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EXPRESSION OF ANION EXCHANGER 2 IN HUMAN GASTRIC CANCER

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Anion exchanger 2 (AE2), which mediates exchange of Cl^-/HCO_3^- across the plasma membrane, is widely expressed in body tissues. It is most abundantly expressed in stomach and is responsible for the uptake of Cl^- ions that are destined to become HCl molecules. ***Aim:*** **To determine whether AE2 expression was altered in gastric tumors.** ***Methods:*** **We have studied AE2 expression in normal human gastric tissues (n = 16) and in gastric tumors (n = 33) using immunohistochemistry and immunofluorescent labeling.** ***Results:*** **In normal gastric tissue positive staining was observed in gastric fundus gland, suggesting parietal cell-related expression of AE2, and AE2 expression was localized in the nuclear membrane and even in cell nuclei. For assay of cancerous gastric tissues, specimens of human gastric cancer arising from the region of the fundus (2 cases), the body (14 cases) and the antrum (17 cases) were randomly selected. Immunohistochemical staining has showed that AE2 was down-regulated in all 14 cancerous gastric body specimens, whereas staining for AE2 in cancerous antrum was less intense and had a diffuse profile.** ***Conclusions:*** **The data suggest that AE2 might be associated with gastric carcinogenesis and the achlorhydria experienced by gastric cancer patients.**

Key Words: **anion exchanger 2, immunohistochemistry, achlorhydria, gastric cancer, carcinogenesis, gastric acid.**

Gastric cancer is the second most common type of cancer worldwide and the leading cause of cancer-related death in the world [1]. Gastric adenocarcinoma comprises 95% of the total number of gastric malignancies, with a frequency that varies greatly among various geographic locations [2–4]. Studies have identified certain risk factors associated with this cancer. *Helicobacter pylori* is an official carcinogen that has been found in most antral gastric cancers and results in increased risk of carcinogenesis of the stomach and the infection of *H. pylori* leads to acid reduction and bacterial overgrowth [5–7]. In addition, genetic analysis has revealed that activation of oncogenes and inactivation of tumor suppressor genes are both involved in human gastric carcinogenesis [8–10]. However, the etiology of gastric cancer remains unclear. Recently, a number of reports have indicated that decreased gastric acid output is often observed in patients with gastric cancer and that a range of bacterial species can be cultured from gastric juice if the intragastric pH rises above 4.0 [11–13].

Achlorhydria is defined as a failure of the intragastric pH to fall to less than 4.0 under maximal stimulation. In several conditions, including pernicious anemia, autoimmune thyroid disease, *H. pylori* infection, long-term treatment with proton pump inhibitors, and mucolipidosis type IV, subnormal acid production is considered to contribute to achlorhydria [14–17]. However, to date, studies describing the molecular mechanism of achlorhydria are lacking, especially explanations for why gastric cancer patients manifest achlorhydria. Thus, questions regarding the cause and effect relationship between achlorhydria and gastric cancer remain unanswered and require further investigation.

Gastric acid is produced by parietal cells in the stomach, which contain an extensive secretory network through which gastric acid is secreted into the lumen of the stomach, which stays at the low pH (2.0–3.0) that is characteristic of normal gastric acid. Gastric acid is an indispensable factor in the digestion of proteins, absorption of nutrients, and prevention of infection by bacteria-laden foods (many bacteria cannot survive in such an acidic environment). Regulation of gastric acid secretion is complex and involves a multitude of factors affecting the integrity of the parietal cell. The hormone gastrin and the paracrine agents histamine and somatostatin, regulate gastric secretion [18]. Several additional intracellular events influence acid secretion from parietal cells such as elevation of intracellular calcium and cAMP and translocation of H^+-K^+-ATPase from cytoplasmic tubulovesicles to the apical plasma membrane [7, 19]. Recent studies in genetically engineered mouse models show that gastric acid secretion requires high levels of Cl^-/HCO_3^- exchange and one chloride exchanger is the anion exchanger 2 (AE2) protein [20, 21]. The AE2 protein is usually considered to be localized in basolateral membrane of the parietal cell and to mediate Cl^-/HCO_3^- exchange, which is an essential element of the secretion process. $AE2^{-/-}$ mice have an achlorhydric phenotype and more alkaline gastric secretions [22, 23]. AE2 generates H^+ for secretion and extrudes intracellular HCO_3^- across the basolateral membrane. Thus, cells support Cl^- secretion through the apical membrane and via Cl^- channels.

