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Chapter 4

Role of Aquaporins in Breast Cancer Progression and Metastasis

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Abstract

There are various limitations regarding the current pharmacological options for the treatment of breast cancer in terms of efficacy, target selectivity, side effect profile and survival. Endocrine-based therapy for hormone-sensitive cancers such as that of the breast is one of the most effective and well-tolerated therapeutic options but is hampered by either intrinsic or acquired resistance, resulting in a more aggressive form of the disease. It is generally agreed that this process occurs in parallel with cellular transition from epithelial to mesenchymal phenotype (EMT), with consequent enhancement of proliferative capacity, migrative ability and invasive potential. Aquaporins (AQPs) represent a large family of water channel proteins which are widely distributed in various tissues and which play a role in the physiological maintenance of the extracellular environment particularly to regulate electrolyte-water balance. Accumulating evidence shows that expression of several AQPs is modulated in cancer tissues, and this correlates with tumor grade. AQPs 1 and 3–5 are also involved in breast cancer invasion, through modulating the activity of various growth factors, signaling molecules and proteolytic enzymes. We review current data on the involvement of these proteins in processes associated with malignant progression and discuss possible applications of AQP-based therapy as an effective means of inhibiting cancer cells from metastasizing.

Keywords: breast cancer, metastasis, aquaporin, transport, ion channels

1. Introduction

Breast cancer remains the leading cause of tumor-associated mortality in women worldwide. Estrogen, acting through predominantly nuclear-located receptors (ER), has a significant

detrimental impact during its pathogenesis [1]. This forms the basis for endocrine therapy, with the application of pharmacological antagonists generally termed selective estrogen receptor modulators, such as tamoxifen. These have resulted in significant improvements in quality of life as well as improved prognosis [2] in a significant proportion of patients with clinically defined ER+ve status [3]. Unfortunately, *de novo* resistance to tamoxifen occurs in about 30–40% of patients (those with very low level of ER expression, clinically designated as ER−ve) and even in about 50% of the clinically defined ER+ve patients. Furthermore, almost all initially responsive patients with late stage metastatic disease eventually relapse due to the development of *acquired* resistance to anti-estrogen therapy. These forms of endocrine resistance invariably lead to a more aggressive form of resurgent disease [4], and occur in parallel with cellular transition from epithelial to mesenchymal phenotype (EMT). There is a strong association between the EMT process and metastasis, which involves detachment of individual epithelial cells from neighboring cells, loss of polarity, scattering, acquisition of enhanced motility and invasion into the extracellular matrix (ECM) before entering blood and lymphatic vessels. Many phenotypic changes occur during this process which includes the loss of cell-cell adhesion as a result of reduced E-cadherin and catenins expression in adherens junctions, reduced claudins and occludins expression at tight junctions and reduced expression of various epithelial cytokeratins such as KRT8, 18 and 19 which presumably aids in disruption of cytoskeletal connections that maintain tissue architecture. These changes are also paralleled with up-regulation of mesenchymal markers such as vimentin, fibronectin, alpha smooth muscle actin (ACTA2), N-cadherin and various matrix metalloproteinases (MMPs) [4, 5]. Attempts to overcome endocrine resistance include the use of pure estrogen antagonists such as fulvestrant (in place of tamoxifen, which is associated with some agonist actions with prolonged administration) or agents which inhibit peripheral extragonadal synthesis of estrogen (aromatase inhibitors such as anastrazole), which delays but does not resolve this problem [6, 7]. In addition, receptor tyrosine kinase (RTK) inhibitors have been used recently in the treatment of endocrine-resistant breast cancer [8], but they have limitations in terms of target specificity and clinical outcomes. For example, the reversible inhibitor of epidermal growth factor receptor (EGFR) erlotinib also blocks ERBB2 [9, 10], AKT (the downstream target of phosphatidylinositide 3-kinases; PI3K) and mitogen-activated protein kinase (MAPK) phosphorylation in breast cancer cells [11]. Furthermore, imatinib inhibits the activity of the tyrosine kinase domain of various targets such as ABL, KIT and platelet-derived growth factor receptor (PDGFR) [12, 13]. The lack of specificity of these agents might increase the risk of side effects and therefore limits their clinical usage and utility. Since the current therapeutic options for endocrine insensitive breast cancer patients have various limitations (including severe side effect profile and resistance), there is a need to find better therapeutic targets to control this condition and improve its prognosis.

