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REVIEW

Aquaporins 1, 3 and 5 in Different Tumors, their Expression, Prognosis Value and Role as New Therapeutic Targets

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Abstract

All different types of metabolism of tumors are dependent on the flow of water molecules through the biological membrane, where fluid transfer interceded by aquaporins (AQPs) are the basis means for water entrance into the cells or outside them. Aquaporins play other roles including cellular migration, cellular expansion and cellular adhesion facilitation. Therefore, regulators of AQPs may be useful anticancer agents. Medline, Scopus, Embase, and Web of Sciences were searched. From among the papers found, 106 were related to the subject. All of the examined cancers in relation to AQP1 included adenoid cystic carcinoma, bladder, breast, cervical, colon, colorectal, hepatocellular, lung, ovarian, plural mesothelioma, prostate, renal cell carcinoma and squamous cell carcinoma. All of the studied cancers in relation with AQP3 included gastric, breast, prostate, lung, pancreas, skin, bladder, squamous cell carcinoma, cervical, adenoid cystic carcinoma, colon, colorectal, ovarian, and hepatocellular cancers and with regard to AQP5 were lung, squamous cell carcinoma, ovarian, adenoid cystic carcinoma, breast, colon, colorectal, hepatic, pancreas, gallbladder, prostate, and gastric cancers. Over or under-expression of AQP1, 3 and is exist in the mentioned cancers across different studies. Over-expression of AQP1, AQP3 and AQP5 is clearly associated with carcinogenesis, metastasis, reduced survival rate, lymph node metastasis, poorer prognosis, and cellular migration. Also, cancer treatments in relation to these markers suggest AQP reduction during the treatment.

Keywords Aquaporin · Cancer · Prognosis

Introduction

Cancer, which is a malignant tumor, is a category of diseases that includes irregular cellular development with a possibility of aggression or spreading within various body parts. Cells known as tumor cells may infiltrate the adjacent area where other tissues reside (aggression) or they can relocate to body parts further away (metastasis). All different types of metabolism of tumors are dependent on the flow of water molecules through the biological membrane, where fluid transfer interceded by aquaporins (AQPs) are the basis means for water entrance into the cells or outside them. Thus, aquaporins can play a significant part concerning metastasis, development and angiogenesis of tumors [1]. Aquaporins structure and functionality, their significance in regard to water physiology and solution movement, in addition to evidence support aquaporins as pharmacological targets is well known [2].

AQPs are attractive targets to complement pharmacotherapy for disorders involving improper water motion including kidney and edema diseases particularly tumors [1].

Aquaporins play other roles in addition to the maintenance of water balance, including cellular migration, cellular expansion and cellular adhesion facilitation [3]. Therefore, regulators of AQPs may be useful anticancer agents [4].

Generally, aquaporins are overexpressed by tumor cells, namely aquaporins which are typically seen in origin cells, in addition to AQPs expressed in cellular plasma membrane and cytoplasm. Often, there is a significant association between aquaporins expression and the grade of tumor [3].

AQPs are a family of membrane, small, hydrophobic proteins that transfer water and small solutions e.g. glycerol. AQPs enhance cellular plasma membrane by 5–50 times in comparison to the membranes through which water primarily moves

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through the lipid layer. Thirteen (0–12) AQPs in mammals are expressed by epithelium, endothelium, and other types of cell. AQPs are categorized into two groups: a subgroup including aquaporins 1–2–4-5-8 that are selective water channels and are water penetrable while rejecting small organic and inorganic molecules; and a subgroup including aquaporins 3–7–9-10 that are nonselective water channels, transferring glycerol and potentially other water solutions and water [5].

The first mammalian Aquaporin, Aquaporin 1 (AQP1) was found in erythrocytes and renal tubules and was initially named 'channel-forming integral membrane protein of 28 KDa (CHIP28).' Later, it was discovered that it physiologically covers Choroid network, corneal endothelium, C-fibres processing pain in Spinal cord, and all vascular endothelial cells except central nervous system. The primary function for AQP1 is carrying water. Other functions include nucleotide gated cation channel that is largely activated by cGMP and by cAMP indirectly. The expression of AQP1 has increased in some human cancers like those affecting bile duct, urinary bladder, Cervix, Colon, Nasopharynx, and Prostate [6].

