Aquaporin 3 Expression Pattern in Gastric Diseases and its significance

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Research

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Abstract

Background Aquaporin 3(AQP3) has been implicated in gastric intestinal metaplasia and gastric cancer, and considered as a biomarker to improve treatment strategy. Accumulating evidence suggests that AQP3 is involved in the gastric carcinogenesis and the disease progression. However, whether AQP3 is involved in the transformation from gastritis to gastric cancer remain elusive. In this study, we intended to realized the expression pattern and its significance of AQP3 in different gastric diseases. Methods A total of 101 patients diagnosed with gastric diseases were included in the study. A gastric tissue biopsy was taken from the gastric antrum during endoscopic examination. Expression of AQP3 protein is determined by immunohistochemistry using polyclonal rabbit anti-AQP3 antibody. Percentage of positive cells and staining intensity were counted and measured. Results The frequency of AQP3 positivity was similar between the disease types of chronic gastritis, gastric ulcer, gastric erosion, and atrophic gastritis, whereas the frequency of AQP3 positivity was significantly higher in patients with gastric intestinal metaplasia□gastric dysplasia □gastric polyps and intestinal-type gastric adenocarcinoma than that in patients with gastritis, gastric ulcer, gastric erosion, or atrophic gastritis($p<0.0001$, $p=0.001$, $p=0.006$, $p=0.0009$, respectively), especially in the patients with hyperplastic polyps ($p<0.0001$). Conclusion The frequency of AQP3 positivity was significantly higher in patients with gastric intestinal metaplasia, gastric dysplasia, and gastric adenocarcinoma, and the frequency between them was similar, suggesting that AQP3 expression is peaked at the stage of gastric intestinal metaplasia, which further confirmed that gastric intestinal metaplasia is a pivotal progression in gastric carcinogenesis pathologically. Interestingly, it is the first time to report AQP3 positive expression in patients with gastric polyps. In short, AQP3 is involved in the progression from gastritis to gastric adenocarcinoma, and might be a potential biomarker to improve the treatment strategy of gastric cancer.

Background

Aquaporins (AQPs) are a group of transmembrane proteins that facilitate transport of water and certain small solutes across plasma membrane following an osmotic gradient [1]. AQPs are expressed in various tissues including the gastrointestinal tract and play important role in transporting the transepithelial fluid in the stomach and intestine and maintain water homeostasis in the gastrointestinal tract [2, 3]. Dysregulation of AQPs could contribute to the pathogenesis of gastrointestinal disorders, such as gastritis and gastric cancer [4–6]. AQP3 is one of the member of AQPs. Accumulating evidence suggests that AQP3 is involved in the gastric carcinogenesis and the disease progression [5, 6]. Increased expression of AQP3 has been found in more than 70% patients with gastric adenocarcinoma. In addition, the AQP3 expression levels are correlated with histological classification, lymph node metastasis, lymphovascular invasion and survival rate, suggesting that increased expression of AQP3 plays an important role in the disease progression [7–9].

Although the underlying mechanism remains elusive, several studies identified molecular pathways that are relevant to AQP3 expression. Earlier studies showed that AQP3 overexpression can be induced by c-Met through ERK signal pathway [8], which was involved in the gastric carcinogenesis, appeared to

stimulate epithelial-messenchymal transition in gastric cancer through PI3K/AKT signaling patway [10], and upregulated CD44 expression through Wnt/GSK-3β/β-catenin signaling pathway and promoted the stem-like properties of cancer cells in gastric cancer [11]. Previous studies showed that gastric intestinal metaplasia(GIM) is a pivotal step in gastric carcinogenesis and AQP3 expression may be used as a potential biomarker for the diagnosis of GIM and involved in the transformation from GIM into gastric cancer [12–18].

It is known that initiation and progression of gastric cancer is a multistep and multi-factorial processes involving various genetic and molecular alterations [19–21]. Better understanding the processes of gastric carcinogenesis and the disease progression will provide more opportunities to develop novel therapies to further improve survival rate of gastric cancer, as well as novel biomarkers for early diagnosis. In the present study, we investigated AQP3 expression pattern in gastric tissues that were collected from patients with different type of gastric diseases including gastritis, erosion, gastric ulcer, atrophic gastritis, dysplasia, gastric intestinal metaplasia, gastric polyps, and gastric adenocarcinoma. We found that the frequency of AQP3 positivity was significantly higher in patients with gastric intestinal metaplasia□gastric dysplasia □gastric polyps and intestinal-type gastric adenocarcinoma than that in patients with gastritis, gastric ulcer, gastric erosion, or atrophic gastritis ($p < 0.0001$, $p = 0.001$, $p = 0.006$, $p = 0.0009$, respectively), especially in the patients with hyperplastic polyps ($p < 0.0001$). All these preliminary findings can impress us better understanding of the role of AQP3 in the transformation from gastritis to gastric cancer.

