Biochimica et Biophysica Acta 1840 (2014) 1550–1553

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbagen

Review

Aquaporins in cancer ☆

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ARTICLE INFO

Article history:
Received 15 June 2013
Received in revised form 12 September 2013
Accepted 17 September 2013
Available online 21 September 2013

Keywords:
Angiogenesis
Aquaporins
Edema
Glioblastoma
Tumor growth

ABSTRACT

Background: The aquaporins (AQPs) are a family of 13 small hydrophobic integral transmembrane water channel proteins involved in transcellular and transepithelial water movement, transport of fluid and cell migration.
Scope of the review: This review article summarizes our knowledge concerning the involvement of AQPs in tumor growth, angiogenesis and metastatic process.
Major conclusions: Tumor cells types express AQPs and a positive correlation exists between histological tumor grade and the AQP expression. Moreover, AQPs are involved also in tumor edema formation and angiogenesis in several solid and hematological tumors.
General significance: AQPs inhibition in endothelial and tumor cells might limit tumor growth and spread, suggesting a potential therapeutic use in the treatment of tumors. This article is part of a Special Issue entitled Aquaporins.

1. Introduction

The aquaporins (AQPs) are a family of 13 small hydrophobic integral transmembrane water channel proteins involved in transcellular and transepithelial water movement, transport of fluid and cell migration [22,54]. They are localized in the plasma membrane and in the cytoplasmic compartments, and their translocation to the plasma membrane is crucial in the regulation of water transfer [47]. AQP1, AQP2, AQP4, AQP5 and AQP8 are primarily water selective, whereas AQP3, AQP7, AQP9 and AQP10 (called "aqua-glyceroporins") also transport glycerol and other small solutes [54].

Tumor cells types express AQPs and a positive correlation exists between histological tumor grade and the AQP expression as compared to normal tissues [47,56]. AQP causes tumor expansion and may exacerbate tumor-associated edema, as occurs in brain tumors where both vasogenic and cytotoxic edema occur [28], and tumor expression correlates with the amount of edema [56,58]. Moreover, in high-grade gliomas, vasogenic edema is associated with blood brain barrier (BBB) damage, interendothelial tight junction opening and an increased vascular permeability [51]. AQP expression has also been correlated with tumor cell migration and metastatic potential [16]. In fact, a consequence of AQP-facilitated tumor cell migration is an enhanced metastatic potential produced by accelerated cell migration across microvessels and into normal tissue.

2. Aquaporin 1

AQP1 is upregulated in colon cancer, mammary carcinoma, lung cancer, brain tumors, in choroid plexus tumors, hemangioblastoma and multiple myeloma [5,7,8,13,16,24,31,40,47,48,53].

During colorectal carcinogenesis, the expression of AQP1 and AQP5 was induced in early stage disease and maintained through the late stages of colon cancer development [31]. During astrocytoma progression, there was a significant increase in the intensity of AQP1 expression from low-grade to high-grade tumors [7]. Moreover, AQP1 was predominantly located perivascularly in areas of tumor infiltration, distant from the necrotic tumor and AQP1 expression correlated with angiogenesis [7].

Nicchia et al. [34] demonstrated that inhibition of AQP1 dependent angiogenesis impairs tumor growth in a mouse model of melanoma. RNA interference experiments were performed by intratumoral injections of AQP1 siRNAs in mice. After 6 days of treatment, AQP1 siRNA treated tumors showed a 75% reduction in volume when compared to controls associated with a significant reduced expression of the endothelial marker factor VIII.

In AQP1-null mice subcutaneously implanted with B16F10 melanoma cells, tumor growth was reduced with reduced tumor vascularity due to impaired angiogenesis and extensive necrosis [49,50]. Cell migration was greatly impaired in AQP1 deficient aortic endothelial cells with abnormal vessel formation in vitro and the AQP1-null mice were observed to have significantly longer survival times compared to the

☆ This article is part of a Special Issue entitled Aquaporins.