Aquaporin 3 (AQP3) is conveyed within epithelial cells of digestive, respiratory, and urinary tracts as well as in kidneys, epidermis, eyes, brain, pancreas, and prostate. In such cellular types, high water permeability is accredited to physiological function in resorption or secretion. Expression of AQP3 is evident in some human carcinomas including scc, skin, lung adenocarcinoma, kidney carcinoma, and colorectal adenocarcinoma [7].

Aquaporin 5 (AQP5) is a member of the family of small hydrophobic proteins of androgen-regulated integral membrane water channel, regulating homeostasis of cellular water and growth signal. Over the past few decades, overexpression of AQP5 has been associated with several cancers (breast, ovarian, lung, colon, cervical, esophageal, etc) [8].

So far, no systematic review study has been performed for more accurate discovery of the relationship between AQP1, AQP3 as well as AQP5 and tumors. In this review paper, the aim is to investigate the function (expression) of AQPs 1, 3 and 5 in different tumors and their importance in the discovery and prognosis of cancer and their role as new therapeutic targets in biology of cancer.

Materials and Methods

To find the studies related to AQP1, AQP3 and AQP5 across different cancers, a search was performed in February 2019 in the following databases: Medline, scopus, embase, and Web of science. The utilized keywords were AQP1 and AQP3 and AQP5, cancer, neoplasms, carcinoma, and carcinogenesis. From among the papers found, 106 were related to the subject, which were further analyzed.

Result

Tables 1, 2 and 3.

Discussion

In this review study, all of the examined cancers in relation to AQP1 included adenoid cystic carcinoma, bladder, breast, cervical, colon, colorectal, hepatocellular, lung, ovarian, plural mesothelioma, prostate, renal cell carcinoma and squamous cell carcinoma. All of the studied cancers in relation with AQP3 included gastric, breast, prostate, lung, pancreas, skin, bladder, squamous cell carcinoma, cervical, adenoid cystic carcinoma, colon, colorectal, ovarian, and hepatocellular cancers. All of the examined cancers with regard to AQP5 were lung, squamous cell carcinoma, ovarian, adenoid cystic carcinoma, breast, colon, colorectal, hepatic, pancreas, gallbladder, prostate, and gastric cancers.

Table 4 indicates over or under expression of AQP1, AQP3 and AQP5 in the mentioned cancers across different studies.

According to the investigations and the results obtained from the papers, AQP1 increase was associated with worse Prognosis, reduced overall survival, Histologic grade, tumor size, TNM stage, metastasis of lymph nodes, relapse, Distant Metastasis, proliferation, invasion, and transformation of cancer cells, Tumor progression, advanced or metastatic cancer, deeper infiltration, Tumor growth, vascular and Lymphatic-vascular and micro-vascular invasion, invasive phenotype of tumor, shorter DFS, longer overall survival, delayed relapse and death in malignant plural mesothelioma, smaller and low-grade tumors, and lack of micro-vascular invasion in clear-cell RCC. In addition, limited expression of AQP1 was associated with shortened cell life, increased cellular Apoptosis in j82 cells in urinary bladder, decreased progression rate in colorectal cancer, poorer prognosis in clear cell carcinoma, reduced cell migration and invasion, reduced sphere formation, faster relapse, and prognosis in malignant plural mesothelioma [9, 10, 12, 15, 18, 19, 21, 22, 26, 27, 29, 30, 33, 42].

Overexpression of AQP3 was associated with progression of cancer, intensity of metaplasia, strengthening the cellular migration and aggression in cancer cells, poorer prognosis, improved progression free survival (PFS) and cancer specific survival (CSS), elevated self-renewal, metastasis of lymph nodes and remote areas. On the other hand, its under expression was related to impaired proliferation of cancer cells, delayed growth and aggression and migration of cancer cells, worse PFS, and less aggressive characteristics [18, 44, 45, 51, 64, 70, 71, 75, 76].