We previously reported an unexpected expression of AE1 in human gastric cancer tissue and the alkalization of the gastric cancer cell [8]. In the present study, we raised polyclonal antibodies against an N-terminal

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Abbreviations used: AE2 – anion exchanger 2; EB – endoscopic biopsy; GC – gastric cancer; NB – needle biopsy; SB – surgical biopsy.

21 amino acid sequence of AE2 in rat to identify and localize AE2 protein in both cancerous and non-cancerous human gastric tissues. The result show that the location of the AE2 protein was restricted to the underside distribution of the fundus glands in both the stomach fundus and the whole gastric body. Intracellular distribution of AE2 was found on the nuclear membrane. The AE2 protein was clearly down-regulated in gastric body tumors.

MATERIALS AND METHODS

Patients. A total of 33 paraffin-embedded gastric tumor specimens from patients with adenocarcinoma (based on clinical and pathologic diagnosis) and 16 non-cancer control patients with diagnosed gastritis (Lishui hospital, Zhejiang, China) were randomly selected for these retrospective studies. Clinical information was available. The patients were primarily diagnosed with gastric cancer and none of them had received chemotherapy or radiation treatments before surgery. After analysis of AE2 expression, the patients were followed for 3–13 months. The experiment is permissioned by the Ethic Committee of Shanghai Jiao Tong University and the patients were informed.

Immunohistochemistry. Gastric tissue specimens were obtained by needle biopsy or during gastric surgery. Processing of samples and immunostaining were described in our previous paper [8]. Briefly, paraffin-embedded human gastric specimens were fixed with 4% paraformaldehyde (pH 7.4). Tissue sections were cut at 2 μm thickness on a rotary microtome (Leica) and dewaxed in xylene and rehydrated using 95% ethanol. To reveal antigens, sections were placed in citrate buffer and heated in a microwave oven for 10 min. After that, 30 min incubations in 3% H_2O_2 were done to block endogenous peroxidase activity. Nonspecific binding was prevented by incubating sections in 5% BSA for 30 min. Sections were incubated overnight at 4 °C with anti-AE2 antibodies, and diluted 1 : 200 in 10 mM PBS (pH 7.4). AE2 polyclonal antibodies (Alpha Diagnostic, USA) are against rat AE2 N-terminal 21 amino acids. The sequence is 85% conserved in humans and the antibody has been used in our previous research [24]. For light microscopy, sections were incubated with HRP-linked goat anti-rabbit secondary antibodies (Maixin, China), visualized by the DAB technique, and counterstained using Mayer's hematoxylin.

Immunofluorescent staining. The paraffin-embedded tissue sections from gastric cancer or non cancer patients were cut and then deparaffinized and rehydrated in a graded series of ethanol. Sections were placed in citrate buffer and heated in a microwave oven for 10 min followed by 5% BSA for 30 min for preventing non-specific binding. Slides were stained overnight at 4 °C with anti-rat polyclonal AE2 antibodies (Alpha Diagnostic, USA). Then they were incubated with secondary goat anti-rabbit antibodies (Santa Cruz, USA) linked with FITC and analyzed by fluorescence microscopy (Leica, Germany).

Pathology grade and score. Immunoreactivity in gastric tissues was graded from 0 to 7 according to both the intensity and the distribution of the staining. The final score for each sample was obtained by adding together the intensity score (0 to 3: 0, negative staining; 1, weakly staining; 2, moderate staining; 3, intense staining) and the distribution score (0 to 4: for < 10%, 11%–25%, 26%–50%, 51%–75%, or > 75% staining, respectively). All cancer patients were classified as grade I–III (total stage I–IV) according to TNM classification.

