REVIEW ARTICLE

Aquaporin: From a mere Transporter to Biomarker of Oral Cancer: A Review

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Abstract

Introduction: Aquaporins (AQPs) are membrane proteins that are involved in the bidirectional transport of water and in some cases small solutes such as glycerol across the cell membrane. Thirteen types of AQPs have been identified so far. AQPs expression have been found in more than 20 types of human cancer, of which oral cancer is one. The important role of aquaporins have received more and more attention in the recent years. Studies show that AQPs could play various roles in tumor-associated edema, tumor cell proliferation, migration and tumor angiogenesis in solid as well as hematological tumors.

Objectives: To assess the role of aquaporin in oral carcinogenesis.

Materials and Methods: A thorough search was done in Google scholar and Pubmed on the role of aquaporin in carcinogenesis; in particular in oral cancer, which were written in English language and about 60 articles were retrieved of which 41 were selected and reviewed.

Conclusion: The paper reviewed the current knowledge regarding AQP expression in oral cancer and how AQP contributes to cancer progression via signaling that modulates cellular mechanisms. Therapeutic targeting of aquaporins may thus be advantageous for oral cancer therapy.

Key words: Aquaporin, Cancer, Oral cancer, Biomarker

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Introduction

Aquaporins (AQPs) are a large family of water channel proteins (monomer size ~30 kDa) that are distributed in various human tissues[1]. It has a very important role in maintaining the electrolyte-water balance of the extracellular environment. These previously unrevealed water channels were eventually discovered by chance in 1992 by Peter Agre and his colleagues, at Johns Hopkins University in Baltimore, while they were working on red blood cell membrane proteins. They named it as CHIP28 which is now known as aquaporin1. Agre received the Nobel Prize in Chemistry in the year 2003 for this great discovery[2]. So far thirteen members of AQPs have been identified[3].

Several studies have investigated the role of aquaporin in cancer involving brain, skin, gastrointestine, lung and also oral cavity[4,5]. About 2% to 4% of all cancer cases accounts for oral cancer and 90% of all oral malignancies are diagnosed as Oral Squamous Cell Carcinoma (OSCC). Even after doing multimodal therapy, the 5-year survival rates of OSCC patients have not crossed 50 % for the past 4 decades. Therefore, improvement in prevention and control of oral cancer is critically important[6]. To achieve this, new biomarkers need to be discovered. According to literature, AQPs have involvement in carcinogenesis. It is expressed in both cell membrane and cytoplasm in tumor cells and its expression is related to tumor grade, suggesting a potential role as a biomarker of oral carcinogenesis[7].

Structure of Aquaporin

The structure of AQP has been studied with the help of the processes such as mutagenesis, epitope tagging, spectroscopy and freeze-fracture electron microscopy methods[8]. The studies of molecular recombinants suggested an hourglass model for aquaporin structure[9]. Hydropathy analysis predicted that AQP1 contains six membrane-spanning segments having five connecting loops (A–E) with N and C termini exposed to cytoplasm. This membrane topology was further confirmed with the help of functional epitope-scanning mutants. Each AQP1 repeat contains the highly conserved asparagine–proline–alanine (NPA) motif. The NPA motifs are located in the cytoplasmic loop B and the extracellular loop E. Since these two loops are rather hydrophobic in nature it was suspected that they were structural components of the aqueous pore[10] (Figure 1). These AQP monomers contain independent water pores and are assembled as homotetramers to

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contribute to the fluid transport (Figure 2).

Types of Aquaporin

Thirteen members of aquaporin have been identified till date, of which AQP1, AQP2, AQP4, AQP5 and AQP8 transports only water, whereas AQP3, AQP7, AQP9 and AQP10 in addition to water, transport small solutes such as glycerol and are called as Aquaglyceroporins[11]. It is found that certain AQPs are permeable to ion and gas flow (e.g., O2, CO2, or nitric oxide) for example AQP1, AQP4, AQP5[12]. Most of the AQPs are situated in the cell membrane to help in maintaining the osmotic pressure- gradient dependent-water transport, but AQP11 and AQP12 are super- aquaporins which are expressed in cytoplasm to control the water transport intracellularly, volume of organelles or intra-vesicular homeostasis[13].