Overexpression of AQP5 was associated with lymph node metastasis, reduced survival rate, prognosis, facilitated cellular migration, lower disease-free survival, and induction of mucin production. Furthermore, it was also associated with

Table 1 Methods and result of aquaporin 1 expression in different cancer type

Cancer type	Methods	Result
Adenoid Cystic Carcinoma	Quantitative Methylation-Specific PCR, Quantitative RT-PCR [9]	AQP1 expression increase/ AQP1 methylation associated with improved prognosis
Bladder cancer	RT-qPCR, Western blot [10]	Combination of AQP-1 inhibition with MMC treatment could be a promising treatment
Pancreatic ductal adenocarcinoma	IHC, Western blot [11]	Positive AQP1 expressions associated with the tumorigenesis and progression of PDAC
Breast cancer	1.qRT-PCR, IHC, Western blot [12] 2.IHC, PCR, Western blot, Immunofluorescence [13] 3.IHC [14]	1. miR-320 downregulation enhance AQP1 expression, favoring tumor progression 2. cytoplasmic expression of AQP1 promoted tumor progression 3. AQP1 and HIF1 interacted each other in oncogenesis
Cervical Carcinoma	Real-time PCR, Immunofluorescence, IHC [15]	AQP1 expression increase in advanced stage, deeper infiltration, metastatic lymph nodes and larger tumor volume
Colon cancer	1.Quantitative PCR, Western blot, IHC, Immunofluorescence [16] 2.RT-PCR, Immunoblot, Immunofluorescence [17] 3.IHC [18] 4.IHC [19]	1.Treatment with AqB013 reduced migration and invasion of colon cancer cells 2. AQP1 has a role in colon cancer migration and expressed in HT20 cells 3.AQP1 overexpression correlate with lymph node metastasis 4.AQP1 expression as an independent poor prognostic factor
Colorectal cancer	IHC [20]	Expression of AQP1 as a biomarker predictive of response to adjuvant chemotherapy
Hepatocellular carcinoma	IHC [21]	High AQP1 expression and IMD associate with tumor progression and prognosis in HCC
Lung adenocarcinoma	IHC [22]	AQP1 overexpression results in a shorter disease-free survival
Lung Cancer	1.RT-PCR, Western Blot, IHC [23] 2.RT-PCR, Western Blot [24]	1.AQP1 Overexpressed in adenocarcinoma and bronchoalveolar carcinoma 2.Cetuximab and afatinib inhibited the growth and migration of cells and downregulated the AQP1 expression
Ovarian cancer	1.Semi-quantitative IHC [25] 2.IHC [26] 3.IHC, RT-qPCR, Western blot [27]	1.AQP1 have not a significant association with important clinicopathological variables in serous EOC 2.High AQP1 expression was associated with worse OS in MC and EC 3.Downregulation of AQP1 inhibited cell migration and invasion
Malignant pleuralmesothelioma	1.IHC [28] 2..Reverse transcriptase-PCR, Western blot [29] 3.IHC [30]	1.AQP1 overexpression was associated with an increased median OS 2.AQP1 inhibition lowered cell adhesion 3.Expression of AQP1 correlated with prognosis in MM, irrespective of treatment
prostate cancer	1.Western blot, Real-time PCR [31] 2..Immunofluorescence, Flow cytometry [32]	1.Ginsenoside Rg3 inhibited expression of AQP1 and cell migration 2.AQP1 could be induced by hypoxia at transcription level, and regulation of AQP1 in PC-3 M cells is dependent on calcium, PKC and p38 MAPK and low oxygen tension
Renal cell carcinoma	1.Real-time quantitative PCR [33] 2.Western blot [34] 3.Western blot [35] 4.Western blot [36] 5.Elisa [37] 6.Western blot [38] 7.Western blot [39]	1.AQP1 shows RCC subtype-specific expression, and its expression level associate with prognosis 2.Urinary AQP1 able to identify patients with kidney cancer 3.AQP1 increase in patients with clear cell and papillary renal cell carcinoma 4.Urine AQP1 had specificity and sensitivity for RCC 5.Urine AQP1 had specificity and sensitivity for RCC 6.AQP1 in fresh urine is useful as a diagnostic tool for detecting RCC 7.Under-expression of AQP1 RCC tissue compared to adjacent normal cortex
Squamous cell carcinoma	1.IHC [40] 2.IHC [41]	1.AQP1 is a marker of a subgroup of aggressive basaloid-like SCC 2.Expression of AQP1 is related to a poor prognosis
Melanoma	1.IHC [42] 2.IHC [43]	1.BRAF V600 mutations significantly associate with AQP1 expression 2.AQP1 expression could be a prognostic marker of brain metastatic potential of melanoma