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http://dx.doi.org/10.1016/j.bbagen.2013.09.025

wild type animals [49,50]. Monzani et al. [30] have investigated the possible relationship between AQP1 and cytoskeleton in endothelial and melanoma cells and demonstrated the involvement of Lin proteins, plasma membrane-associated proteins containing one or several PDZ domains required for the organization of the cytoskeleton and involved in cell migration [66]. B16F10 melanoma cells and 4T1 mammary gland tumor cells transfected with AQP1 increase their plasma membrane osmotic water permeability by 5- to 10-fold and a greater number of lung metastases were also found after intravenous delivering of AQP1-expressing tumor cells [17].

AQP1 is strongly expressed in proliferating tumor microvessels in human [47,48] and rat [8] and in the chick embryo chorioallantoic membrane (CAM) microvessels [45]. Moreover, AQP1 specific dsRNA oligonucleotides (siRNA) caused a significant reduction in the growth of new blood vessels in the CAM [2].

A positive correlation between AQP1, microvascular density and vascular endothelial growth factor (VEGF) expression in tumor progression of endometrial adenocarcinoma has been established [41]. A positive correlation between AQP1 and AQP5 expression and intratumoral microvessel density in epithelial ovarian tumors, and between AQP1 and AQP5 expression and ascites formation has been also demonstrated [62,63]. Moreover, in epithelial ovarian tumors, AQP1 expression correlated with intratumoral microvascular density and tumor stage [62].

AQP1 expression in the plasma membrane of HT20 colon cancer cells and adenovirus-mediated high expression of AQP1 increased plasma membrane water permeability and migration rate in both wound healing and invasive transwell migration assay [20]. A significant correlation between AQP1 expression and high tumor grade as well as cytokeratin 14, actin expression and poor prognosis has been established in invasive breast carcinoma [39].

Hoque et al. [16] examined the distribution of AQP1 protein in several types of primary lung tumors by immunohistochemistry and demonstrated that AQP1 was overexpressed in 62% and 75% of adenocarcinoma and bronchoalveolar carcinoma, respectively, whereas all cases of squamous cell carcinoma and normal lung tissues were negative. The same authors reported that AQP1 was expressed in infiltrating lymphocytes and dendritic cells near lung and other cancers [32].

AQP1 expression is up-regulated in glioblastoma multiforme (GBM) in tumor cells and peritumoral astrocytes [8,38,47] and is involved in the formation of brain edema [42]. Moreover, AQP1 is up-regulated by increased glucose consumption and glycolysis in glioma cells [14] and the coordinate up-regulation of AQP1 and cathepsin B at the tumor periphery provides a favorable microenvironment for glioma cell invasion [10].

Expression of AQP1 correlated significantly with prognosis in malignant mesothelioma, irrespective of treatment or established prognostic factors [21]. Moreover, gene expression profile of AQP1 has been analyzed in malignant pleural mesothelioma and AQP1 associated markers has been estimated in the context of mesothelioma disease phenotype, CDKN2A gene deletion, sex and asbestos exposure [19].

2.1. Aquaporin 3 and 4

AQP3 expression is increased in squamous cell carcinomas of the skin and AQP-3-knockout mice are resistant to skin tumor formation through reduced cell glycerol content and ATP energy for biosynthesis [11,12]. Lung carcinomas produce AQP3 in connection with their functional activity [67], and an increase in AQP3 levels was found in bronchioloalveolar carcinomas [26].

Changes to AQP3 protein expression were demonstrated in cancerous human prostate cells [29,55], the proliferation and metastasis potential of esophageal and oral squamous cell carcinoma were correlated to AQP3 expression [23], and inhibition of AQP3 by siRNA increased the sensitivity of prostate cancer cells to cryotherapy [68].

Warth et al. [59] analyzed the presence of all AQPs transcripts in normal and non-small cell lung cancer samples and demonstrated higher transcript and protein levels of AQP4 in well differentiated lung adenocarcinomas, suggesting an association with a more favorable prognosis and indicating an involvement of AQP4 in cell–cell signaling, cellular movement and lipid metabolism.

AQP4 expression is up-regulated in edematous astrocytomas and metastatic tumors [47,48], and an increased AQP4 expression has been demonstrated in GBM associated with loss of polarized expression around the vessels, AQP4 redistribution across the surface of glioma cells and peritumoral vasogenic edema formation [56–58].