Aquaporins (AQPs) represent a family of 13–14 small hydrophobic integral transmembrane water channel proteins which are widely distributed in various tissues in the body. Their function is to transport mainly water (through passive transport), glycerol, solutes (such as urea, carbon dioxide, ammonia and nitric oxide) [14–20], as well as larger polar solutes (such as sugars and hydrogen peroxide) [21–23]. The first discovered family member of these proteins was initially called CHIP28, but it is now known as AQP 1 [24, 25]. AQPs are classified

on the basis of their substrate permeability: (a) the classical water permeable AQPs 0, 1, 2, 4, 5, 6 and 8; (b) the water and small solute (e.g., glycerol and urea) permeable aquaglyceroporins AQPs 3, 7, 9, 10 and 12; (c) gas (carbon dioxide and nitric oxide) and ammonia permeable AQPs 1, 4 and 5; and (d) small ion (e.g., sodium and potassium) conducting AQP 1 [25]. Besides their main role in maintaining salt and water homeostasis, recent evidence suggests their involvement in various disease conditions including neoplasms such as breast cancer. These membrane channels have received much attention in recent years as potential novel drug targets for reducing cancer angiogenesis and metastasis. This chapter will provide evidence from recent studies regarding the involvement of various AQPs in breast cancer pathogenesis and will highlight their role in disease diagnosis, prognosis and treatment.

2. Structure of AQPs

Unlike other types of channels, AQPs do not show gating, saturation or membrane potential-dependent behavior. AQP family members share 25–60% protein sequence homology [14, 26, 27], and are assembled on the cell membrane and cytoplasmic compartments as homotetramers [28]. Each monomer is about 28–30 kDa in size and has its own water pore. Some members of this family such as AQPs 0 and 4 have unique features in that their tetramers assemble into higher order supramolecular structures described as orthogonal arrays of particles [29, 30]. The monomeric units of AQPs consist of six transmembrane α-helices (M 1, 2, 4–7 and 8), two half helices (M 3 and 7) and five connecting loops (a–e) [31]. Both the N- and carboxyterminal domains are present in the cytoplasmic compartment. Water movement occurs through a narrow pore (<0.3 nm) in which steric and electrostatic factors prevent the transport of protons and other small molecules [32]. Several studies have also indicated that the central pore allows the rapid transport of oxygen, carbon dioxide and nitric oxide (seen in AQPs 1, 4 and 5) [19, 33]. On the other hand, the aquaglyceroporins have a less constricted pore with a larger proportion of hydrophobic residues [34, 35]. **Figure 1** illustrates a schematic arrangement of an AQP channel.

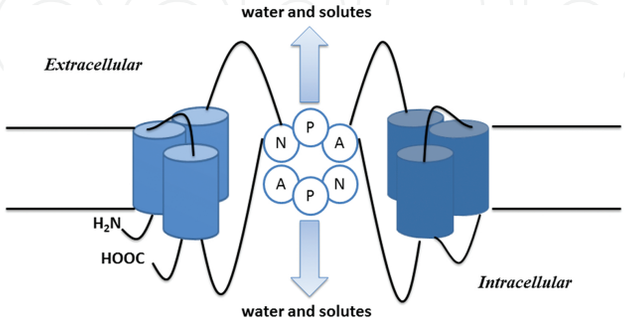

Figure 1. Schematic diagram of the aquaporin channel. The aquaporins are formed by two tandem repeats of three membrane-spanning helices. Two connecting loops, each containing a conserved sequence motif of Asn-Pro-Ala (NPA) on the loops, bend into molecules to pair with each other and form a channel in the plasma membrane through which water and solutes can pass between the cell and its environment.

3. Expression profile of AQPs

3.1. Normal tissues

These channel proteins exhibit a wide tissue distribution. Several AQPs (1–4) play a role in kidney function [36, 37]. For example, AQP 2 translocates from the intracellular vesicles to the apical plasma membrane of the collecting duct in response to vasopressin stimulation leading to water reabsorption by the kidney [37, 38]. AQP 1 allows carbon dioxide transport in the proximal tubules, for regulation of arterial pH during metabolic acidosis [39]. In the brain, AQP 4 is expressed in the perivascular astrocyte foot process region and plays a role in solute clearance from the interstitial fluid [40] and the neuro-excitatory processes [41]. In the skin, AQP 3 is expressed in the stratum corneum (SC) and plays a role in maintaining skin hydration and elasticity, and epidermal proliferation [42]. In the adipocytes, AQP 7 is involved in glycerol movement across the cell [36]. Several AQPs are expressed in various regions of the eye and play a role in ocular surface hydration, intraocular pressure regulation and visual signal transduction [43]. Other AQPs are expressed elsewhere but their physiological functions remain to be determined. For example, AQP 4 is expressed in the basolateral region of gastric parietal cells but its deletion in mice does not alter acid secretion [36, 44]. Furthermore, tissue-specific expression of AQP 4 in skeletal muscle [45], AQP 5 in sweat glands [46] and AQP 8 in various tissues [47] have not yet been linked with any specific physiological role.

