SP70 is a Potential Biomarker to Identify Gastric Fundic Gland Neoplasms

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Research Article

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Abstract

Background Gastric neoplasms with fundic gland differentiation include oxyntic gland adenomas (OGAs) and gastric adenocarcinomas of fundic gland type (GA-FGs). Due to their extremely well differentiation and morphological similarity to normal fundic glands, it is usually challenging to identify these lesions in pathological diagnosis, especially in biopsy specimens. This study aims to explore and verify the potential role of a newly developed monoclonal antibody (McAb) NJ001 (SP70) in differentiating fundic neoplasms from non-neoplastic fundic gland lesions.

Methods Twenty-three cases of histological confirmed gastric fundic gland neoplasms were obtained, including 12 cases of OGAs and 11 of GA-FGs. Fifty cases of fundic gland polyps (FGPs) were also obtained in the control group. Key clinicopathological information was collected. SP70 immunostaining was performed, the intensity, as well as the staining pattern was analyzed and compared. The para-tumor normal fundic glands were used as internal control.

Results In normal gastric mucosa, SP70 was strongly and diffusely stained on the cytoplasm in fundic glands, but not in foveolar epithelium. Therefore, a zonal distribution of SP70 was observed in normal mucosa. FGPs (50/50, 100%) shared a similar expression pattern with normal fundic glands. In fundic gland neoplasms, a significant down-expression of SP70 was observed in both OGAs and GA-FGs. The positive rate of SP70 in fundic gland neoplasms (6/23, 26.1%) was significantly lower than that in FGPs (100%) ($P=0.0001$). There was no difference of SP70 positivity between OGAs (3/12, 25.0%) and GA-FGs (3/11, 27.2%) group ($P>0.05$).

Conclusion Down-expression of SP70 is a specific feature to fundic gland neoplasms including OGAs and GA-FGs. Therefore, SP70 can serve as a potential biomarker in the identification and differential diagnosis of fundic gland neoplasms.

Introduction

Gastric neoplasm with differentiation toward the fundic gland is a novel entity [1]. First discovered by Ueyama et al. [2] in 2010, gastric adenocarcinoma of fundic gland type (GA-FG) was proposed as a rare neoplastic lesion (with the ability to invade the stroma) mainly composed of chief cells. Distinct from other gastric carcinomas, GA-FG is identified to have a low-grade malignancy (easily submucosal invasion but rarely perineural or lymphovascular invasion) and a good prognosis [3]. Two years later, from a prognostic perspective, Singhi et al. [4] suggested that the terminology of oxyntic gland polyp/adenoma (OGA) was more suitable for the lesions limited within mucosa. This subtype shows the features of slow progression and a rather benign clinical course [5]. Currently, both entities (OGA and GA-FG) have been adopted by the World Health Organization's (WHO) classification of digestive system tumors (5th edition) [6].

Due to its well histopathological differentiation, the morphological characters of gastric fundic gland neoplasms may resemble to that of normal fundic glands [7]. Despite of the architectural abnormalities

that are helpful to identify them, the minimal cellular atypia makes the diagnosis of these neoplasms very challenging, and may lead to the misdiagnosis as benign fundic gland lesions such as FGPs, especially in biopsy specimens [3]. It is of clinical importance to distinguish neoplastic lesions (OGA and GA-FG) from the non-neoplastic lesions of fundic glands, for the latter may not require a clinical intervention [8, 9]. Previous studies indicated that sporadic FGPs were self-limiting neoplasms, which had little chance of transforming into carcinomas [4], and the patients only needed to undergo routine follow-up. However, neoplasms with fundic gland differentiation (OGAs and GA-FGs) are considered to share similar histogenesis [4, 10], frequently show submucosa invasion, indicating their malignancy nature. Therefore, further clinical intervention including endoscopic resection or even complete surgical excision [11] is appropriate for such neoplasms, in case of further progression [12].

A panel of immunohistochemical markers has been used as the auxiliary methodology to generate a precise diagnosis, when a diagnosis could not be made by routine H&E staining. The current using markers include MUC5AC, MUC6, Pepsinogen I and H⁺/K⁺-ATPase, and these markers are very helpful to verify fundic glands differentiation [13]. Nevertheless, because normal fundic glands or non-neoplastic lesions of fundic glands (FGPs) harbor same IHC phenotype as well, it may be unlikely to make the diagnosis only based on IHC findings. Therefore, these markers can only be used as support data when morphological findings indicate a neoplasm. Newly developed specific IHC biomarkers that can distinguish fundic gland neoplasms from non-neoplastic lesions are needed to improve the diagnostic difficulties, especially in cases with atypical morphology and in biopsy specimens with limited tissue.