Statistical analyses. The association of AE2 expression with cancerous and non-cancerous tissues from gastric fundus, body and antrum was evaluated by Mann-Whitney U test. An immunoreactivity score was obtained from an average of summation calculated by adding together all final scores. The formula used was score = mean ± SEM.

RESULTS AND DISCUSSION

The AE family includes AE1, AE2 and AE3 and mediates the exchange of Cl^- and HCO_3^- across the plasma membrane. It is involved in the regulation of cellular pH, cell volume and cellular metabolism. AE1 is expressed in erythrocytes and in gastric adenocarcinoma. AE2 is ubiquitously expressed in tissues and AE3 is found in brain, retina and heart.

Studies of mRNA levels show that AE2 is most abundantly expressed in stomach and is apparently located in the basolateral plasma membrane [25, 26]. However, the contradictory results for the AE2 protein have been reported in choroid plexus epithelial cells [27]. Using immunohistochemistry, we have found positive AE2 immunostaining in human normal gastric specimens, distributed across the underside of gastric fundus glands and body. However, AE2 immunostaining in the gastric body was more dense and centralized than in the fundus. In contrast, positive staining is rarely found in the antrum (Fig. 1, *a*, *c*, *e*). To further confirm the distribution of AE2, immunofluorescent staining was done on the same human gastric specimens. As shown on Fig. 1, *b*, *d*, *f*, AE2 was expressed in cells that were mainly located in the glandular area of the gastric fundus and the body, and is therefore consistent with immunohistochemical data. The staining distribution mostly overlapped with parietal cells, suggesting parietal cell-related expression of AE2 protein. All 16 non-cancer specimens that were analyzed had positive staining in both gastric fundus and gastric body. In addition, the protein was mainly localized at the nuclear membrane in gastric body (Fig. 2, *d*). However, the same profile was not found in the gastric fundus (Fig. 2, *a*). This differs from the plasma membrane location of AE2 in other epithelial cells. Previous reports have demonstrated that different variants of AE2 protein were located in the different regions in different tissues. For example, AE2a was located in the apical plasma membrane in biliary and intestinal epithelial cells whereas other AE2 variants have been shown to be localized in Golgi apparatus and mitochondria. All these data suggest that one or more AE2 variants may