3.2. Tumors

There is accumulating evidence to suggest a role for several AQPs in cancer pathogenesis through their modulated expression profile in several tumors. It is speculated that AQPs facilitate water penetration into the growing tumor leading to its expansion through edema formation [48, 49]. They also appear to be involved in angiogenesis, tumor proliferation and migration/invasion [50–53]. About twenty types of tumors have been shown to express AQPs *in vivo*. For example, the expression level of AQPs 1, 4 and 9 are increased in astrocytoma [48, 54–57], while the level of AQP 1 was shown to be either increased [58] or decreased [59] in cholangiocarcinoma. Increased levels of AQPs 1, 3 and 5 [60–62] and decreased level of AQP 8 [63, 64] have been reported in colorectal cancer. In lung cancer, AQPs 1, 3, 4 and 5 were shown to be overexpressed [65–67]. Increased levels of AQPs 1, 3 and 5 were observed in cervical cancer [68, 69]. AQP 5 was increased in chronic myelogenous leukemia [70] and esophageal cancer [71]. In liver cancer, high levels of AQPs 3 and 5 [72] and low levels of AQPs 8 and 9 were observed [73].

There is a direct correlation between the expression level of several AQPs and tumor grade. High levels of AQPs 1, 4 and 9 were observed in astrocytoma correlating with advanced disease stage [48, 54–57]. Enhanced AQP 9 expression was evident in malignant compared to benign ovarian tissues and was positively correlated with tumor grade [74]. Furthermore, enhanced expression of AQP 1 was seen in lung adenocarcinoma and its inhibition reduced cell invasion [66].

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4. Physiological role of AQPs

4.1. Fluid transport and osmotic equilibrium

It has been suggested that at least eight (of the known 13) AQPs transport water, while others such as AQPs 3, 7, 9 and 10 are also able to transport glycerol (termed aquaglyceroporins) [44, 75]. Their expression in various organs such as the kidney tubules, lung and alveoli facilitate active fluid absorption and secretion by the creation of an osmotic gradient across the cell membrane and subsequent fluid movement through these channels. Genetic knockout of AQP 5 in mice resulted in impaired salivary [76, 77] and airway submucosal gland secretion [78]. In addition, tissue-specific knockout of AQP 1 in mice leads to impaired secretion of the cerebrospinal fluid [79] and ocular aqueous fluid [80], and inappropriate hypertonic fluid absorption in the proximal kidney tubules [81]. It should be noted, however, that other data suggest that knockout of various AQPs does not lead to impaired fluid absorption or secretion [82–86], suggesting that the requirement of AQPs to facilitate active fluid transport depends on the rate of such transport in each compartment. AQPs (specifically 1–4 and 7) are also involved in maintaining the osmotic equilibrium across the kidney tubules and the formation of concentrated urine. Marked polyuria and low urine osmolality was seen in AQPs 1 and 3 knockout mice, which led to severe dehydration [87, 88]. Reduced expression of AQP 2 also leads to acquired forms of nephrogenic diabetes insipidus (NDI) due to the inability of the kidneys to concentrate urine owing to the insensitivity of the distal nephron to the antidiuretic hormone arginine vasopressin [89]. AQP 4 is expressed in the glial cells of the brain and spinal cord, and plays an important role in water balance in the brain. A significant reduction in osmotic water permeability in glial cells was demonstrated in AQP-4-deficient mice which led to brain edema and swelling [90, 91]. In addition, several AQPs (0, 1, 3, 4 and 5) are expressed in various compartments of the eye and play an important role in the regulation of fluid movement and intraocular pressure [92–95].