AQP1 aquaporin 1, *IHC* immunohistochemistry, *MMC* mitomycin c, *PDAC* pancreatic ductal adenocarcinoma, *HIF* hypoxia inducible factor, *IMD* intratumoral microvessel density, *HCC* hepatocellular carcinoma, *EOC* epithelial ovarian cancer, *OS* overall survival, *MC* mucinous carcinoma, *EC* endometrioid carcinoma, *MM* malignant mesothelioma, *Rg3* ginsenoside Rg3, *MAPK* mitogen activated protein kinase, *PKC* protein kinase c, *RCC* renal cell carcinoma, *SCC* squamous cell carcinoma

Table 2 Methods and result of aquaporin 3 expression in different cancer type

Cancer type	Methods	Result
Gastric cancer	1.IHC,RT-qPCR, Western blot, Immunofluorescence [44] 2.IHC,RT-qPCR, Western blot, Immunofluorescence [45] 3.IHC [46] 4.IHC [47] 5.IHC, Western blot, Reverse transcriptase PCR [48] 6.Real-time PCR, Western blot [49] 7.IHC, Western blot, RT-qPCR [50] 8.Western blot, Real-time PCR [51] 9.qRT-PCR, miRNA RT-PCR, Western blot [52] 10.Western blot, RT-qPCR [53]	1.AQP3 promoted stem-like properties of human GC cells 2.Upregulation of AQP3 associate with EMT-related proteins which correlated with poor prognosis for GC 3.AQP3 provide a strategy for screening at-risk candidates with GIM 4.AQP3 play an important role in gastric carcinogenesis from GIM 5.C-Met expression in GC tissues was associated with AQP3 expression 6.AQP3 regulate MMPs proteins expression 7.H.pylori infection induce migration and proliferation of GC cells via AQP3 8.AQP3 inhibition induce glycerol absent and impaired lipid generation in cancer cells 9.AQP3 involve in the regulation of cell proliferation, migration and invasion by miR-874 10.HG promote migration and proliferation of GC cells via AQP3
Breast cancer	1.IHC [54] 2.Western blot [55] 3.IHC [56] 4..Immunofluorescence, Immunoblot, RT-PCR [57] 5.RT-qPCR, Western blot [58]	1.AQP3 over-expression associate with worse prognosis for HER2-over- expressing EBC 2.AQP3 require for FGF-2-induced cell migration 3.Upregulation of AQP3 result in cell migration and invasion in ER-positive breast cancer cells 4.Overexpressing AQP3 increase H2O2 uptake and cell migration upon CXCL12 stimulation 5.Silencing AQP3 mRNA cause a reduction in cellular migration
Prostate cancer	1.IHC, Western blot [59] 2.RT-qPCR, Western blot [60] 3.Western blot, Reverse transcriptase-qPCR [61] 4.RT-PCR, Immunocytochemistry, IHC [62]	1.AQP3 expresse in the epithelial area of the prostate in prostatic hyperplasia and cytoplasm of the epithelial cells in prostate cancer 2.Inhibition of AQP3 increase the sensitivity of prostate cancer cells to freezing 3.AQP3 upregulate the expression and secretion of MMP-3 via the ERK pathway 4.AQP3 mRNA expresse in normal and cancerous epithelia of human prostate tissues
Lung cancer	1.qRT-PCR, Western blot [63] 2.qRT-PCR [64]	1.Inhibition of AQP3 retarded the growth and invasiveness of XWLC-05 lung cancer cells 2.AQP3 knockdown retarded the growth of NSCLC cells
Pancreatic cancer	1.IHC [65] 2.IHC,Western blot [11] 3.Western blot [66] 4.Western blot [67]	1.AQP3 involve in PDA development 2. Positive AQP3 expressions associate with the tumorigenesis and progression of PDAC 3.AQP3 promote tumor growth of pancreatic cancer cells by activating Mtor signaling pathway 4.Expression of AQP3 up-regulate by EGF in MPC-83 pancreatic cancer cells
Nonmelanoma skin cancer	1.IHC [68] 2.IHC [69]	1.AQP3 have a role in the differentiation of tumors more than proliferation 2.AQP3 play a role in NMSC pathogenesis
Urothelial bladder cancer	IHC [70]	Loss of AQP3 expression play a key role in disease progression and was associated with worse PFS
Muscle-invasive bladder cancer	IHC [71]	High expression of AQP3 was associated with a significant improved PFS and CSS
Squamous cell carcinoma	1.IHC [72] 2.RT-PCR, Western blot [73] 3..IHC, Western blot [74]	1.AQP3 play an important role in cell growth 2.Reduced AQP3 in hypoxic conditions indicated less aggressive OSCC properties 3.Inhibition of AQP3 function via the use of specific siRNA implied a novel role in the treatment of SCC