Distribution and functions of Aquaporin

AQPs are distributed throughout human tissues of which majority are located in epithelium, endothelium, astrocytes, erythrocytes, skeletal muscles and adipocytes[14]. Expression of AQP0 in human lens has been shown to have involvement in its transparency and homeostasis[15]. AQP1 is found in the blood vessels, kidney proximal tubules, eye, and ear. In kidney AQP2 and AQP6 have urinary concentration regulatory function[16]. Human skin expresses AQP3 in stratum corneum layer[17]. AQP4 is present in the brain astrocytes, eye, ear, skeletal muscle, stomach parietal cells, and kidney collecting ducts. AQP5 is expressed in GIT, secretory glands and lungs whereas AQP7 is seen in skeletal muscle, kidney, heart and adipocytes[18]. AQP8 is expressed in the kidney, testis, and liver. AQP9 is present in the liver and leukocytes. AQP10 is expressed in the intestine. The main function of aquaporin is transcellular/ transepithelial water movement, transport of fluid and cell migration[19]. They have many important biological roles also, which have been implicated in several pathophysiological conditions such as urine concentration, skin moisturization, fat metabolism, brain water homeostasis and exocrine gland secretion[20].

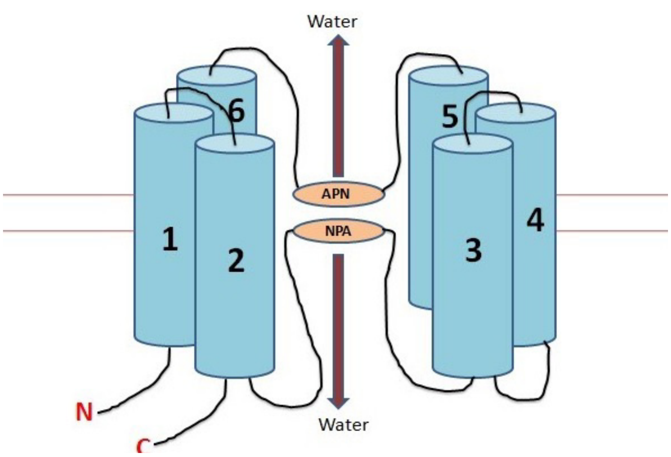

Fig 1: Structure of AQP with six membrane-spanning α-helical domains and conserved NPA motifs

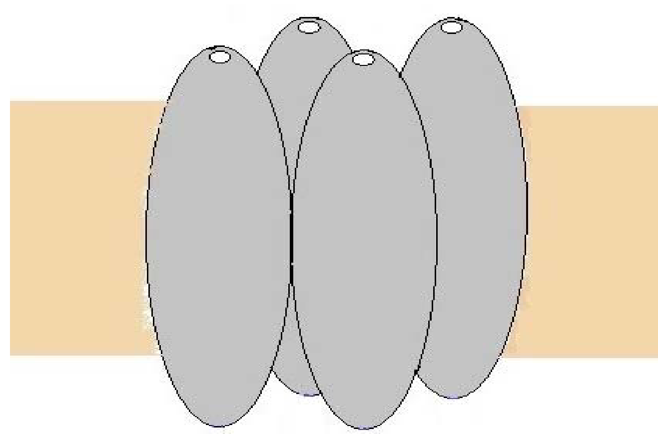

Fig. 2: AQP monomers assemble as homotetramers with independent water pores.

