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Fetal-type Glycogen Phosphorylase Expression in Intestinal Metaplasia as a Predictor of the Development of Gastric Cancer

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Abstract

Glycogen phosphorylase (GP; EC 2.4.1.1) plays a central role in the mobilization of carbohydrate reserves in a wide variety of organs and tissues. There are three major isoforms of mammalian GP; i.e., the muscle, liver, and brain isoforms. The physiological roles of muscle and liver GP are to provide fuel for energy production (to produce the energy required for muscle contraction) and to ensure a constant supply of glucose to extra hepatic tissues, respectively. However, the physiological role of brain GP (BGP) is poorly understood. It has been demonstrated that BGP is the major isoform of GP found in fetal tissue and tumor tissue, and BGP is identical to fetal-type GF (FGP).

We have demonstrated that the significant enzymatic activity of FGP in the gastric carcinoma and proliferating cells of particular Intestinal Metaplasia (IM). We studied 136 specimens with gastric carcinoma and the adjacent IM using specific anti-FGP antibody. FGP was expressed in 80% of the intestinal type and 19% of the diffuse type of carcinoma and in 88% and 42% in the generative zone of IM adjacent to each type of cancer foci, respectively. The proportion of the positivity of FGP expression in the cancer and IM was significantly greater in intestinal type carcinoma than in diffuse type. In addition, according to the proliferating cell nuclear antigen labeling index analysis, IM with FGP expression (FGP-IM) were significantly higher in a proliferating state than in IM without FGP, and some of them were co-expressed accumulated p53 in the generative cells. These data indicate that FGP could be one of the fetal biomarkers and FGP-IM could be a premalignant lesion of intestinal type adenocarcinoma.

We conducted another study to investigate the incidence of FGP-IM in gastric biopsy specimens and to identify FGP-IM as a predictor of the coexistence of accessory carcinoma and/or metachronous carcinoma. Eight endoscopic biopsy specimens of methylene blue-positive mucosa of the stomach were obtained from the patients with multiple gastric carcinomas (n=14), a single carcinoma (n=25) and atrophic gastritis (n=20), examined the incidence of FGP-IM. FGP positivity was 93.3% in the multiple carcinomas and 80.0% in the single carcinomas. The incidences of FGP-IM in the stomachs with multiple carcinomas, single carcinoma and atrophic gastritis were 83.2 ± 22.8%, 36.5 ± 41.3% and 7.1 ± 18.0%, respectively. The incidence of FGP-IM was significantly higher in the stomachs with multiple carcinomas than in those with a single carcinoma or atrophic gastritis. It is suggested that the frequent appearance of FGP-IM reflects the high potential of carcinogenesis of intestinal type gastric carcinoma and FGP-IM could be a predictive indicator of metachronous gastric carcinoma. Recently, there are increasing opportunities where endoscopic and laparoscopic local treatments are applied for the early gastric carcinoma, therefore, it is significantly important to identify the high-risk group of metachronous recurrence of gastric carcinoma.

FGP could serve as a potential predictor of the risk of the development of multiple and/or metachronous carcinomas. It might be possible to follow-up new lesions using this method, and follow-up studies would provide better information on whether FGP-IM positivity is a good predictor of metachronous recurrence after local treatment for gastric cancer.

Keywords: Fetal-type glycogen phosphorylase; Gastric cancer; Intestinal metaplasia

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Introduction

Glycogen phosphorylase (GP; EC 2.4.1.1) plays a central role in the mobilization of carbohydrate reserves in a wide variety of organs and tissues [1,2]. There are three major isoforms of mammalian GP; i.e., the muscle, liver, and brain isoforms, and it is possible to distinguish between them based on their functional and structural properties, as well as based on the tissues in which they are predominantly expressed [2-4]. Complementary DNA encoding the three human GP isoforms have been cloned and sequenced, and the tissue and organism-specific expression patterns and chromosomal localization of GP genes have been clarified [2,5]. Chromosome mapping analyses have revealed that the genes encoding muscle, liver, and brain GP (BGP) are located on chromosomes 11, 14, and 20, respectively, suggesting that distinct cis-acting elements govern the differential expression patterns of the three GP isoforms in various tissues. The physiological roles of muscle and liver GP are to provide fuel for energy production (to produce the energy required for muscle contraction) and to ensure a constant supply of glucose to extrahepatic tissues, respectively. However, the physiological role of BGP is poorly understood, although BGP is generally considered to be involved in the provision of emergency glucose supplies during stressful and/or ischemic periods [2,4,6,7]. In addition, it has been demonstrated that BGP is the major isoform of GP found in fetal tissue and tumor tissue, and BGP is identical to fetal-type GP (FGP) [6,7].