SP70 is an antigen of non-small-cell lung cancer (NSCLC) specifically identified by the McAb NJ001 [14, 15]. It has been successfully produced by immunizing mice with human SPC-A1 lung adenocarcinoma live cell antigen [15]. In this study, we explored the expression pattern of SP70 in a series of gastric neoplasms with fundic glands differentiation and non-neoplastic fundic gland lesions. We found that the down expression of SP70 was a characteristic feature of neoplastic lesions (OGAs and GA-FGs), and the biomarker may serve as a diagnostic marker for this rare entity.

Materials And Methods

Patients

Archival paraffin blocks of 23 cases of fundic gland neoplasms were obtained from Zhongshan hospital, Fudan University (Shanghai, China) from Jan. 2017 to Dec. 2020, among which 12 cases were OGAs, and 11 were GA-FGs. The adjacent normal fundic glands served as internal control. Fifty cases of FGPs were taken as control group. The study protocol and the comprehensive written informed consent used in this study protocol were reviewed.

Immunohistochemistry

Paraffin-embedded specimens were sectioned and were subjected to immunohistochemistry. Monoclonal antibodies used in this study were mouse mAb NJ001 (1:400; NM001-1; Code Biotech, Jiangsu, China). Besides, the markers for chief cell and parietal cell differentiation were also used, including Pepsinogen-I (1:400; 7G3; Abcam, Shanghai, China), MUC 6 (1:100; MRQ-20; Gene Tech, Shanghai, China), MUC 5AC (1:400; 45M1; Gene Tech, Shanghai, China) and H⁺/K⁺-ATPase (1:400; poly; Jiehao Biotechnology, Shanghai, China).

SP70 was mainly localized in the cellular cytoplasm. Five hundred cells were assessed, and the percentage of SP70 positive cells (cytoplasmic staining) was counted. The result was assigned as negative when the SP70 positive cells was <5%, and ≥5% as positive.

Histopathological Assessment

Histological features, immunohistochemical staining and clinicopathological data (including age, gender, site and size of the lesion, and medical history) were assessed. Histopathological reviews and immunohistochemical analysis were performed by three pathologists. Diagnostic criterion takes reference from the 5th edition of WHO classification of gastrointestinal tract tumors (2019) [6].

Statistical analysis

SPSS statistics 21.0 software was used to carry out statistical analyses. The statistical differences between different groups were compared by the χ^2 test. The *P*-value <0.05 was considered to be of statistical significance.

Results

Clinicopathological data

Histopathological and clinical findings were presented in Table 1, with 12 cases of OGAs and 11 cases of GA-FGs. The patients ranged in age from 37 to 80 years old (median, 63 years old), with a male-to-female ratio of 14: 9. The lesions were located in fundus ventriculi (n=9) and corpus ventriculi (n=14), and measured 0.3-2.0 cm in diameter.

Endoscopic Findings

Endoscopic findings showed that 47.8% (11/23) tumors had a protruding type (Fig. 1A); superficial flat shape was noted in 34.8% (8/23) cases (Fig. 1B and 1C); 1 (1/23, 4.3%) case had a superficial elevated appearance (Fig. 1D); the submucosal tumor (SMT)-like shape was noted in 8.7% (2/23) tumors (Fig. 1E); only 1 (1/23, 4.3%) case was recognized by an infiltrative ulcerative appearance (Fig. 1F).

Histopathological Analysis

Histologically, all lesions of OGAs were located in mucosa layer (Fig. 2A and 2C). Pigments could be observed in 2 cases of OGAs (Fig. 2B). As for the GA-FGs, 10 of the tumors extended into the submucosa with an infiltrative pattern (Fig. 2D and 2E); and 1 case showed invasion into the sub-serosa.