Materials And Methods

Human gastric tissue specimens

A total of 101 patients diagnosed with different gastric diseases at The Affiliated Huai'an Hospital of Xuzhou Medical University participated in this study during March 2018 to September 2018. The informed consent was obtained from all participants according to an established protocol approved by Institutional Review Board of the Affiliated Huai'an Hospital of Xuzhou Medical University, and the study was in compliance with the Declaration of Helsinki. The median age of the patients receiving endoscopic examination was 57 years old ranging from 22 to 86, including 58 (57.4%) male and 43 female. Of the 101 patients, 20, 8, 12, 6, 23, 11, 12, and 9 patients were diagnosed respectively as chronic gastritis, gastric ulcer, gastric erosion, atrophic gastritis, gastric intestinal metaplasia, gastric dysplasia, gastric polyps, and intestinal-type gastric adenocarcinoma. The general demographic features of each disease type are listed in Table 1. Gastric tissue biopsies were taken from the gastric antrum during endoscopic examination. Each gastric tissue specimen was immediately fixed in 10% phosphate-buffered formalin, followed by paraffin embedding, sectioning, and staining.

Immunohistochemistry of AQP3

Expression of AQP3 protein was determined by immunohistochemistry (IHC) as described previously [10]. A polyclonal rabbit anti-AQP3 antibody (NBP1-9792) was obtained from Novus Biologicals (Centennial,

CO, USA). The ultra-view universal DAB detection kit was used for detection (Roche, Shanghai, China). Percentage of positive cells (from 0 to 100%) were counted and staining intensity (from 0 to 3) was measured. Positive AQP3 protein expression was defined as ≥ 25% positive cells with staining intensity of ≥ 2. The pathological results were determined by two experienced pathologists blinded to this study.

Statistical analysis

All statistical analyses were performed using SPSS version 17.0 (SPSS Inc, Chicago, IL, USA). A logistic regression was used to investigate differential expression of AQP3 protein between the disease types. Age and sex were included in the model as covariates. Fisher's exact test was used as needed. $P < 0.05$ was considered statistically significant.

Results

AQP3 protein expression in patients with gastric diseases

Of the 20 patients with chronic gastritis, 9 were mild, 3 were moderate, and 8 were severe cases. AQP3 positivity was detected in 2 severe and 1 moderate cases (15%). No mild cases were positive for AQP3 (Fig. 1, 1A). The results suggest a potential correlation between AQP3 expression and disease severity of chronic gastritis. Of the 8 patients with chronic gastric ulcer, one patient was positive for AQP3 (12.5%) (Fig. 1, 1B). Of the 12 patients with gastritis erosion, one patient was positive for AQP3 (8.3%) (Fig. 1, 1C). Of the 6 patients with atrophic gastritis, one patient was positive for AQP3 (16.7%) (Fig. 1, 1D). Of the 23 patients with gastric intestinal metaplasia, 18 were positive for AQP3 (78.3%) (Fig. 2, 1E). Of the 11 patients with gastric dysplasia, 8 were positive for AQP3 (72.7%) (Fig. 2, 1F). Of the 12 patients with gastric polyps, 9 had hyperplastic polyps, 2 had inflammatory polyps, and one had adenomatous polyps. AQP3 positivity was detected in 7 patients with gastric polyps (58.3%) (Fig. 2, 1G). Interestingly, all 7 patients who were positive for AQP3 had hyperplastic polyps. No patients with inflammatory polyps or adenomatous polyps were positive for AQP3. Of the 9 patients with intestinal-type gastric adenocarcinoma, 7 were positive for AQP3 (77.8%) (Fig. 2, 1H).