Histochemical staining has detected GP in differentiated hepatic and muscular tissues and in some proliferating tissues, including fetal tissue and carcinoma [8,9]. In the human stomach, phosphorylase is present in the undifferentiated gastric epithelium at the midpoint of fetal life, but is not detected in the gastric epithelium after birth. In a previous study, we histochemically detected intense GP activity in gastric cancer cells, especially well-differentiated adenocarcinoma cells, and in the proliferative zones of some intestinal metaplasia (IM) lesions, despite phosphorylase staining producing a negative result in the normal gastric epithelium, even in the proliferative zones. Positive reactions to GP staining were observed in all of the well-differentiated adenocarcinomas, whereas only a few poorly differentiated adenocarcinomas reacted positively. Positive reactions were noted in the proliferative zone in 69.5% and 25.7% of metaplastic glands in stomachs with well-differentiated and poorly differentiated adenocarcinoma, respectively, whereas they were rarely observed in glands from patients with peptic ulcers. Moreover, there was an apparent concordance between the locations of well-differentiated adenocarcinomas and the distribution of IM lesions with GP-positive proliferative zones [10].

We developed an immunehistochemical method, involving specific antibodies raised against highly purified GP isoforms from rat brain, muscle, and liver tissue, for detecting each GP isoform in human tissues [3], and immunohistochemical staining of the three GP isoforms was performed to identify the types of GP present in well-differentiated adenocarcinoma and in the proliferative zones of IM lesions in the human stomach [11]. Only the FGP isoform was observed in carcinoma cells and the proliferative zones of some IM lesions. The detection of FGP in both well-differentiated adenocarcinoma and the proliferative zones of IM lesions suggests that these two pathological entities share the same isoform and are histogenetically related. Moreover, FGP-positive IM (FGP-IM) could be regarded as a precursor of well-differentiated adenocarcinoma [11].

Subtyping of IM in the Human Stomach based on FGP Expression

It has been found that IM in the stomach increases the risk of gastric cancer [12-16]. Little genetic rearrangement is seen in IM or carcinoma; however, this makes it difficult to establish a direct carcinogenic link between them. IM has been classified into subtypes with the aim of clarifying the pathogenesis of gastric carcinoma [17-20]. In previous studies, different authors used different definitions for each subtype, which were based on their morphological, enzymatic, and mucin-secretion characteristics [17-20]. In such classifications, the subtyping is complicated and subjective, resulting in the existence of many variants. However, some studies have suggested that IM is a good marker of a high risk of gastric cancer, but the sub classification of IM is not important [14,21]. We studied 136 specimens of gastric carcinoma and the adjacent IM, which were surgically resected from gastric cancer patients (intestinal type, 72 patients; diffuse type, 64 patients), using a specific anti-FGP antibody and investigated 1) FGP expression in the gastric tumors and the adjacent IM lesions, 2) the relationship between the conventional subtypes (i.e., the complete and incomplete subtypes) and FGP expression in IM

lesions, 3) the proliferation state of and oncogenic changes seen in the generative cells of FGP-IM lesions, and 4) whether it was possible to develop an IM classification based on FGP expression in generative cells [22].

As shown in **Table 1**, 80.6% (58/72) of the intestinal-type carcinomas expressed FGP, while 18.8% (12/64) of the diffuse type were positive for FGP. The frequency of immunohistochemical positivity for FGP was significantly higher in intestinal-type carcinoma than in diffuse-type carcinoma (P<0.001). IM lesions were found adjacent to the carcinomas in 88.9% (64/72) and 37.5% (24/64) of the intestinal- and diffuse-type carcinoma cases, respectively. In the intestinal type, 87.5% (56/64) of the adjacent IM lesions exhibited FGP positivity. On the other hand, 41.7% (10/24) of the adjacent IM lesions displayed FGP positivity in the diffuse type. The frequency of FGP-IM lesions was significantly higher in the intestinal-type carcinoma cases than in the diffuse-type cases (P<0.001).

The expression of FGP in the generative zones of IM lesions was compared between the complete and incomplete types of IM. We selected 64 cases in which the mucosa adjacent to an intestinal-type carcinoma exhibited IM. Morphological and mucin-based histochemical examinations revealed that the adjacent IM lesions were classified as complete and incomplete in 23 (36%) and 41 (64%) cases, respectively. In the intestinal type of cancer, the incidence of incomplete-type IM was significantly higher than that of complete-type IM. However, there was no significant relationship between the conventional subtype of IM and the expression of FGP. Strong FGP expression was seen in both complete and incomplete IM lesions adjacent to gastric carcinomas (complete: 19/23, 82.6%; incomplete: 37/41, 90.6%).

Abnormal p53 accumulation was observed in 10 of 56 (17.9%) of the FGP-IM lesions adjacent to the intestinal carcinomas (**Table 1**). The p53 staining was restricted to the FGP-IM lesions and was mainly found in the generative zone (**Figure 1**). No p53 staining was detected in the FGP-negative IM lesions. In cancer foci, the overexpression of p53 was observed in 42 of 58 (72.4%), 8 of 14

Table 1 Frequency of FGP and p53 positivity in gastric carcinoma and IM.