According to the previous study of Tetsuo et al. [5], we attempted to classify all the cases into 3 groups. Based on the criteria (histologic assessment), the patients were classified as group A (intramucosal tumor) in 11 cases, group B (submucosal invasive tumor with typical histologic features) in 7 cases, and group C (submucosal invasive tumors with atypical histologic features) in 4. Only 1 patient was complicated uncertainty in classification (shown in Table 1).

Intravascular cancer emboli could be observed in 2 patients (case 14 and 23, as shown in Table 1). Case 23 was lost in the follow-up with a final follow-up time of 12.5 months (operative time as a starting point, to patient final visiting for end); no recurrence or metastasis was found in the rest 22 patients (followed up for 10-49 months).

Expressions Of Fundic Glands Associated Markers

MUC6 presented a strong expression in fundic gland cells (in contrast with MUC5AC in foveolar epithelium) (Fig. 3A2, B2, C2). The markers for parietal cell (H+/K+-ATPase) (Fig. 3A3, B3, C3) and chief cell (pepsinogen-Ⅱ) (Fig. 3A4, B4, C4) differentiation could be observed in this study.

Expression Of Sp70 In Different Tissues

Immunohistochemical analysis showed the diffuse and strong positivity for SP70 in normal fundic glands, but not in gastric pit cells (Fig. 4A1 and A2). A similar expression pattern of SP70 could be observed in all cases of FGPs (100%). In contrast, SP70 was down-expressed in the neoplastic group (Fig. 4C-4F).

The positive rate of SP70 in neoplastic group (6/23, 26.1%) was significantly lower than that in FGPs (100%) ($P < 0.0001$). There was no difference of SP70 expression between OGAs (3/12, 25.0%) and GA-FGs (3/11, 27.2%) group ($P > 0.05$).

Discussion

SP70, a protein with a Mr of 70 kDa, particularly expresses in lung cancer cells, but rare positively or negatively reacts to human small-cell lung cancer (SCLC), pulmonary pseudotumor and other epithelial tumors [15]. It has been proven to be a key protein that can regulate tumor proliferation and apoptosis, as well as a biomarker for NSCLC [16].

SP70 has not been used as a diagnostic biomarker. In this study, we testified and compared the SP70 expression pattern in different lesions with fundic gland differentiation, including FGPs, OGAs and GA-FGs. Our IHC analysis showed that SP70 staining pattern of fundic gland neoplasms (OGAs and GA-FGs) differed from that of FGPs. Unlike diffuse and strong cytoplasm staining in normal fundic glands and FGPs, a significant down-expression or complete loss of SP70 was observed in OGAs and GA-FGs. These findings indicated that SP70 could be used as diagnostic biomarker with high sensitivity and specificity for the diagnosis of neoplasms with fundic gland differentiation.

Introduction of SP70 as an auxiliary biomarker can be very helpful in the diagnosis of gastric neoplasm of the fundic gland differentiation. The challenges in pathological diagnosis lies in, first, it is a relatively rare entity; second, the extremely well differentiation; third, cytological atypia is mild, despite of discernible architectural abnormalities. These features may easily lead to misdiagnosis in the inexperienced hands, especially in biopsy specimens. Particularly, it would be more difficult to discriminate GA-FGs from less commonly dysplastic FGPs (with mild atypia) [17] and OGAs (with a confusing submucosal involvement) [1] in biopsy specimens. Current auxiliary IHC biomarkers (including pepsinogen-I, MUC6, and focal H+/K+-ATPase) could only serve to confirm fundic gland differentiation, but not be able to distinguish neoplastic lesions from non-neoplastic lesions. Therefore, the clear-cut difference in SP70 staining pattern of fundic gland neoplasms (OGAs and GA-FGs) could be an ideal biomarker to identify this neoplasm. It would be really useful in cases with atypical morphology.

The differential diagnosis of fundic gland neoplasms and non-neoplastic lesions is clinically relevant. Although most of GA-FGs appear to show an indolent behavior [18], a small subset of these tumors with deeper submucosal invasion could transform into poorly differentiated adenocarcinomas with the ability to invade and metastasize [5, 19, 20]. Ueyama et al. [2, 19] reported some cases showing the shift in cell differentiation from a GA-FG component into high-grade adenocarcinoma with lymph node metastasis. Moreover, OGAs and GA-FGs were of similar histogenesis [4, 10]; and chief cell adenoma was considered to be a precursor to the chief cell-predominant adenocarcinoma. As a result, endoscopic resection should be performed at the time of diagnosis of neoplastic fundic glands (OGA and GA-FG), in case of further progression [12]. According to the previous study, sporadic FGPs were self-limiting neoplasms, which had little chance of transforming into carcinomas [4]. Therefore, the patients only need to undergo routine follow-up.