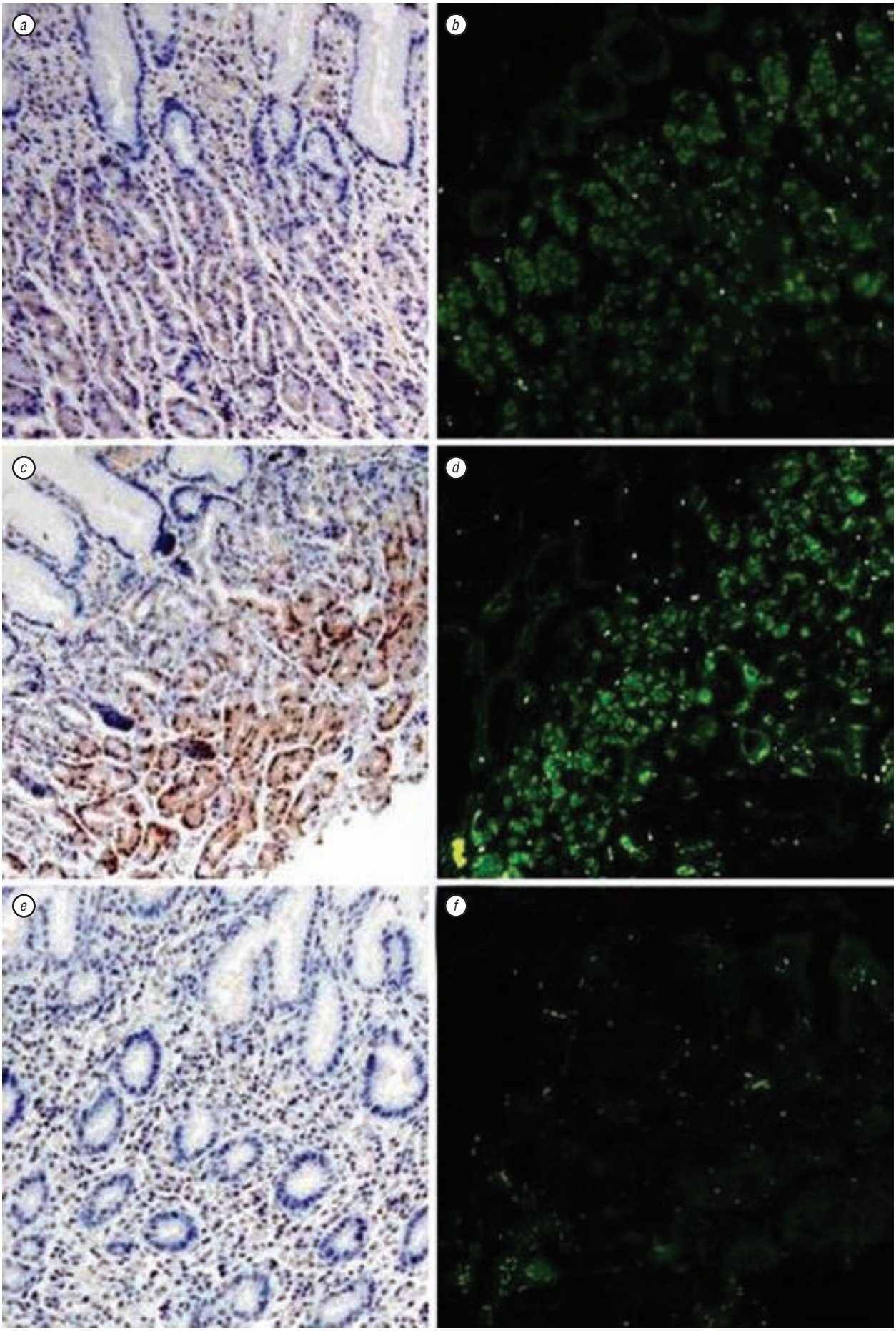

Fig. 1. Immunostaining of AE2 protein expression in normal gastric mucosa. Left panel: immunohistochemical staining; Right panel: immunofluorescence staining; *a* and *b*, gastric fundus; *c* and *d*, gastric body; *e* and *f*, gastric antrum. Original magnification ×10

take part in the regulation of secretion of gastric acid in the parietal cells. In addition, it is interesting that in two from six noncancerous antrum specimens have shown positive staining for AE2 protein.

Next, we initiated an investigation of AE2 expression in human gastric tumor samples and compared that data with nontransformed tissue (Table). In 33 human gastric cancer tissue specimens, immunohistochemical staining of AE2 was significantly decreased in tumors of gastric body. In contrast, tumors of antrum only weakly expressed AE2 protein. Fig. 3 shows a typical immunohistochemical staining of tumor tissues from gastric fundus (*a*, × 100), body (*b*, × 100) and antrum (*c*, × 100). The differential expression of AE2 protein in fundus, body and antrum of both non-cancerous and cancerous tissues was statistically analyzed by comparing protein immunoreactivity scores (Fig. 4). The finding of decreased AE2 immunoreactivity in cancerous gastric body tissue suggests that the expression of the AE2 protein expression is lower in gastric cancer patients. It was assumed that such reduction in AE2 expression resulted from loss of parietal cells because of the intestinal metaplasia of gastric glands. However, the decreased expression of AE2 was observed in all the subtypes of gastric cancer specimens studied by us. Moreover, the AE2 protein was also expressed in normal intestinal mucosa. On the other hand, the loss of parietal cells did not occur in all gastric cancer specimens, whereas decreased expression of AE2 was found in all types of gastric body cancer investigated in our experiment including normal tissue adjacent to tumor. AE2 expression was not robustly correlated with gastric cancer. Gastric acid secretion by parietal cells is regulated both centrally and peripherally. Until recently, there had not been strong evidence that the AE2 protein has an essential role in gastric acid secretion. Analysis of gastric secretions after stimulation by histamine shows that $AE2^{-/-}$ mice develop achlorhydria and that their gastric secretions are more alkaline. These findings are supported by data from other experiments [22, 23], thus, reinforcing our conclusion that AE2 has a central role in the regulation of acid secretion. Low

Table. Histopathological and clinicopathological data from studies of patients with gastric cancer and of controls.