Table 2 (continued)

Cancer type	Methods	Result
Adenoid cystic carcinoma	IHC [72]	There is no reports on the expression of AQP3 on malignant salivary gland tumors
Cervical carcinoma	1.Real-time PCR, Immunofluorescent, IHC [75] 2.Real-time PCR, Immunofluorescent, IHC [15]	1.AQP3 participate in the initiation and progression of cervical carcinoma 2.AQP3 expression increased in advanced stage, deeper infiltration, metastatic lymph nodes and larger tumor volume
Colorectal carcinoma	IHC, Western blot [76]	AQP3 overexpression facilitate colorectal carcinoma cell migration
Colon cancer	IHC [18]	A significant correlation was found between AQP3 expression and lymph node metastasis
Ovarian cancer	1.RT-PCR [77] 2.Western blot [78]	1.AQPs associate with chemotherapy sensitivity of ovarian cancer 2. Curcumin inhibited EGF-induced upregulation of AQP3 and cell migration
Hepatocellular carcinoma	1.IHC, Western blot, RT-PCR [79] 2.IHC, Western blot, qRT-PCR [80]	1.Auphen and dbcAMP inhibit HCC development and could be considered targets for HCC diagnosis and therapy 2. AQP3 up regulate in HCC and promoted the proliferation and migration of HCC cells

AQP3 aquaporin 3, *IHC* immunohistochemistry, *GC* gastric carcinoma, *EMT* epithelial mesenchymal transition, *GIM* gastric intestinal metaplasia, *MMPs* matrix metalloproteinases, *HG* hyperglycemia, *EBC* early breast cancer, *FGF-2* fibroblast growth factor-2, *ER* estrogen receptor, *ERK* extracellular signal-regulated kinase, *PDA* pancreatic ductal adenocarcinoma, *EGF* epidermal growth factor, *NMSC* nonmelanoma skin cancer, *PFS* progression-free survival, *CSS* cancer specific survival, *HCC* hepatocellular carcinoma, *SCC* squamous cell carcinoma

the histologic type and TNM stage, depth of advanced aggression, and remote metastasis. Overexpression affected cellular growth of proliferating versions, and could be used as a useful biomarker for detecting the primary stages of the disease. On the other hand, under expression of AQP5 was related to inhibited adhesion and cellular growth, inhibited cellular proliferation and migration, and inhibited tumor metastasis, and had anticancer effects [18, 72, 83–85, 94, 97].

Aquaporin 5 can be a beneficial specific and sensitive barometer for primary PDA stages. On the other hand, it seems that AQP3 expression is associated with late and more aggressive disease stages [65].

The suggested mechanism in migration of tumor cells via AQP1 is inducing water flow across Plasma Membrane by AQP1 in response to Osmotic Gradient, and is possible by actin depolymerization and active insertion of actively dissolved materials in edges of migrating cells. Inserting water via AQP1 can add to hydrostatic pressure and consequently, to local development of Plasma Membrane and then actin repolymerization for fixing protrusion of plasma membrane. Up-regulation of Aquaporin 1 around astrocytoma where infiltration of tumor cells occurs is in response to low expression in necrotic center, indicating a relation between AQP1 and tumor Angiogenesis [6].

The fundamental process of involvement of aquaporin 3 and aquaporin 5 concerning cancer progression remain controversial. Aquaporin 5 is conveyed in apical membrane of tumor ductal cells, expediting water transfers via cellular membranes, required for the creation of lamelliopodium and in turn for cellular relocation and proliferation. Moreover, glycerol transfer via aquaporin 3 may be applied for biosynthesis of lipids and ATP creation, supporting procedures such as relocation and multiplication. Also, extracellular H2O2 absorption through aquaporin 3 or aquaporin 5 can modify intracellular signaling pathways [65].