To our knowledge, SP70 is the first diagnostic biomarker that can be used to distinguish gastric fundic gland neoplasms from non-neoplastic lesions. Based on the findings of this study, we proposed a diagnosis flow chart which we believe could improve the accuracy and reliability of diagnosing the neoplasms in biopsy specimens. The specimens will be stained with current used biomarkers including muc6, H+/K+-ATPase and Pepsinogen-I to confirm the fundic gland differentiation. Subsequently, a diagnosis of a neoplasm or a non-neoplastic lesion can be made based on the staining intensity and pattern of SP70 (Figure 5.).

There are several limitations in this study. Firstly, its respective nature with relatively small sample number of the study; Secondly, OGAs and GA-FGs share similar staining patterns and are not be able to distinguish by SP70. A morphological continuum exists from OGA to GA-FG, and there is ongoing discussion with regard to whether OGA should be regarded as an intramucosal component of GA-FG. Therefore, these two entities may share identical IHC phenotype and are unnecessary to differentiate them by IHC.

Conclusion

In summary, this study demonstrated that SP70 was strongly and diffused expressed in normal fundic glands and FGPs; while it showed an down-expression or loss of expression in fundic gland neoplasms, including OGPs and GA-FGs. Therefore, down-expression of SP70 is a specific feature of gastric fundic gland neoplasms. The application of SP70 protein coupled with other fundic gland associated markers, could improve the diagnostic accuracy of neoplastic lesions with fundic gland differentiation. SP70 could be used as a new diagnostic biomarker to identify gastric fundic gland neoplasms.

Declarations

Ethics approval and consent to participate This study was approved by the Institutional Review Board (IRB) of Zhongshan Hospital Fudan University. Consent to participate was acquired.

Consent for publication Written informed consent was obtained from individual or guardian participants.

Data availability Data could be accessed on request from the authors.

Conflict of interest The authors declare no potential conflict of interest.

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Authors' contributions RL conceived the idea and collected the data. WH drafted the manuscript. LC analyzed the data. YL helped perform the analysis with constructive discussions. LX and XZ performed the experiment. CX and YH revised and edited the manuscript. All authors read and approved the final manuscript.

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References

1. Chan K, Brown IS, Kyle T, Lauwers GY, Kumarasinghe MP. Chief cell-predominant gastric polyps: a series of 12 cases with literature review. *Histopathology*. 2016;68:825–33.