Patient		Disease	Type of	Tumor	Tumor	Tumor	Follow-up	Location	AE2 Immunoreactivity Score		
No.	Age(y)/Sex		Biopsy	Size (cm)	Stage	Grade	Statistics (mo)		Intensity	Range	Final Score
1	67/M	N	EB					Fundus	1	3	4
2	50/M	N	EB					Fundus	2	4	6
3	56/F	N	EB					Fundus	2	4	6
4	34/F	N	EB					Fundus	2	3	5
5	37/F	N	EB					Fundus	2	3	5
6	47/F	N	EB					Body	3	4	7
7	45/M	N	EB					Body	2	4	6
8	46/M	N	EB					Body	3	4	7
9	49/M	N	EB					Body	3	4	7
10	46/M	N	EB					Body	2	4	6
11	55/F	N	EB					Antrum	0	0	0
12	43/M	N	EB					Antrum	0	0	0
13	26/M	N	NB					Antrum	2	0	2
14	43/M	N	NB					Antrum	0	0	0
15	29/M	N	EB					Antrum	2	0	2
16	53/F	N	EB					Antrum	0	0	0
17	71/M	GC	SB	5.0*5.0	III	III	11	Fundus	1	3	4
18	51/M	GC	SB	10.0*8.0	III	III	died	Fundus	0	0	0
19	74/M	GC	SB	2.5*2.5	I	II–III	10	Body	0	0	0
20	46/M	GC	SB	5.0*4.5	IV	III	12	Body	0	0	0
21	51/M	GC	SB	5.0*10.0	III	III	12	Body	0	0	0
22	74/F	GC	SB	4.0*4.0	I	I–II	10	Body	0	0	0
23	55/M	GC	SB	2.0*1.0	II	III	11	Body	1	1	2
24	36/F	GC	SB	2.5*2.0	I	III	13	Body	0**	0	0
25	75/M	GC	SB	10.0*7.0	II	III	13	Body	0	0	0
26	54/F	GC	SB	2.0*2.0	I	III	12	Body	0	0	0
27	70/M	GC	SB	7.0*5.0	IV	II–III	died	Body	0	0	0
28	48/M	GC	SB	5.5*7.0	III	II	13	Body	0	0	0
29	62/M	GC	SB	3.0*5.0	I	II–III	10	Body	0	0	0
30	73/M	GC	SB	1.0*0.5	IV	II–III	13	Body	0	0	0
31	77/M	GC	SB	2.0*1.5	I	I	11	Body	0	0	0
32	79/M	GC	SB	10.0*8.0	IV	II	3	Body	0	0	0
33	60/M	GC	SB	8.0*5.0	III	III	12	Antrum	1	1	2
34	37/M	GC	SB	3.0*3.0	II	II–III	10	Antrum	1	4	5
35	71/M	GC	SB	3.0*4.0	I	II	13	Antrum	1	0	1
36	54/F	GC	SB	5.0*7.0	IV	III	died	Antrum	1	4	5
37	73/M	GC	SB	4.0*2.0	II	II–III	10	Antrum	1	3	4
38	55/M	GC	SB	2.0*1.0	II	III	11	Antrum	1	3	4
39	70/M	GC	SB	3.0*5.0	I	II–III	10	Antrum	1	3	4
40	81/M	GC	SB	2.2*2.0	III	III	13	Antrum	1	4	5
41	76/M	GC	SB	2.0*2.0	III	II	12	Antrum	1	1	2
42	60/M	GC	SB	8.5*5.0	III	III	12	Antrum	1	1	2
43	87/M	GC	SB	5.0*4.0	II	II	12	Antrum	1	0	1
44	65/M	GC	SB	1.0*1.0	II	II–III	10	Antrum	1	3	4
45	57/M	GC	SB	4.0*4.0	III	II–III	11	Antrum	1	0	1
46	37/M	GC	SB	3.0*3.0	II	II–III	10	Antrum	1	4	5
47	55/F	GC	SB	4.0*4.0	III	II–III	10	Antrum	1	0	1
48	69/M	GC	SB	4.0*4.0	III	II	10	Antrum	1	4	5
49	61/M	GC	SB	4.0*4.0	III	III	11	Antrum	1	3	4

Notes: ** Evaluation was not feasible because of background; EB – endoscopic biopsy; SB – surgical biopsy; NB – needle biopsy; GC – gastric cancer; mo – month.