4.2. CNS functions

AQP 4 was shown to be expressed in the glial cells in the brain particularly at astrocyte end-feet at the blood-brain barrier and the ependymal-cerebrospinal fluid barrier [96]. AQP 4 deficiency in mice resulted in reduced seizure susceptibility in response to pentylenetetrazol treatment [97], as well as in electrically-induced seizure following hippocampal stimulation [98]. Delayed potassium uptake from the brain extracellular space (ECS) [98, 99], and expanded ECS which dilutes the released potassium levels [100, 101], has been suggested to be responsible for the reduced seizure susceptibility in AQP-4-deficient mice. AQP 4 also increases water exit from the brain in vasogenic edema, as AQP-4-deficient mice show greater water accumulation in various models of brain edema [102–105]. Also, AQP 1 was shown to be expressed in the dorsal root ganglion neurons and nociceptive C-fibers, and AQP 1 deficiency in mice leads to reduced pain perception in response to thermal inflammatory pain in part through modulation of voltage gated sodium channel Nav 1.8 activity [105–107].

4.3. Glycerol transport

AQP 3 was shown to be expressed in the stratum corneum (SC) at the basal layer of the keratinocytes and plays a role in skin hydration. In AQP-3-deficient mice, SC hydration was significantly reduced due to reduced water content, decreased skin elasticity and wound healing [108]. An important factor which was also attributed to reduced skin hydration in AQP-3-deficient mice is the impaired glycerol transport from the blood to the epidermis through the basal keratinocytes, suggesting the importance of AQP 3 in glycerol transport. Dysregulated expression of AQP 3 has been found in various skin disorders associated with altered epidermal proliferation [109, 110]. In fact, topical or systemic replacement of glycerol prevented skin abnormalities (less hydration and elasticity and impaired barrier function) in the deficient mice [111].

4.4. Cell proliferation

A role for AQP 3 in cell proliferation has been suggested in various cell types. Using corneal epithelial cells, delayed restoration of full-thickness epithelia was seen in AQP-3-deficient mice after scraping. This was confirmed by reduction in proliferating BrdU-positive cells during healing [112]. Reduced keratinocyte cell proliferation was also evident in AQP-3-deficient mice or with siRNA-mediated knockout of AQP 3 in keratinocytes in part through reduction of p38 MAPK activity [113]. Furthermore, the proliferative rate of mouse colonic epithelial cells was significantly reduced in AQP-3-deficient mice, which might explain the enhanced colitis severity in these mice compared to WT mice in the dextran sulfate sodium model of colitis [114].

4.5. Cell adhesion

AQP 0 is thought to be involved in cell-cell adhesion. It has been found to be expressed in lens fiber cells in the eye and plays a role in maintaining their structure [115]. Loss-of-function mutation of AQP 0 in humans and mice resulted in congenital cataracts [34, 92]. In addition, AQP 4 was shown to mediate weak cell-cell interaction through its short helix in the extracellular loop [116]. Overexpression of AQP 4 in L-cells (which lack endogenous adhesion molecules) resulted in cell cluster formation, which supports the role of this AQP in intercellular adhesion.

4.6. Cell migration

Various AQPs have been shown to be involved in the cell migrative process. AQP 1 is expressed on the leading edge of migrating cultured endothelial cells in association with increased lamellipodia formation. AQP 1 deficiency in cultured endothelial cells results in significant reduction in their migration. Overexpression of AQP 1 or 4 enhanced cell migration along with prominent membrane ruffling at the leading edge [53]. The role of AQP 1 in cell migration was also confirmed using kidney proximal tubule cells where its deficiency reduced cell migration and its overexpression led to enhanced cell migration through the formation of lamella-like membrane protrusions at the cell leading edge [50]. Furthermore, AQP 4 was localized on the leading edge of migrating cultured astroglia cells, and its expression was increased by inducing

a small extracellular osmotic gradient. AQP 4 deficiency (by siRNA treatment or cell isolation from AQP-4-deficient mice) resulted in marked reduction in their migratory potential [51, 52]. AQP 3 deficiency in mammalian corneal epithelial cells [51], keratinocytes [113] and fibroblasts [117] also reduced their migrative ability both *in vitro* and *in vivo.*

AQPs enhance cell migration through various mechanisms. They facilitate rapid changes in cell volume and shape, which allows the cells to squeeze through the narrow and irregularly shaped extracellular space; this has been referred to as amoeboidal movement [118]. Also, they increase the local hydrostatic pressure (that push apart adjacent stationary cells), and actin repolymerization, to stabilize cell membrane protrusions at the leading edge which is required for the migratory process [119]. There is some evidence regarding the role of AQP 4 in regulating a complex of intracellular molecules such as alpha-syntrophin involved in membrane protrusions [120]. Some evidence also suggests a role for AQP 3 in reducing keratinocyte cell migration through reduced p38 MAPK activity [113]; this is generally recognized as an important signaling molecule for cell migration.