2. Ueyama H, Yao T, Nakashima Y, Hirakawa K, Oshiro Y, Hirahashi M, Iwashita A, Watanabe S. Gastric adenocarcinoma of fundic gland type (chief cell predominant type): proposal for a new entity of gastric adenocarcinoma. *Am J Surg Pathol*. 2010;34:609–19.
3. Miyazawa M, Matsuda M, Yano M, Hara Y, Arihara F, Horita Y, Matsuda K, Sakai A, Noda Y. Gastric adenocarcinoma of the fundic gland (chief cell-predominant type): A review of endoscopic and clinicopathological features. *World J Gastroenterol*. 2016;22:10523–31.
4. Singhi AD, Lazenby AJ, Montgomery EA. Gastric adenocarcinoma with chief cell differentiation: a proposal for reclassification as oxyntic gland polyp/adenoma. *Am J Surg Pathol*. 2012;36:1030–5.
5. Ushiku T, Kunita A, Kuroda R, Shinozaki-Ushiku A, Yamazawa S, Tsuji Y, Fujishiro M, Fukayama M. Oxyntic gland neoplasm of the stomach: expanding the spectrum and proposal of terminology. *Mod Pathol*. 2020;33:206–16.
6. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, Washington KM, Carneiro F, Cree IA, Board WHCoTE. The 2019 WHO classification of tumours of the digestive system. *Histopathology*. 2020;76:182–8.
7. Fan X, Yang XS, Bai P, Ren YB, Zhang L, Li X, Wang L, Wang Y, Ding YM, Zeng RR, Lin XC. Gastric adenocarcinoma of the fundic gland type: A case report. *Medicine*. 2020;99:e20361.
8. Lee TI, Jang JY, Kim S, Kim JW, Chang YW, Kim YW. Oxyntic gland adenoma endoscopically mimicking a gastric neuroendocrine tumor: A case report. *World J Gastroenterol*. 2015;21:5099–104.
9. Peng T, Deng L, Hou L, Wang Y, Wang R, Gao R, Ye X. A Case Report: Endoscopic Diagnosis and Treatment of Gastric Adenocarcinoma of Fundic Gland Type. *J Gastrointest Cancer*. 2020;51:673–6.
10. Ueyama H, Yao T, Nakashima Y, Hirakawa K, Oshiro Y, Hirahashi M, Iwashita A, Watanabe S. **Gastric adenocarcinoma of fundic gland type (chief cell predominant type): proposal for a new entity of gastric adenocarcinoma.** *American Journal of Surgical Pathology* 2010, 34.
11. Miyazawa M, Matsuda M, Yano M, Hara Y, Arihara F, Horita Y, Matsuda K, Sakai A, Noda Y. Gastric adenocarcinoma of fundic gland type: Five cases treated with endoscopic resection. *World J Gastroenterol*. 2015;21:8208–14.
12. Okumura Y, Takamatsu M, Ohashi M, Yamamoto Y, Yamamoto N, Kawachi H, Ida S, Kumagai K, Nunobe S, Hiki N, Sano T. Gastric Adenocarcinoma of Fundic Gland Type with Aggressive Transformation and Lymph Node Metastasis: a Case Report. *J Gastric Cancer*. 2018;18:409–16.
13. Ishibashi F, Fukushima K, Ito T, Kobayashi K, Tanaka R, Onizuka R. Influence of Helicobacter pylori Infection on Endoscopic Findings of Gastric Adenocarcinoma of the Fundic Gland Type. *J Gastric Cancer*. 2019;19:225–33.
14. Gu C, Luo Y, Zhang S, Xu J, Zhang J, Ju H, Liu J, Zhang L, Zhang Y, Wu L, et al. MAb NJ001 inhibits lung adenocarcinoma invasiveness by directly regulating TIMP-3 promoter activity via FOXP1 binding sites. *Thorac Cancer*. 2020;11:2630–8.
15. Pan S, Wang F, Huang P, Xu T, Zhang L, Xu J, Li Q, Xia W, Sun R, Huang L, et al. The study on newly developed McAb NJ001 specific to non-small cell lung cancer and its biological characteristics. *PLoS One*. 2012;7:e33009.

16. Xu J, Zhang S, Zhang W, Xie E, Gu M, Wang Y, Yang L, Zhang B, Zhang J, Gu C, et al. SP70-Targeted Imaging for the Early Detection of Lung Adenocarcinoma. *Sci Rep.* 2020;10:2509.
17. Tohda G, Osawa T, Asada Y, Dochin M, Terahata S. Gastric adenocarcinoma of fundic gland type: Endoscopic and clinicopathological features. *World J Gastrointest Endosc.* 2016;8:244–51.
18. Terada T. Well differentiated adenocarcinoma of the stomach composed of chief cell-like cells and parietal cell s (Gastric adenocarcinoma of fundic gland type). *Int J Clin Exp Pathol.* 2011;4:797–8.
19. Ueo T, Yonemasu H, Ishida T. Gastric adenocarcinoma of fundic gland type with unusual behavior. *Dig Endosc.* 2014;26:293–4.
20. Benedict MA, Lauwers GY, Jain D. Gastric Adenocarcinoma of the Fundic Gland Type: Update and Literature Review. *Am J Clin Pathol.* 2018;149:461–73.