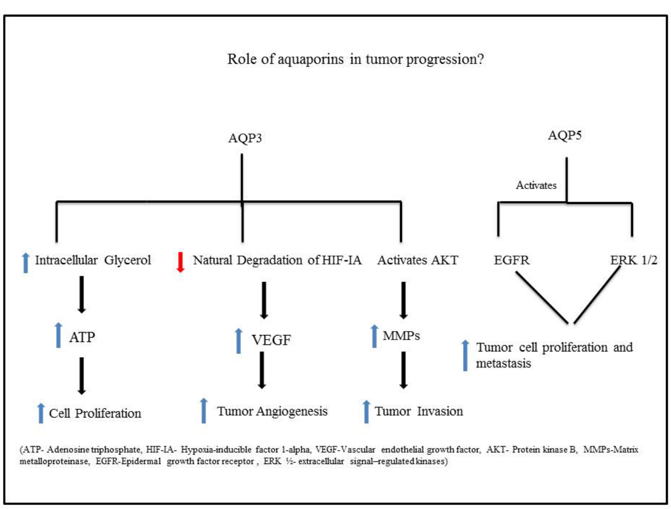

Fig. 3: Mechanism by which AQP3 and AQP5 helps in tumor progression

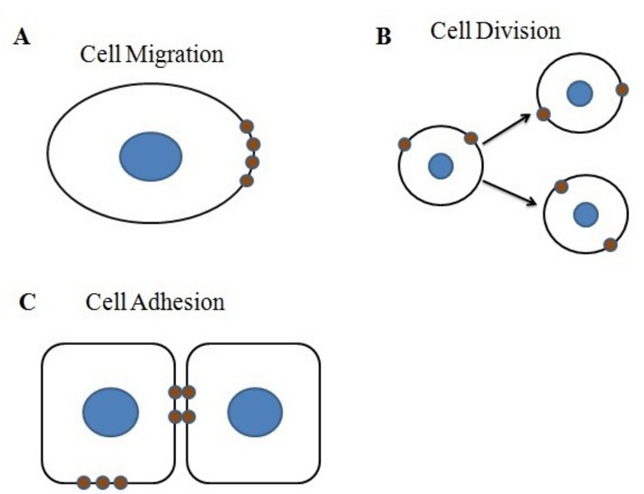

Fig. 4: Role of aquaporin in cancer A. Cell migration-AQP concentrates to the leading end of the cell. B. Cell proliferation-Aquaglyceroporin helps in cell proliferation C. Cell adhesion- AQPs helps in cell adhesion

Aquaporin in Cancers

Aquaporins are found to have numerous roles in many cancers. The expression of AQP in cancer cells lack tumor- specific property that is, one type can have expression in many cancers and one cancer can have different AQPs involvement. AQP1 is up regulated in lung, breast, ovarian, brain and colorectal cancers[21, 22]. AQP3 is overexpressed in cutaneous, renal, pulmonary, hepatocellular, esophageal and oral squamous cancers[23, 24]. AQP4 expression is increased in lung, thyroid or brain cancers[25, 26]. The expression of AQP5 is increased in chronic myelogenous leukemia (CML), ovarian, lung, stomach, oral and colorectal cancers[27, 28]. AQP7 is overexpressed in thyroid cancer, whereas AQP9 in ovarian and brain cancers[29, 30]. But AQP8 is found to have a down expression in colorectal and hepatocellular cancers[31].

Expression of Aquaporin in Oral Cancers

The expression of AQP on tumor cells and its role in oral cancer has been studied in recent researches. Mainly AQP3 and AQP5 have been found to show expression in oral squamous cell carcinoma[32, 33] (Figure 3). Ishimoto et al and Kusayama et al have shown that there is overexpression of AQP3 and AQP5 in human primary squamous cell carcinomas such as esophageal and lingual cancers and implied an important role of AQP3 in cell growth and proliferation. In their studies they have reported that AQP3 suppression can inhibit cell growth in tumor cells of squamous cell carcinoma[33, 34]. Kusayama et al have demonstrated that the action of AQP3 in squamous cell carcinoma cell adhesion and survival is more than its function in normal cells[34]. Liu et al. study showed overexpression of AQP3 and AQP5 in esophageal squamous cell carcinoma patients using immunohistochemical staining. Their results significantly correlate AQP's action in advanced invasion depth, aggressive lymph node status, and positive distant metastasis[35]. All these studies show the upregulation of aquaporin in cancer.

Contrary to this, in a study done by Matsuo and Kawano, investigated the immunohistochemical expression of AQP3 in OSCC and correlated it with lymph node metastasis. They demonstrated that the AQP3 expression is decreased with more aggressive tumor behavior and increased the incidence of lymphatic metastasis[36].

AQPs have multifactorial action in oral cancer progression. In cancer cells AQP's expression is shown to have a good correlation with tumor types, tumor-associated edema and metastatic potential[37]. AQPs also influence cell migration, cell proliferation and cell adhesion (Figure 4). All these observations are shedding light on the biomarker role of AQP in the treatment of oral squamous cell carcinoma. The increased rate of AQP expression in OSCC may be useful as one of the methods of early detection which is the most important step in increasing the survival rate of patients.

Future Applications of Aquaporin

Aquaporins play many roles in normal cells as well as in cancer cells. It is involved in tumor cell proliferation, migration, angiogenesis and tumor- associated edema[38]. Identifying aquaporin function is important for assessing and screening for new activity modulators that can help in the development of efficient medicines[39]. AQPs are attractive targets for the development of novel drug therapies especially tumors[40]. The development of gold-based compounds as selective inhibitors of aquaglyceroporin isoforms may provide new chemical tools for therapeutic applications of aquaporin, especially in cancer[41]. However, more researches and studies should be done to clearly understand the role of AQP in oral cancer.

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