5. Involvement of AQPs in the etiology of cancer

There is accumulating evidence for the involvement of several forms of AQPs in various types of cancer which also correlates with tumor stage.

With respect to tumor proliferation, AQP 5 interacts with the Ras-MAPK pathway and cyclin D1/CDK4 complexes in colon cancer [121] and with the EGFR/ERK1/2/p38 MAPK signaling cascade in lung cancer [122], resulting in enhanced proliferation, differentiation and survival. A role for AQP 3 has also been suggested for controlling proliferation of epidermal cancer cells through the facilitation of glycerol transport and increase in ATP generation [123]. In non-small-cell lung cancer cells, its effects appear to be associated with enhancement of the expression of p53, increase in the ratio of cleaved to procaspase 3 and reduction in the expression of proliferating cell nuclear antigen and B-cell lymphoma-2 (Bcl-2) [124]. AQP 4 is involved in glioblastoma cell proliferation; siRNA-mediated knockdown of AQP 4 induced cell apoptosis in part through modulation of key proteins involved in this process such as cytochrome c, Bcl-2 and Bad [125].

With regard to tumor migration/invasion and angiogenesis, AQP 3 silencing in non-small lung cancer cells resulted in significant inhibition of cell invasion through reduction of the activity of matrix metalloproteinases (MMPs) 2 and 9 and AKT phosphorylation, as well as reduction in angiogenesis through interaction with the HIF-2α-VEGF pathway [124]. Overexpression of AQP 1 in B16F10 melanoma cells and 4T1 breast cancer cells resulted in enhanced cell invasion and tumor spread when injected through the tail vein in mice [53, 126]. siRNA-mediated knockdown of AQP 1 in melanoma cells also resulted in reduced cell proliferation and invasion [127]. Overexpression of AQP 1 in colon cancer cells increased their invasive potential through actin relocalization and RhoA and Rac activation [128]. In glioma cells, AQP 1 facilitated the shunting of H^+ from the intracellular to the extracellular compartment and the release of lactate dehydrogenase (LDH) and cathepsin B, which results in the acidification of the tumor

microenvironment leading to enhanced tumor angiogenesis and invasion [129]. AQP 4 also plays a role in glioblastoma cell migration and invasion through rearrangement of the actin cytoskeleton [130]. Furthermore, overexpression of AQP 5 in non-small lung cancer cells enhanced cell metastasis through c-Src activation and induction of the EMT process [122].

6. Role of AQPs in the pathogenesis of breast cancer

While AQPs have been shown to be involved in the delivery of water to the mammary glands which is critical for milk production and secretion during lactation [131], their expression in breast tumors is modified and correlates with tumor grade.

6.1. AQP 1

Immunostaining indicates a predominantly membranous localization with some presence in the cytoplasm in large tumor cells (more pronounced at the tumor invasion front), but no expression was seen in smaller tumor cells. All of the AQP 1 positive invasive carcinomas are found to be of ductal type, ER−ve and HER2/neu −ve (triple −ve form), and its expression was significantly associated with poor clinical prognosis [132, 133]. A recent report suggested that the cytoplasmic expression of AQP 1 promotes breast cancer progression and was associated with a shorter survival rate especially in luminal subtype patients [134]. Its cytoplasmic expression was positively correlated with advanced pathological features of invasive ductal carcinoma and lymph node metastasis [134]. Another study reported that AQP 1 was highly expressed in blood vessels (mainly in CD31+ve endothelial cells) of human breast and endometrial carcinoma tissues, suggesting a role in tumor angiogenesis [135]. Using human umbilical vein endothelial cells (HUVECs), Zou et al. [135] showed that estrogen treatment significantly up-regulated AQP 1 expression in a time- and dose-dependent fashion, which was mediated through a functional estrogen response element motif in the promoter region of the AQP1 gene. Estrogen treatment significantly increased HUVEC proliferation, migration, invasion and tubule formation; all of these effects were inhibited by pretreatment of cells with AQP1-specific siRNA. These data suggest an important role of AQP 1 in cell invasion in part through regulating actin stress fiber formation through colocalization with the ezrin/radixin/moesin protein complex [135]. Qin et al. [134] showed that overexpression of AQP 1 in MCF-7 and MDA-MB-231 cells significantly enhanced (by approximately 2 fold) cell proliferation and invasion. Epidermal growth factor (EGF) stimulation induced AQP 1 redistribution from the cytoplasm to the cell membrane, further supporting a role in promoting cell invasion. In the mouse mammary tumor virus-driven polyoma middle T oncogene (MMTV-PyVT) model (which spontaneously develops a well-differentiated luminal-type breast carcinoma with lung metastasis), AQP 1 deficiency significantly reduced the breast tumor mass (by 46%) and volume (by 50%), vessel density and the number of lung metastases compared to the control group [136]. This effect was in part due to decreased expression of vascular endothelial growth factor receptor-2 (VEGFR2) and increased levels of hypoxia inducible factor-1α (HIF-1α) in the AQP 1 knockout mice [136].