Nico et al. [35] demonstrated that, in the relapse after chemotherapy and radiotherapy GBM, AQP4 reduced in parallel with VEGF–VEGF receptor-2 (VEGFR-2) expression as compared with primary tumors and, in the peripheral areas of relapsed tumors, AQP4 mimicked normal findings of perivascular rearrangements, expression of a process of normalization of tumor blood vessels. These data suggest that in GBM chemotherapy and radiotherapy induce a down-regulation in AQP4 expression restoring its perivascular rearrangement and indicate its potential role in the resolution of brain edema.

Tumor implantation experiments into AQP4-null mice have shown that the intracranial pressure is higher than in wild-type controls [42,43]. Melanoma cells implanted into the striatum of wild type and AQP4-null mice produce peritumoral edema and comparable sized-tumors in both groups after a week, even if the AQP4-null mice have a higher intracerebral pressure and water content [27].

McCoy et al. [69] using D54MG glioma cells stably transfected with AQP4 demonstrated that protein kinase C (PKC) activity regulates water permeability through phosphorylation of AQP4. Activation of PKC with either phorbol 12-myristate 13-acetate or thrombin enhanced AQP4 phosphorylation, reduced water permeability and significantly decreased tumor cell invasion. Conversely, inhibition of PKC activity with chelerythrine reduced AQP4 phosphorylation and enhanced water permeability and tumor cell invasion.

Mou et al. [33] demonstrated that expression of AQP4 in gliomas was higher in the tumor and highest in the peritumoral tissue. Moreover, AQP4 protein in tumor tissue of gliomas of different grades was not statistically different, and the degree of peritumoral edema positively correlated with the expression level of AQP4 protein and this latter correlated with VEGF and hypoxia inducible factor 1 alpha (HIF-1α) expression.

Ng et al. [36] have demonstrated that overexpression of AQP4 in human meningiomas was associated with significant peritumoral edema. AQP4 deletion in astroglial cells markedly impaired cell migration toward a stab wound in adult mouse brain and glial scar formation was impaired in AQP4-null mice with reduced migration of reactive astroglia towards a site of brain injury ([49,50,70]). AQP4 could be involved in brain tumor migration and invasion and may accelerate glioma migration by facilitating the rapid changes in cell volume that accompany changes in cell shape.

More recently, Noel et al. [37], combining freeze-fracture electron microscopy, immunohistochemistry and Western blotting, analyzed alterations of expression and distribution of AQP4, dystroglycan, agrin, and matrix metalloproteinase (MMP)-2, MMP-3, and MMP-9 in human primary glioblastomas. They demonstrated that AQP4 expression increased in glioblastoma compared to control tissue and that increase of MMPs immunoreactivities was associated with loss of agrin and dystroglycan, respectively. These data suggest that loss of glioma cell polarity is one of the factors responsible for the disturbance of the neurovascular unit and contributes to edema formation.

3. Aquaporins 5, 8 and 9

Expression of AQP5 was increased in pancreatic cancer [1] and in chronic myelogenous leukemia cells and plays a role in promoting cell proliferation and inhibiting apoptosis [3]. In vitro invasion assay using BEAS-2B and NIH3T3 cells stably transfected with overexpression

constructs for full length wild-type AQP5 and its two mutants, N185D which blocks membrane trafficking and S156A which blocks phosphorylation on Ser156 showed that AQP5 induced cell invasions while both mutants did not [4]. AQP5, through its phosphorylation on Ser 156 and subsequent interaction with c-Src, plays an important role in non-small lung cancer invasion [4]. Other studies have demonstrated an increase in AQP5 expression in pancreatic and colon cancer tissues [60] and in myelogenous leukemia cells [26,65]. AQP5 expression has been linked to proliferation of the human ovarian cancer cell line [64] and increased AQP5 expression correlated with imatinib resistance in chronic myelogenous leukemia [3].

A decreased expression of AQP8 and AQP9 leads to an increased resistance to apoptosis in hepatocellular carcinoma [18]. Foss et al. [9] investigated the expression and localization of AQP1 and AQP9 in glioblastoma biopsies and in tumor stem cells grown in culture as neurospheres as wells as differentiated cells isolated from these tumors. They demonstrated a marked up-regulation of AQP9 mRNA in tumor stem cells followed by high expression in differentiated cells, while AQP4 was down-regulated in differentiated cells, and suggested that AQP9 may have a central role in glioblastoma tumorigenesis.