Tables

Table 1 The clinical and histopathological features of 23 cases

case	sex	age(y)	Group by MP2019	ki67	SP70	Microscopic type	location	size (mm)	treatment	pigment	Mitosis (/HPF)	Cellular atypia	invasion depth	Vascular invasion	ulcer	Follow up
1	M	38	A	1%	+	protruding	fundus	6	biopsy+polypectomy	absent	0	mild	M	absent	absent	NED
2	F	57	A	2%	+	protruding	corpus	6	polypectomy	absent	0	mild	M	absent	absent	NED
3	F	54	A	5%	-	protruding	corpus	6	polypectomy	absent	0	mild	M	absent	absent	NED
4	F	59	unclassified	5%	-	superficial elevated	corpus	7	surgery	absent	1	moderate	M	absent	absent	NED
5	F	80	A	2%	-	protruding	fundus	6	polypectomy	absent	0	mild	M	absent	absent	NED
6	M	64	A	5%	-	protruding	corpus	5	biopsy+ESD	absent	0	mild	M	absent	absent	NED
7	F	67	A	5%	-	protruding	corpus	5	EMR	absent	0	mild	M	absent	absent	NED
8	M	71	A	2%	-	superficial elevated	corpus	15	ESD	absent	0	mild	M	absent	absent	NED
9	M	68	A	5%	-	superficial flat	corpus	5	ESD	absent	0	mild	M	absent	absent	NED
10	M	51	unclassified	5%	-	superficial elevated	fundus	15	Proximal Gastrectomy	absent	1	moderate	M	absent	absent	NED
11	F	66	A	2%	-	protruding	corpus	6	biopsy	absent	0	mild	M	absent	absent	NED
12	M	73	A	5%	+	protruding	corpus	10	ESD	absent	0	mild	M	absent	absent	NED
13	M	60	B	10%	+	protruding	corpus	10	ESD	absent	0	mild	SM1(110µm)	absent	absent	NED
14	M	37	C	1%	-	superficial flat	corpus	8	ESD	absent	1	mild to moderate	SM1(363µm)	present	absent	NED
15	M	71	C	8%	+	protruding	fundus	20	EMR	absent	2	moderate	SM1(134µm)	absent	absent	NED
16	F	54	B	5%	+	Submucosal tumor	fundus	5	Proximal Gastrectomy	absent	0	mild	SM1(235µm)	absent	absent	NED
17	M	56	C	60%	-	Submucosal tumor	fundus	15	ESD+Total gastrectomy	present	1	marked	SM2(597µm)	absent	absent	NED
18	M	63	B	10%	-	protruding	fundus	5	ESD	absent	0	mild	SM1(100µm)	absent	absent	NED
19	M	45	B	10%	-	superficial elevated	fundus	6	ESD	absent	0	mild	SM1(159µm)	absent	absent	NED
20	M	55	B	2%	-	superficial elevated	corpus	15	ESD	present	0	mild	SM1(150µm)	absent	absent	NED
21	F	74	B	2%	-	superficial elevated	corpus	6	ESD	absent	0	mild	SM1(100µm)	absent	absent	NED
22	F	60	B	2%	-	superficial elevated	fundus	8	ESD	absent	0	mild to moderate	SM2(1500µm)	absent	absent	NED
23	M	71	C	15%	-	infiltrative ulcerative	corpus	20	biopsy+Total gastrectomy	absent	4	marked	Subserosa	present	presen	12*

M=mucosal,SM=submucosal, ESD,Endoscopic submucosal dissection; EMR,Endoscopic mucosal resection; NED, no evidence of disease; *Lost to follow-up after 12 months

Figures

Figure 1

Representative endoscopic imaging from the above 23 cases. White light endoscopy revealed A. a protruding lesion; B and C. superficial flat type; D. tumor with superficial elevated appearance; E. submucosal tumor (SMT)-like shape was noted; F. an infiltrative ulcerative tumor

Figure 2

Histopathological features of fundic gland neoplasm. (A) Oxyntic gland adenoma (OGA) always consists of clustered and irregular fundic glands (HE×100). (B) Chief cell–predominant OGAs with scattered parietal cells. Pigments could be observed in the dilated glands. (C) Complex glands with mild atypia neoplastic cells. (D) Gastric adenocarcinoma of fundic gland type (GA-FG) with submucosal invasion. (E) Muscular infiltration and vascular invasion (as indicated by the arrows) could be observed. (F) GA-FG (black arrow) with gastritis cystica profunda (white arrow).

Figure 3

The expression of muc6, H+/K+-ATPase and Pepsinogen-Ⅱ in FGPs/ normal fundic glands, OGP and GA-FGs.

Figure 4

HE staining and Immunostaining of SP70 in normal gastric mucosa,FGP and different subtypes of fundic gland type neoplasm.

Figure 5

Pathways for diagnosis of fundus gland tumors based on immunohistochemistry.

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