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6.2. AQP 3

AQP 3 overexpression in early breast cancer patients was shown to be associated with worse prognosis in patients with HER2-overexpressing phenotype after curative surgery [137]. Its expression was correlated with advanced stage, large tumor size and lymphatic and vascular invasion, highlighting its role in angiogenesis and invasion. In addition, Huang et al. [138] showed higher AQP 3 protein expression in breast cancer tissues (mainly in the cell membrane and the cytoplasm) of premenopausal compared to postmenopausal patients, and was associated with higher histopathological grade and lymph node metastasis in ER+ve breast cancer patients. Estrogen stimulation significantly up-regulated AQP 3 expression in ER+ve breast cancer cells (MCF-7 and T47D) by activating the estrogen response elements (EREs) in the promoter region of the AQP 3 gene. siRNA mediated knockdown of AQP 3 in ER+ve breast cancer cells significantly reduced estrogen-induced cell migration (by 30–70%) and invasion (by 43–71%). Overexpression of AQP 3 in T47D cells significantly enhanced cell migration and invasion. The role of AQP 3 in cell invasion was suggested to be in part through mediating actin cytoskeleton rearrangement (by the formation of filopodia and stress fibers required for invasion) and EMT induction (evident by reduced expression of the epithelial marker E-cadherin, and increased levels of the mesenchymal markers N-cadherin and snail-1) [138]. Using breast cancer cell lines MDA-MB-231 and Bcap-37, Cao et al. [139] showed that fibroblast growth factor-2 (FGF-2) significantly increased AQP 3 expression, and lentivirus-mediated shRNA inhibition of AQP3 expression significantly reduced FGF-2 induced cell migration by approximately 50%. This effect was mediated through AQP-3-induced activation of Akt and ERK1/2. A recent report showed that AQP 3 expression in the triple negative breast cancer cell lines MDA-MB-231 and DU4475 (as well as in HUVEC) was required for the transport of extracellular hydrogen peroxide into the cells in response to CXCL-12 stimulation to induce directional cell migration [140]. AQP 3 silencing in these cells was associated with impaired CXCL-12 induced directional migration due to impaired F-actin polymerization, PTEN and PTP1B oxidation, Akt phosphorylation, and the accumulation of the intracellular hydrogen peroxide at the reading edge of migrating cells was needed for polarity sensing. Furthermore, the role of AQP3 in invasion was tested by the injection of fluorescently labeled breast cancer cells into severe combined immunodeficient (SCID) mice. Lung metastasis was significantly reduced in AQP-3-deficient breast cancer cells, whereas its overexpression significantly increased the number of cells migrating to the lungs [140]. In addition, the expression of AQP 3 was also increased in MCF-7 cells by treatment with the chemotherapeutic agent 5′-deoxy-5-fluorouridine (5′-DFUR) [141], which was required for the 5′-DFUR-induced cell cycle arrest (through its action on G1/S phase transition and up-regulation of p21 and FAS).

6.3. AQP 4

The role of this AQP is not well studied in breast cancer, however, one report showed that AQP 4 expression (at both mRNA and protein level) was significantly higher in normal compared to cancer tissue [133], and was mainly expressed in the cell membrane and the cytoplasmic compartments.