Differences of AQP3 expression between disease types

The frequency of AQP3 positivity was similar between the disease types of chronic gastritis, gastric ulcer, gastric erosion, and atrophic gastritis. These disease types were combined as a group in the comparison with other disease types. Age and sex did not show a significant effect on AQP3 positivity. The frequency of AQP3 positivity was significantly higher in patients with gastric intestinal metaplasia than patients with gastritis, gastric ulcer, gastric erosion, or atrophic gastritis by a logistic regression model ($p < 0.0001$) (Table 2). Similarly, the frequency of AQP3 positivity was significantly higher in patients with gastric dysplasia than patients with gastritis, gastric ulcer, gastric erosion, or atrophic gastritis ($p = 0.001$) (Table 2). Interestingly, the frequency of AQP3 positivity was also significantly higher in patients with gastric polyps than patients with gastritis, gastric ulcer, gastric erosion, or atrophic gastritis ($p = 0.006$), especially in the patients with hyperplastic polyps ($p < 0.0001$) (Table 2). In addition, the frequency of

AQP3 positivity was significantly higher in patients with intestinal-type gastric adenocarcinoma than patients with gastritis, gastric ulcer, gastric erosion, or atrophic gastritis ($p = 0.0009$) (Table 2).

Discussion

Development of gastric adenocarcinomas is a stepwise progression of histologic lesions, starting with gastritis, followed by intestinal metaplasia, dysplasia, and eventually invasive adenocarcinoma. AQP3 has been reported to associate with human cancer progression and metastasis, such as pancreatic ductal adenocarcinoma, prostate cancer, cervical intraepithelial neoplasia, and triple-negative breast cancer [22–26]. However, the role of AQP3 and its expression pattern in gastric carcinogenesis remain unclear. To better understand the role of AQP3 in gastric diseases, we investigated AQP3 expression pattern in gastric tissues that were collected from patients with different type of gastric diseases including gastritis, gastric erosion, gastric ulcer, atrophic gastritis, gastric dysplasia, gastric intestinal metaplasia, gastric polyps, and gastric adenocarcinoma. AQP3 expression was detected in patients with gastritis, gastric erosion, gastric ulcer, and gastric atrophic gastritis, but the frequency of AQP3 positivity was low. There were no significant differences of AQP3 expression between these disease types. In contrast, the frequency of AQP3 positivity was significantly higher in patients with gastric intestinal metaplasia, gastric dysplasia, and gastric adenocarcinoma than patients with gastritis, gastric ulcer, gastric erosion, or gastric atrophic gastritis. In addition, the frequency of AQP3 positivity in patients with gastric intestinal metaplasia, gastric dysplasia, and gastric adenocarcinoma is comparable to the frequency reported in previous studies. The overall results confirm the involvement of AQP3 in gastric carcinogenesis. Interestingly, the frequency of AQP3 positivity between gastric intestinal metaplasia (78.3%), gastric dysplasia (72.7%), and gastric adenocarcinoma (77.8%) was similar, suggesting that AQP3 expression is peaked at the stage of gastric intestinal metaplasia, which further confirmed that gastric intestinal metaplasia is a pivotal progression in gastric carcinogenesis pathologically.

The risk of progression from gastric intestinal metaplasia and gastric dysplasia to gastric adenocarcinoma has been reported in several studies [27, 28]. The progression rate of gastric intestinal metaplasia and gastric dysplasia to gastric cancer varies from 0 to 10% and 0 to 73% per year, respectively [19–21]. A recent systematic review and meta-analysis indicated that progression rate from gastric dysplasia to gastric adenocarcinoma was about 16 times greater in patients with high-grade dysplasia lesions than those with low-grade dysplasia lesions [29]. No significant difference of AQP3 expression between gastric intestinal metaplasia, gastric dysplasia, and gastric adenocarcinoma suggests that increased expression of AQP3 mainly contributes to the progression from premalignant stages of gastric diseases to gastric adenocarcinoma. Interestingly, a previous study reported a strong association between AQP3 expression and gastric intestinal metaplasia severity, and proposed to use AQP3 expression as a biomarker to improve the treatment strategy for gastric adenocarcinoma [12]. Longitudinal studies are required to continue evaluating the impact of AQP3 expression on progression from the premalignant stages to gastric adenocarcinoma. In addition, it would be of great interest to investigate the differences of treatment response and survival rate between the patients with AQP3-positive and -negative gastric adenocarcinoma.