4. Therapeutic perspectives

AQPs involvement in cell migration, proliferation, and angiogenesis suggests that AQPs play a crucial role in tumor growth. Accordingly, AQPs are strongly expressed in tumor cells of different origins (Table 1); AQPs expression in tumor cells may increase local tumor invasiveness and tumor angiogenesis. Finally, the correlation between the level of AQPs expression in tumor cells and the amount of tumor edema, as revealed by MRI, has suggested the involvement of AQPs in tumor edema formation [35].

AQPs are therefore potential pharmacological targets and their inhibition in endothelial and tumor cells might limit tumor growth and spread. Inhibition of AQP1 and AQP4 expression (by small interference RNA technology) or their function (with a blocking antibody or a small inhibitory molecule) may result in increased intracellular acidosis and cytotoxicity and reduced invasive potential of glioma cells. Ding et al. [6], using small interference RNA and a pharmaceutical inhibitor to knock down the expression of AQP4, demonstrated a specific and massive impairment of glioblastoma cell migration and invasion in vitro and in vivo, and showed that down-regulation of MMP-2 expression coincides with decreased cell invasive ability.

Inhibition of AQPs expression and/or AQP-mediated water influx by acetozolamide, cyclophosphamide, topiramate, thiopenthal, phenobarbital and propofol affects cancer cell proliferation, migration, metastasis and angiogenic potential [71]. Acetazolamide inhibits the osmotically induced water swelling and can suppress tumor metastasis, in part by inhibiting AQP1 gene expression [44]. Xiang et al. [61] hypothesized that the suppressive action of carbonic anhydrase inhibitors on AQP1 might contribute to their inhibitory effect on cancer invasion and metastasis.

The antiepileptic agent topiramate inhibits AQP1 expression and attenuates water influx at the leading edge, thereby affecting membrane protrusion, cell migration and metastasis [25]. Corticosteroids are largely used in combination with chemotherapy and contribute to significantly reduce peritumoral brain edema by decreasing the permeability of tumor vessels and/or enhance the clearance of extracellular water [52], suggesting that AQP4 may be considered a target of the steroid treatment in brain edema. Accordingly, animal experiments showed a decrease of cerebral AQP4 protein expression upon dexamethasone treatment [46]. Moreover, corticosteroids reduced AQP4 mRNA level in experimental brain tumor model and after intracerebral hemorrhage in rats ([15,72]).

To date, specific AQPs inhibitors suitable for clinical use have not been identified; however, our current knowledge of AQP pore structure/function relationships and the structure of the carboxy terminus of the molecule should permit the development of “designer drugs” that can target specific AQPs.

Table 1
AQPs expression in different human tumors.

Tumor type	[Ref.]	Correlation with
Astrocytoma/AQP1	[7]	Tumor stage, proliferation and angiogenesis
Breast cancer/AQP1	[39]	Tumor stage and poor prognosis
Choroid plexus tumors/AQP1	[24]	Tumor proliferation
Chronic myelogeneous leukemia/AQP5	[3]	Tumor proliferation
Endometrial adenocarcinoma/AQP1	[41]	Tumor angiogenesis
Esophageal carcinoma/AQP3	[23]	Tumor proliferation and invasion
Glioma/AQPs 1,4,9	[47,56,58]	Tumor proliferation and edema formation
Hemangioblastoma/AQP1	[5]	Tumor proliferation
Hepatocellular carcinoma/AQPs 8, 9	[18]	Increased resistance to apoptosis
Lung cancer/AQPs1, 3, 4, 5	[16,59]	Tumor stage and prognosis
Multiple myeloma/AQP1	[53]	Tumor stage and angiogenesis
Ovarian cancer/AQPs 1, 5	[63]	Tumor stage and angiogenesis
Pancreatic cancer/AQP5	[1]	Tumor proliferation

Acknowledgements

The research leading to these results has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 278570 to D.R.

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