6.4. AQP 5

Immunohistochemical analysis shows significant overexpression of AQP 5 in breast tumors from early breast cancer patients, and was correlated with the disease prognosis particularly in patients with ER/PR+ve tumors [142]. This observation was also confirmed by another group who showed that AQP 5 was not detectable in normal breast tissues, but was expressed mainly in the cell membrane of mammary carcinoma and associated with cellular differentiation, lymph node invasion and tumor stage [133]. The 5-year survival rate was decreased from 80% in AQP 5 −ve patients to 50% in AQP5+ve patients, suggesting that its expression was associated with short overall survival [133]. In another report, AQP 5 expression was observed in the ductal epithelial cells of human breast tissues with significant overexpression in invasive compared to benign tumors [143]. It was also expressed in MCF7 and MDA-MB-231 breast cancer cell lines (at mRNA and protein level); shRNA, or hyperosmotic stress-induced reduction in AQP 5 expression significantly reduced cell proliferation and migration toward fetal bovine serum (FBS) gradient. Some reports have suggested that AQP 5 induces tumorigenesis (at least in lung epithelial cells) upon phosphorylation of the cAMP protein kinase consensus site located in its cytoplasmic loop [144, 145].

7. AQPs: cancer diagnostic markers in breast cancer

There is no clinical data so far which confirms the use of AQPs as diagnostic markers for breast cancer. However, many reports suggest a strong correlation between the expression profile of certain types of AQPs and breast cancer pathogenesis and prognosis. For example, AQP 1 expression was associated with poor clinical prognosis in ductal type, ER −ve and HER2/neu −ve breast cancer patients [132]. The cytoplasmic expression of AQP 1 was also correlated with advanced pathological features of invasive ductal carcinoma, lymph node metastasis and shorter survival [134]. Overexpression of AQP 3 in HER2-overexpressing patients [137] as well as in premenopausal ER+ve breast cancer patients [138] was associated with advanced stage. AQP 5 expression was also shown to be associated with poor clinical prognosis [133], particularly in patients with ER/PR+ve tumors [142], and in the ductal epithelial cells of human breast tissues [143].

Detection of serum AQP 4 auto-antibodies has shown promising indication as a diagnostic tool in neuromyelitis optica (NMO), an inflammatory demyelinating disease that selectively affects optic nerves and spinal cord. It is claimed to be significantly associated with a higher number of relapses and longer disease duration [146, 147]. There are also reports suggesting a role for other AQPs: AQP 2 in determining the etiology of metabolic disorders dependent on the arginine vasopressin [148], AQP 3 in eczema [149] and AQP 4 in epilepsy [150].

8. AQPs: therapeutic targets for breast cancer

There appears to be potential for the use of AQP-based therapies (such as cysteine-reactive heavy metal-based inhibitors, AQP-induced water permeation, monoclonal AQP-specific

antibodies and AQP gene transfer) to treat various conditions including breast cancer. Several heavy metals have been shown to inhibit AQP 1. These include mercury II chloride (through covalent interaction with the Cys189 residue in the water pore of AQP 1) [151, 152] and silver and gold III compounds (through interaction with the cysteine residue near the conserved NPA domain) [153, 154]. Gold III compounds were also shown to inhibit AQP 3 through interaction with the Cys40 in its extracellular domain [154, 155]. Other nonmetal containing small molecule inhibitors include tetraethylammonium (TEA^+), which reversibly inhibits AQP 1 through interaction with the Tyr186 site [156, 157]. The carbonic anhydrase inhibitor acetazolamide was also shown to inhibit AQPs 1 and 4 [158, 159]. Several antiepileptics, and the loop diuretic bumetanide, are reported to inhibit AQP 4 [159–161]. The other loop diuretic furosemide was also found to inhibit AQP 1 [162]. Furthermore, AQP gene transfer therapy is also in its early phases; AQP 1 cDNA transfer into the parotid glands for treating salivary gland hypofunction after radiation therapy is currently in phase I clinical trials [163–165].

In noncancerous conditions, some AQPs (1–4 and 7) are required for the formation of concentrated urine, which suggests that AQP-inhibitors might act as a unique form of diuretics to treat various disorders such as heart failure [87, 88]. Increased expression of AQP 4 exacerbated water accumulation in the brain, suggesting that AQP 4 inhibitors might be used to treat cytotoxic edema [90, 91]. Other potential therapeutic uses of AQP-therapies include treatment of various exocrine disorders, obesity and glaucoma [166].

AQP 1 is expressed on the endothelial cells of microvessels in various tumors including the breast [167], with a clear role in mediating angiogenesis and invasion through interaction with the actin cytoskeletal machinery, EGF, VEGF and HIF-1α. It has been suggested that the carbonic anhydrase inhibitor acetozolamide, and the antiepileptic drug topiramate, suppress tumor invasion in part through inhibiting AQP 1 gene expression [168, 169]. AQP 3 was also shown to be involved in breast cancer cell invasion through interaction with the actin cytoskeleton proteins, ER, chemokines and growth factors (CXCL-12, FGF-2), downstream signaling molecules (ERK1/2, Akt, PTEN and PTP1B) and induction of the EMT process. Furthermore, AQP 5 also enhanced breast cancer invasion in part through interaction with cAMP. The chemotherapeutic drug cisplatin inhibits the expression of AQP 5 in ovarian cancer and leads to reduced lymph node metastasis [170]. Therefore [171], inhibitors of the above-mentioned AQPs may have potential applications in breast cancer therapy through their inhibitory actions on tumor angiogenesis and invasion.

