therapeutics that target the proliferating tumor cells.

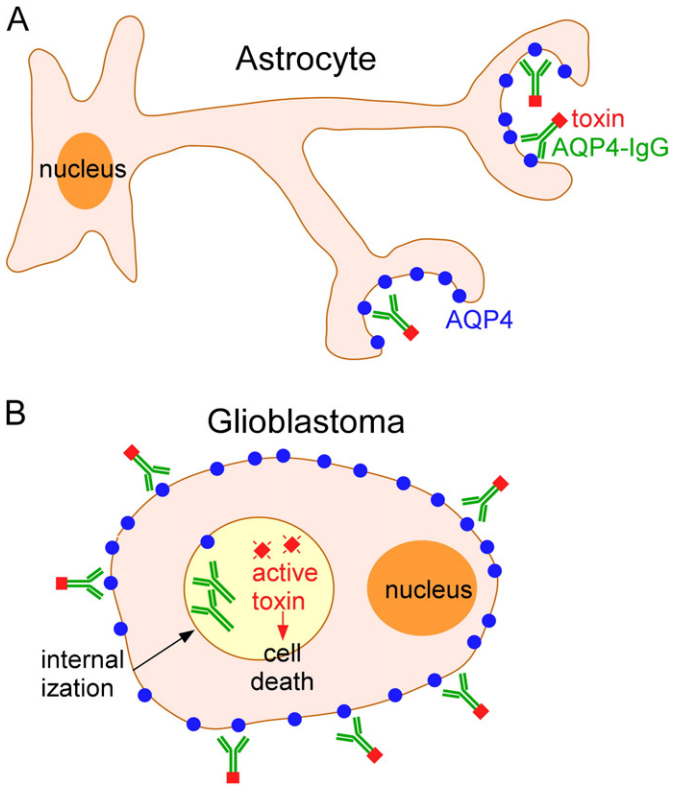

Fig. 3. AQP4-IgG linked to toxin as a potential treatment for glioblastoma. A. AQP4-IgG binds AQP4 on astrocyte foot processes and is not internalized. Toxin remains linked to AQP4-IgG. B. AQP4-IgG binds AQP4 on glioblastoma cell and becomes internalized. Toxin is released from AQP4-IgG and kills the cell.

6. Conclusion

Over the last few years there emerged a surprising link between AQPs and cancer. AQPs appear to play a key role in several tumor-related processes including tumor edema, tumor cell migration, tumor proliferation and angiogenesis. AQP inhibitors may thus be useful anti-cancer drugs. Unfortunately, no such inhibitors are available to date.

Acknowledgments

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