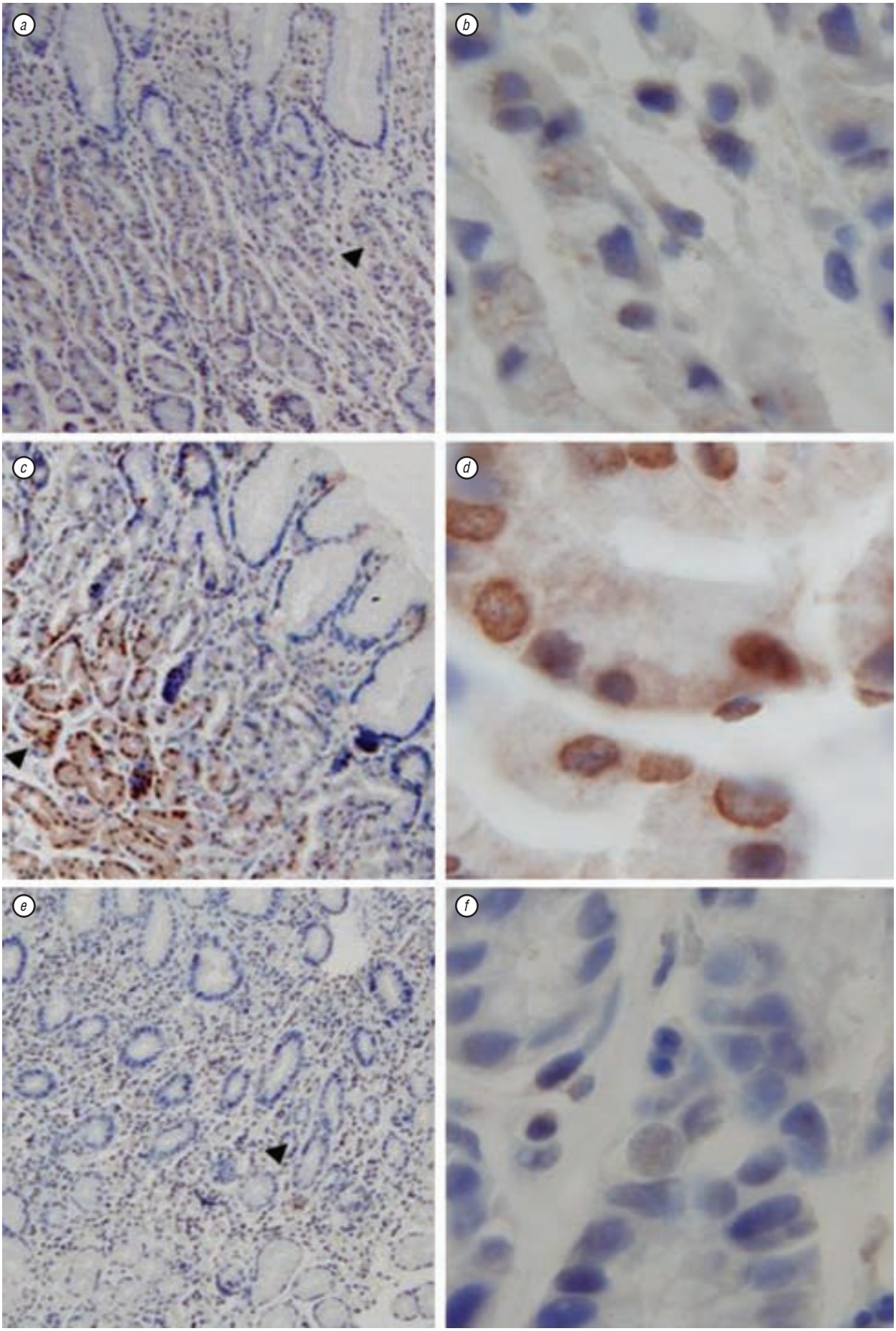

Fig. 2. Immunohistochemical staining of AE2 expression in cells of human normal gastric fundus (*a, b*), body (*c, d*) and antrum (*e, f*). For easier viewing of the staining, the structures indicated by an arrow were magnified (left, × 10, right, × 100)

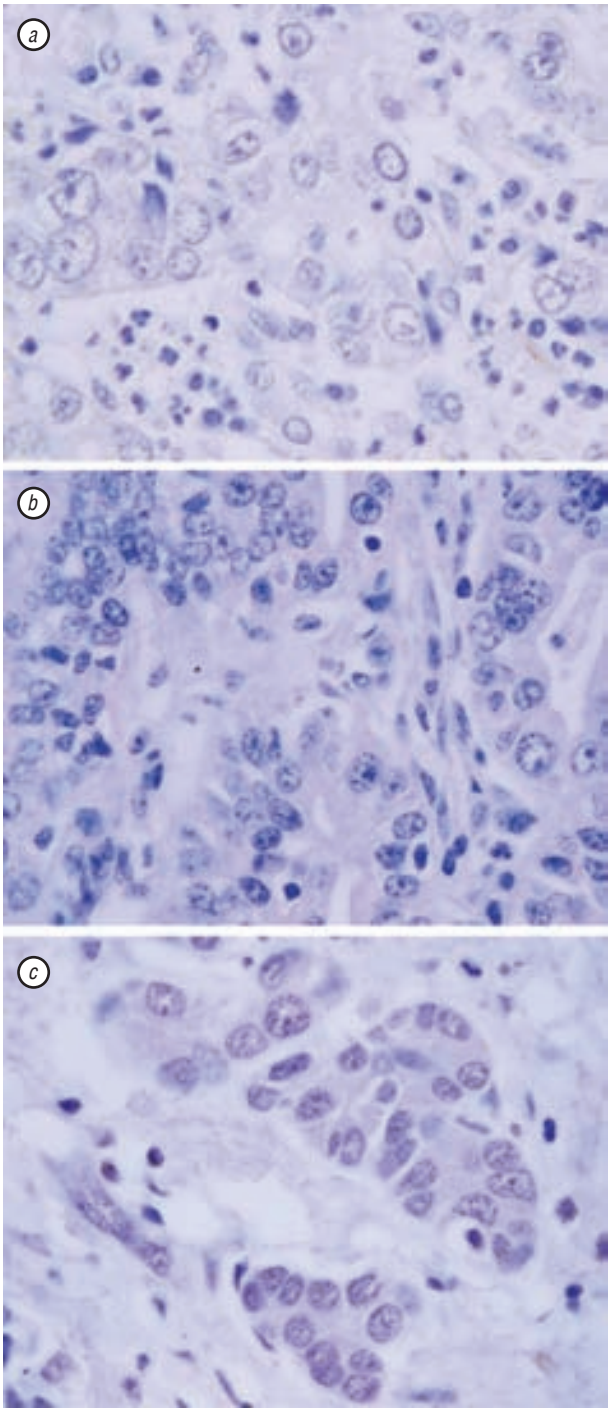

Fig. 3. Immunohistochemical staining of AE2 expression in gastric tumor tissue: gastric fundus (*a*), body (*b*) and antrum (*c*). Original magnification × 100

expression and functional insufficiency of AE2 in the stomach results in low acid secretion, which can lead to gastritis and adenocarcinoma.