The Importance of Cellular and Molecular Markers in the Diagnosis and Treatment of Cancers

It has well been demonstrated that the tumor development, expansion, aggression, and metastasis are dependent on the metabolism and microenvironment of tumor. AQPs play a significant role in balancing tissue water as a reaction towards osmotic gradients, which is a prerequisite to maintaining cellular function including malignant cells. Furthermore, aquaporins may enable tumor development, metastasis and local infiltration, through strengthening cellular relocation and angiogenesis in regard to chemotactic stimulus [3, 107].

AQPs may enhance cell-matrix attachment, which is important for the spread and cellular migration of tumor. Also, AQPs are associated with tumor multiplication through enabling glycerol uptake that is a requirement for cellular biosynthesis and thus cellular segregation. Thus, the expression of aquaporin may be useful for high metabolic turnover or

Table 3 Methods and result of aquaporin 5 expression in different cancer type

Cancer type	Methods	Result
Lung cancer	1.IHC, Western blot, Real-time RT-PCR [81] 2.IHC [82] 3.IHC [83] 4.IHC [84]	1. AQP5 expression up-regulate in invading lung cancer cell 2.AQP5 expression associate with DFS in ADC of the lung and tumor grade of NSCLC 3.AQP5 facilitate incidence, progression and metastasis of NSCLC 4.AQP5 associate with worse prognosis
Squamous cell carcinoma	1.IHC [85] 2.IHC, Western blot, Real-time quantitative RT-PCR [86] 3.IHC [40] 4.IHC, Western blot [72]	1.High expression of AQP5 is an independent poor prognostic factor in ESCC patients 2.AQP5 expression affect cell proliferation, survival and prognosis of ESCC patients 3.AQP5 expression associate with the absence of Bcl-2 and p16 expression 4.AQP5 play an important role in cell growth
Adenoid cystic carcinoma	IHC, Western blot [72]	Positive staining of AQP5 is observe in non-tumor area of ACC tissues
Ovarian cancer	1.IHC, Western blot, RT-PCR [87] 2.Western blot, RT-PCR [88] 3.IHC, Western blot [89] 4.IHC [26] 5.IHC, Western blot, RT-PCR [90] 6.Western blot, RT-qPCR [91]	1.EGCG inhibit the proliferation and induce the apoptosis of ovarian cancer SKOV3 cells 2.Proliferation inhibition of cisplatin is related with AQP5 expression 3.Topotecan down-regulate the expression of AQP5 and NF-κB 4.High AQP5 expression correlate with poorer prognosis in serous carcinoma 5.Overexpression of AQP5 play an important role in tumorigenesis of epithelial ovarian tumors 6.Effect of hyperosmotic stress on sensitivity to CDDP associat with AQP5 expression in ovarian tumors
Breast cancer	1.IHC, RT-PCR, Immunoblot [92] 2.IHC [93] 3.IHC [94] 4.IHC [95]	1.AQP5 overexpression play a role in cell growth and metastasis 2. Rac1 is a potential downstream signaling partner of AQP5 in vivo 3.AQP5 expression is a prognostic marker in EBC 4.Expression of AQP5 is independent poor prognostic factor for OS and DFS
Lung adenocarcinoma	1.Western blot [96] 2..IHC, Western blot, Real-time RT-PCR [97]	1.NFAT5 play important role in proliferation and migration of lung adenocarcinoma cells 2.Mucin production induced by AQP5 expression play important role in enhanced metastasis
Colorectal cancer	1.Western blot, RT-PCR [98] 2.Western blot, RT-PCR [99]	1.Multiple AQP expression is advantageous to tumorigenesis 2.CE serve as a promising drug for the treatment of CRC metastasis
Colon cancer	1.IHC [18] 2.Western blot, Quantitative real-time RT-PCR [100]	1.AQP5 overexpression correlate with lymph node metastasis 2.AQP5-P38 MAPK pathway represent a potential drug target to improve drug resistance of CC cells
Hepatocellular carcinoma	1.IHC [101] 2.Western blot, qRT-PCR [102] 3.Western blot, Immunofluorescent [103]	1.Aberrant expression of AQP5 relates to tumor progression and prognosis in HCC 2.AQP5 down-regulation inhibite HCC metastasis and EMT via inactivation of the NF-κB signaling pathway 3.Heat shock and AQP5 knockdown exert similar anticancer effects
Pancreatic ductal adenocarcinoma	IHC [65]	AQP5 involve in PDA development
Prostate cancer	IHC [104]	AQP5 could be both overexpressed and lost in subgroups of prostate cancers and link to unfavorable outcome
Gastric cancer	1.IHC, Western blot, Immunocytochemistry [105] 2.IHC, Western blot, RT-PCR [106]	1.Upregulation of AQP5 involves in differentiation of gastric cancer cells 2.AQP5 play an important role in the tumorigenesis and progression of GC