To the best of our knowledge, it is the first time to report the frequency of AQP3 positivity in patients with gastric polyps. All polyps were small (< 1 cm) and occurred in the antrum. Seven out of twelve patients with gastric polyps were positive for AQP3. Strikingly, all seven patients who were positive for AQP3 had hyperplastic polyps, and no AQP3 expression was detected in inflammatory polyps in our study. The results suggest an association between the hyperplastic polyps and AQP3 expression (Fisher's exact test, $p = 0.046$). The hyperplastic polyps typically occur in the antrum, and is the most common type of gastric polyps associated with inflammatory disorders such as chronic gastritis, H pylori gastritis, and reactive gastritis [29, 30]. Histologically, gastric hyperplastic polyps themselves have little neoplastic potential but the risk of malignancy in hyperplastic polyps is increased if the size is increased to > 1 cm and the shape becomes pedunculated [31, 32]. It is not known why AQP3 is commonly expressed in gastric hyperplastic polyps. Researchers have revealed the relationship between H.pylori infection and AQP3 expression that AQP3 expression was positively associated with gastric mucosal disease progression and H. pylori infection [31–34], so we speculate that AQP3 expression in gastric hyperplastic polyps may be induced by H. pylori infection directly or indirectly.

All the results above confirmed pathologically that AQP3 is involved the progression from gastritis to gastric adenocarcinoma. Further mechanistic studies on AQP3 expression in gastric intestinal metaplasia, gastric dysplasia, and gastric hyperplastic polyps will shed more light on the role of AQP3 in the progression of gastric diseases, and determine whether AQP3 is a therapeutic target for gastric cancer.

Conclusion

In the present study, AQP3 expression was positive in gastritis, gastric ulcer, gastric erosion, or gastric atrophic gastritis, and the intensity was especially higher in gastric intestinal metaplasia, gastric dysplasia, gastric hyperplastic polyps, and gastric adenocarcinoma. All the results above suggest that AQP3 is involved the progression from gastritis to gastric adenocarcinoma, and confirm pathologically that GIM is a pivotal progression in gastric carcinogenesis pathologically. Interestingly, it is the first time to report AQP3 positive expression in patients with gastric polyps. In short, AQP3 is involved in the progression from gastritis to gastric adenocarcinoma, and might be a potential biomarker to improve the treatment strategy of gastric cancer.

Declarations

Ethics approval and consent to participate

This study was approved by Institutional Review Board of the Affiliated Huai'an Hospital of Xuzhou Medical University , and was in compliance with the Declaration of Helsinki.

Consent for publication

Not applicable

Availability of data and materials

The data analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Haijian Zhao has made the design of the work and written this article; Heng Li, Xudong Dai, Jin Dou and Hualin Xu have done the acquisition, analysis, and interpretation of data; Qi Min, Lun Zhu, Yuewu Li,Haiwen Zhuang and Xiaoyu Zhang have drafted the work and substantively revised it. All authors read and approved the final manuscript.

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Tables

Table 1. Demographics by disease types.

Diseases	N	Age*	Sex (female)
Gastritis	20	52 (32 - 81)	30%
Gastric ulcer	8	56 (29 - 84)	0%
Gastric erosion	12	44 (32 - 65)	41.70%
Atrophic gastritis	6	65 (22 - 75)	33.30%
Gastric dysplasia	11	62 (37 - 86)	45.50%
Gastric intestinal metaplasia	23	62 (52 - 81)	60.90%
Gastric polyps	12	46 (26 - 62)	58.30%
Gastric adenocarcinoma	9	64 (43 - 81)	44.40%
*Values are median age (range of age).			

Table 2. Differences of AQP3 expression between disease types.

Disease types	AQP3 positive	AQP3 negative	P-value*
Gastric intestinal metaplasia	18 (78.3%)	5 (21.7%)	<0.0001
Gastric dysplasia	8 (72.7%)	3 (27.3)	0.001
Gastric polyps	7 (58.3%)	5 (41.7%)	0.006
Gastric adenocarcinoma	7 (77.8%)	2 (22.2%)	0.0009
Control group	7 (15.2%)	39 (84.8%)	
Control group consists of gastritis, ulcer, erosion, and atrophic gastritis.			
*Compare to control group.			