Our findings raise a question about whether the manifestation of achlorhydria in gastric cancers results from the loss of parietal cells or atrophy and impaired viability of parietal cells in the stomach. Several findings based on the $AE2^{-/-}$ animal model suggest that loss of AE2 does not have a major effect on parietal cell viability and indicate that any reduction in the number of parietal cells was not excessive and not sufficient to account for the achlorhydria phenotype. Decreased expression of AE2 reduced the overall secretory capacity of the parietal cells, which are important for maintaining a balance between apical and basolateral transport mechanisms that lead to achlorhydria. Our results indicate that decreased expression of AE2 may involve a failure of pH homeostasis during acid secretion in gastric cancer cells. The full significance of AE2 expression for understanding and treating gastric cancer will require further study.

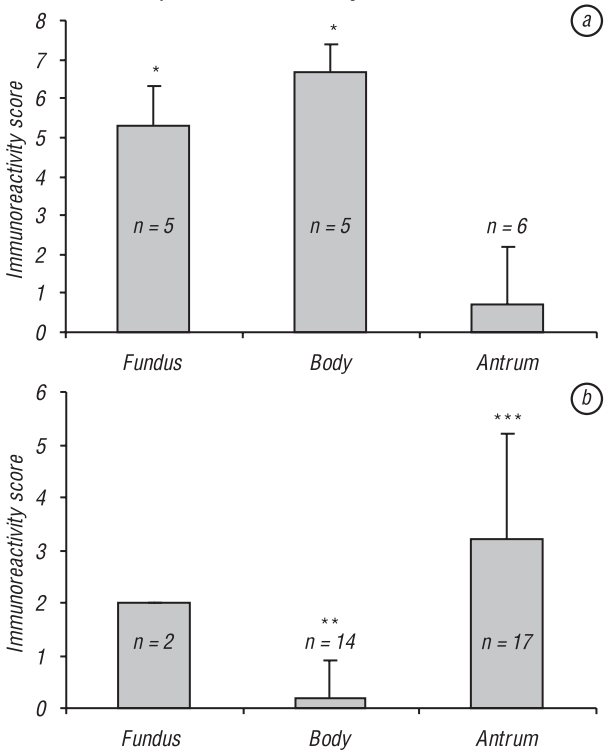

Fig. 4. Immunoreactivity scores for AE2 expression in gastric tissues. *a*: normal gastric tissue; *b:* gastric tumor. In each group, the score is expressed as mean ± SD
*$P < 0.01$, is for comparisons with the gastric antrum group; **$P < 0.01$, is for comparisons with the non-cancerous gastric body group; ***$P < 0.05$ is for comparisons with the non-cancerous gastric antrum group.

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ЭКСПРЕССИЯ АНИОННОГО ОБМЕННИКА 2 В ОПУХОЛЕВОЙ ТКАНИ ЖЕЛУДКА

Анионный обменник 2 (AE2), который опосредует перенос Cl^-/HCO_3^- через плазматическую мембрану, экспрессируется клетками разных тканей. Самый высокий уровень экспрессии AE2 в желудке, поскольку этот белок отвечает за поглощение ионов Cl^-, которые впоследствии используются для секреции HCl. *Цель:* Изучить изменения в экспрессии AE2 при раке желудка. *Методы:* исследована экспрессия AE2 в нормальных тканях (n = 16) и опухолях желудка (n = 33) с применением методов иммуногистохимии и иммунофлуоресценции. *Результаты:* в нетрансформированной ткани желудка в фундальной железе выявляли сильную положительную реакцию, что свидетельствует об экспрессии AE2 париетальными клетками, причем экспрессия AE2 была локализирована в ядерной мембране и в ядре. В опухолях желудка (фундального отдела (n = 2), тела (n = 14) и антрального отдела (n = 17)), отобранных случайным образом, был проведен анализ экспрессии AE2. Иммуногистохимическое исследование показало снижение экспрессии AE2 во всех 14 случаях рака тела желудка. Окрашивание AE2 в образцах рака антрального отдела желудка было менее интенсивным и диффузным. *Выводы:* полученные данные позволяют предположить наличие связи между экспрессией AE2 и развитием рака желудка, а также ахлоргидрией, отмечаемой у больных раком желудка.

Ключевые слова: **анионный обменник 2, иммуногистохимия, ахлоргидрия, рак желудка, канцерогенез, кислота желудочного сока.**