9. Conclusion

There is growing evidence in several tumors (including that of the breast) to indicate that several growth factors (e.g., EGF, VEGF and FGF-2) which are known to enhance cell invasion, may do so, at least in part, through increasing expression of a number of AQPs, suggesting a prometastatic role for these channels. This is likely to be mediated by interaction with various signaling molecules involved in cell invasion such as Ras, MAPK and PI3K, leading to rearrangement of the actin cytoskeleton (through interaction with RhoA/Rac), extracellular

acidification (through interaction with LDH and HIF-1α, which by itself enhances cell invasion), enhanced secretion of proteolytic enzymes needed to degrade the extracellular matrix (ECM) (e.g., MMP2/9 and cathepsin B) and induction of the EMT process. AQPs also enhance cell invasion through a 'rounding' of the cell to enable it to squeeze through the ECM (termed amoeboidal motility). **Figure 2** summarizes the putative role of AQPs in cancer pathogenesis.

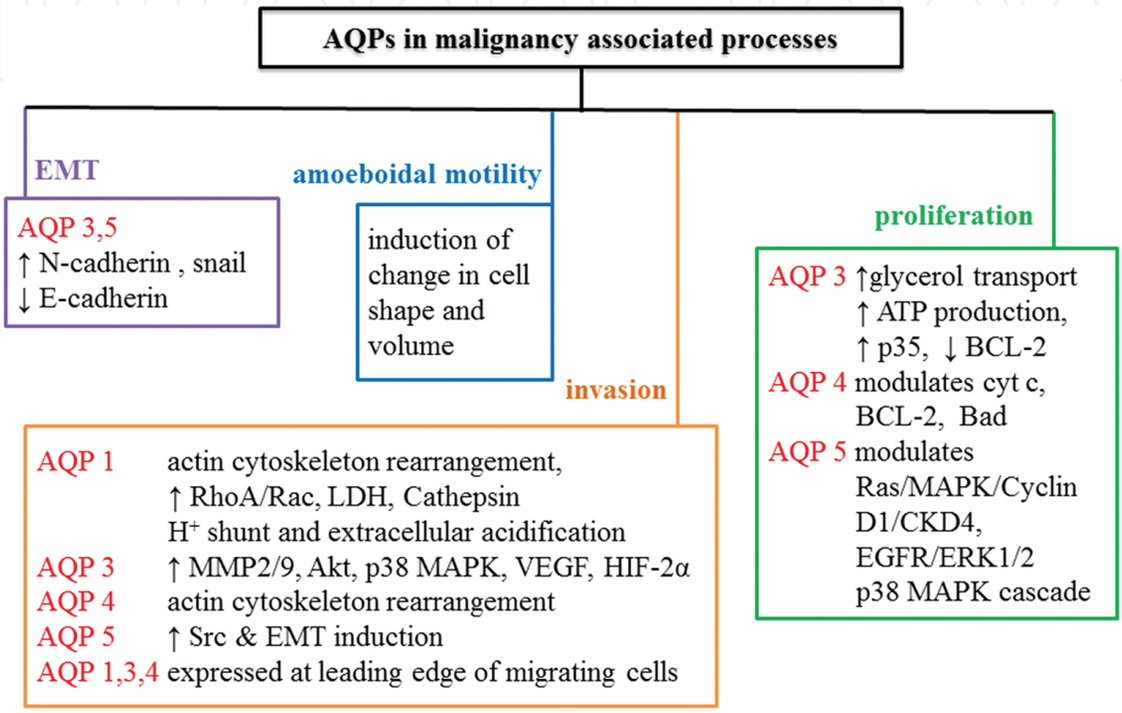

Figure 2. Role of AQPs in cancer pathogenesis. AQPs play an important role in cancer pathogenesis through enhancement of cancer cell proliferation, invasion and induction of epithelial to mesenchymal transition (EMT) as well as induction of amoeboidal motility. The mediators through which each AQP modulates these functions are elaborated in the scheme.

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