Figures

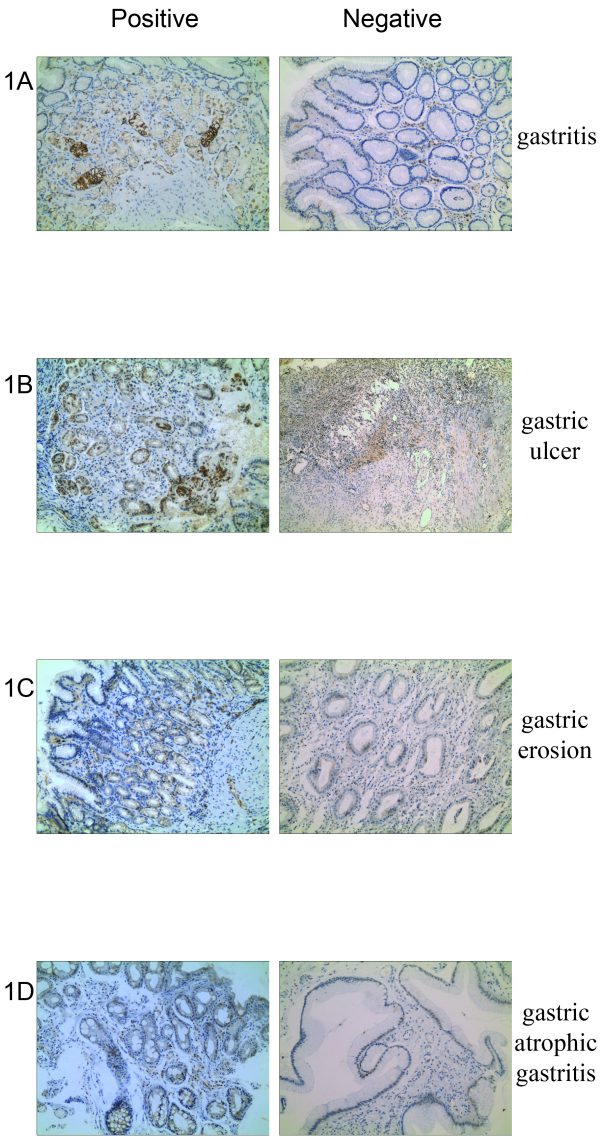

Figure 1

The images show positive and negative staining of AQP3 in gastric tissues from patients with gastritis (Figure1,1A), gastric ulcer (Figure1,1B), gastric erosion (Figure1,1C), gastric atrophic gastritis (Figure1,1D). Original magnification 20 X.

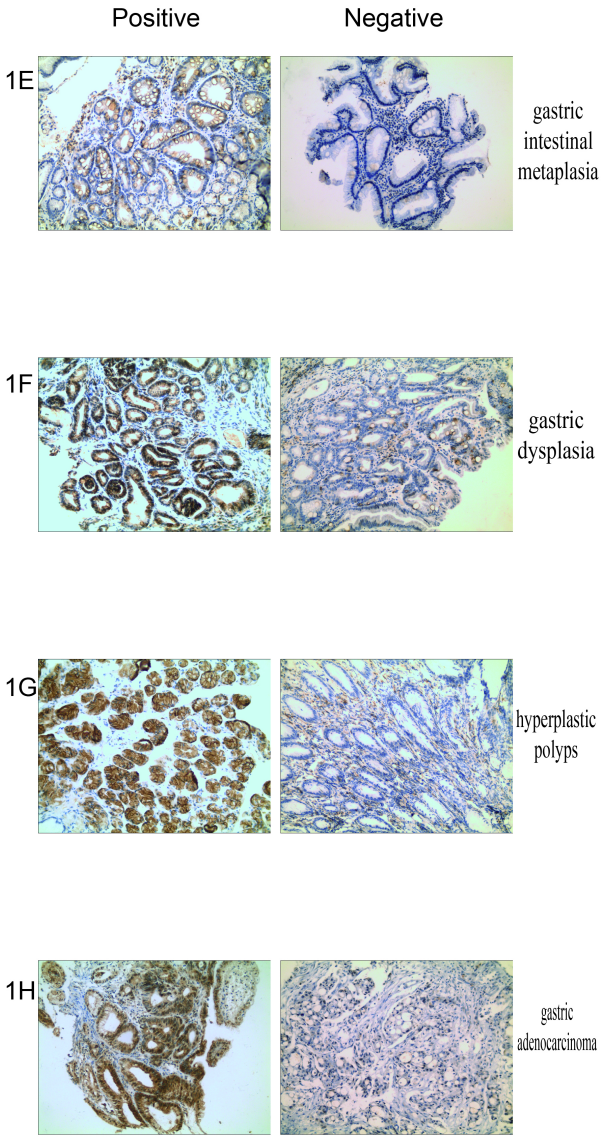

Figure 2

The images show positive and negative staining of AQP3 in gastric tissues from patients with gastric intestinal metaplasia (Figure2,1E), gastric dysplasia (Figure2,1F), hyperplastic polyps (Figure2,1G), and gastric adenocarcinoma (Figure2,1H). Original magnification 20 X.