AQP5 aquaporin 5, *IHC* immunohistochemistry, *ADC* adenocarcinoma, *NSCLC* non-small cell lung cancer, *ACC* adenoid cystic carcinoma, *CDDP* cisplatin, *EBC* early breast cancer, *OS* overall survival, *DFS* disease free survival, *CE* cairicoside E, *CRC* colorectal cancer, *CC* colon cancer, *MAPK* mitogen-activated protein kinase, *HCC* hepatocellular carcinoma, *EMT* epithelial mesenchymal transition, *GC* gastric cancer, *SQCC* squamous cell carcinoma, *EGCG* epigallocatechin gallate

Table 4 Over or under expression of AQP1, AQP3 and AQP5 in different cancers

Cancer type	Number of AQP1 articles with result of		Number of AQP3 articles with result of		Number of AQP5 articles with result of	
Gastric	↑Exp	–	↑Exp	10	↑Exp	2
	↓Exp	–	↓Exp	–	↓Exp	–
Breast	↑Exp	3	↑Exp	5	↑Exp	4
	↓Exp	–	↓Exp	–	↓Exp	–
Panceratic	↑Exp	1	↑Exp	4	↑Exp	1
	↓Exp	–	↓Exp	–	↓Exp	–
SCC	↑Exp	2	↑Exp	3	↑Exp	4
	↓Exp	–	↓Exp	–	↓Exp	–
Colon	↑Exp	4	↑Exp	1	↑Exp	2
	↓Exp	–	↓Exp	–	↓Exp	–
Colorectal	↑Exp	1	↑Exp	1	↑Exp	2
	↓Exp	–	↓Exp	–	↓Exp	–
Ovarian	↑Exp	3	↑Exp	2	↑Exp	3
	↓Exp	–	↓Exp	–	↓Exp	–
Hepatocellular	↑Exp	1	↑Exp	2	↑Exp	2
	↓Exp	–	↓Exp	–	↓Exp	–
Lung	↑Exp	2	↑Exp	–	↑Exp	6
	↓Exp	–	↓Exp	–	↓Exp	–
Prostate	↑Exp	1	↑Exp	4	–	–
	↓Exp	–	↓Exp	–	–	–
BCC	↑Exp	–	↑Exp	1	–	–
	↓Exp	–	↓Exp	–	–	–
Cervical	↑Exp	1	↑Exp	2	–	–
	↓Exp	–	↓Exp	–	–	–
Adenoid cystic carcinoma	↑Exp	1	–	–	–	–
	↓Exp	–	–	–	–	–
Plural mesothelioma	↑Exp	2	–	–	–	–
	↓Exp	–	–	–	–	–
Renal	↑Exp	6	–	–	–	–
	↓Exp	–	–	–	–	–
Melanoma	↑Exp	2	–	–	–	–
	↓Exp	–	–	–	–	–

special metabolic pathways of tumor required for malignant cells to survive [4].

It is possible to use miRNA as either tumor suppressors or as oncogenes in many forms of cancer through adjusting the suppression of translation or targeting the reduction of mRNA. miRNA expression has decreased in breast cancer, colon cancer and AML and inhibit Cell proliferation in prostate cancer. miR-320 expression is possibly correlated with survival without relapse in colon cancer [12]. Tumors with great AQP1 expressions displayed loss of E-cadherin and increased expression of vimentin, suggesting that AQP1 might play a role in tumor progression via epithelial mesenchymal transition [22].

Resistance to Apoptosis is considered as a part of background mechanism for proliferation of cells expressing AQP1. The potential downsream effectors along the signaling that contribute to tumor progression are TGF-β, FAK, β-catenin, RhoA, and Rac [26]. Any decrease in Aquaporin 1 with siRNA leads to increase in cell TE5, TE15, and ESCC except sub-phase G1. Moreover, ESCC cells free of AQP1 are induced towards Apoptosis, indicating that AQP1 can inhibit Apoptosis. AQP1 is often found in Cytoplasm of TE5 and TE15 cells although it can be found in membrane of Cell nucleus of KYSE70. Several molecules such as E-cadherin, β-catenin, ZO-1, ZO-2, and claudin-1 affect tumor progression due to their changed localization [41].

Overexpression of AQP5 is associated with increased proliferation of Ki67 cellular marker. Expression of AQP3 and AQP5 grows by EGFR signaling pathway (epidermal growth factor receptor). Overexpression of EGFR is commonly found

in tumors such as pancreatic cancer, whose activation results in transcription of the genes contributing to the development and multiplication. The expression of EGFR is related to weak prognosis and enhanced aggression in PDA. Furthermore, aquaporin 3 and aquaporin 5 are also involved in epithelial mesenchymal transition (EMT) [45, 65], a procedure in malignant tumors participating in aggression and metastasis, through which the cells are deprived of their epithelial features, namely attachment to the cell and immobility, while obtaining migration mesenchymal characteristics. A large number of studies indicate that AQPs including aquaporin 1, aquaporin 3 and aquaporin 5 have been conveyed in various tumors, and can be used as a valuable biomarker in cancer diagnosis [65].

Blocking AQPs can inhibit angiogenesis as well as growth and metastasis of tumors. New therapeutic approaches may be developed by antagonizing their biological activity [108].

In the course of expression, the epithelial adhesion molecules expression e.g. E-cadherin (E-cad) diminish, while mesenchymal cellular markers such as vimentin grow.

Overexpression of AQP5 enhances pseudo-mesenchymal phototype as well as Epithelial mesenchymal transition (EMT) mechanism in SW480 and HCT-116 along with low metastasis of CRC and HT-29 cells. Conversely, when aquaporin 5 is off, it results in EMT inhibition in SW40 and HCT-29 cells. It is proven that aquaporin 5 is associated with cellular movement and aggression. There is also evidence suggesting that AQP5 can induce EMT process, thereby enhancing migration and aggression of CRC cell [92].

EMT is modulated by intracellular and extracellular signals. In particular, TGF-B is an extracellular cytokine which is a vital instigator of EMT, called cancer metastasis inducer. TGF-B1 enhances expression of AQP5 and activates ETM. Cairicoside E (CE) inhibits migration and aggression by inducing TGF-B1, and reverses up-regulation of aquaporin 5 and EMT. TGFB has been known as an EMT inducer through smads signaling. In the TGFB/smad signaling pathway, TGFB attaches to the cellular membrane autonomous receptor, TGFB R1/2, and induces signaling cascade via phosphorylating smad2/3. Phosphorylating smad2/3 creates a set with smad4, displaces from cytoplasm to the nucleus in order to control the transcription of the target gene which leads to EMT stimulation.

The up-regulation of AQP5 enhances p-smad2/3 expression, whilst deactivation of aquaporin 5 represses p-smad2/3 levels. It is suggested that AQP5 enhances EMT through activating smad2/3. Moreover, once aquaporin 5 is turned off, CE does not have a considerable impact on initiation of smad2/3 and EMT induced by TGFB1. AQP5 regulation in repressing EMT by CE depends on repressing p-smad2/3 [99].

Thus, according to the collected data, overexpression of AQP1, AQP3 and AQP5 is clearly associated with carcinogenesis, metastasis, reduced survival rate, lymph node metastasis, poorer prognosis, and cellular migration.

In the studies conducted on the effect of cancer treatments in relation to these markers, all suggest AQP reduction during the treatment.

Conclusion

According to this review of about 106 papers, it can be concluded that definitely AQP1, AQP3 and AQP5 in different epithelial and mesenchymal tissues are associated with the course of carcinogenesis and aggravation of cancer prognosis.

Compliance with Ethical Standards

Conflicts of Interest There was no conflict of interest for this study.

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