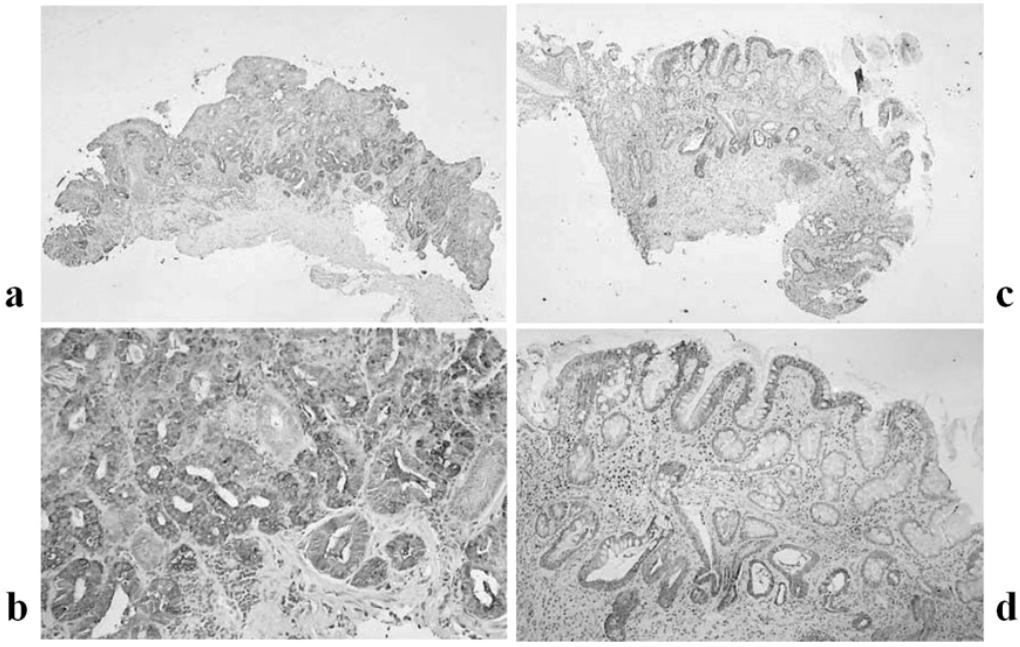
	Intestinal-type carcinoma (n=72)		IM (n=64)	
	No. (%) FGP-positive	No. (%) FGP-negative	No. (%) FGP-positive	No. (%) FGP-negative
	58 (80.6)*	14 (19.4)	56 (87.5)**	8 (12.5)
p53 positivity (%)	42 (72.4)***	8 (57.1)	10 (17.9)	0 (0.0)
	Diffuse-type carcinoma (n=64)		**IM (n=24)**	
	No. (%) FGP-positive	**No. (%) FGP-negative**	**No. (%) FGP-positive**	**No. (%) FGP-negative**
	12 (18.8)*	52 (81.2)	10 (41.7)**	14 (58.3)
p53 positivity (%)	2 (16.7)***	10 (19.2)	0 (0.0)	0 (0.0)

Note: FGP= Fetal-type Glycogen Phosphorylase; IM= Intestinal Metaplasia

* The frequency of positivity for FGP was significantly higher in intestinal-type carcinoma than in diffuse-type carcinoma (P<0.001).

** The frequency of FGP-IM lesions was significantly higher in the intestinal-type carcinoma cases than in the diffuse-type cases (P<0.001).

*** The frequency of p53 staining was significantly higher in intestinal-type carcinoma than in diffuse-type carcinoma (P<0.001).



a: FGP-positive carcinoma, ×60; **b:** high-power view, ×260; **c:** FGP-positive IM, ×60; **d:** high-power view, ×260

Figure 1 Immunohistochemical staining of biopsy specimens with anti-FGP antibody.

(57.1%), 2 of 12 (16.7%), and 10 of 52 (19.2%) of the intestinal-type carcinomas with and without FGP and the diffuse-type carcinomas with and without FGP, respectively. The frequency of p53 staining was significantly higher in intestinal-type carcinoma than in diffuse-type carcinoma (P <0.001), and the FGP-positive intestinal-type carcinomas tended to be p53-positive more frequently than those without FGP. The immunohistochemical staining of allophycocyanin (APC) and c-K-ras consistently produced negative results in IM.

These results indicate that a close association exists between FGP-IM and intestinal-type gastric carcinoma. Interestingly, morphological and mucin characterization revealed that there was no significant correlation between the subtype of IM (i.e., complete or incomplete) and the expression of FGP in the generative cells of IM lesions adjacent to intestinal-type carcinomas.

Furthermore, some of the FGP-IM lesions accumulated p53 in their generative cells, although other oncogene products (APC and c-K-ras) that are commonly found in the adenoma-carcinoma sequence in the colon were not detected in any of the IM generative cells [23]. The timing of genetic alterations in p53 has been investigated in the pathway from chronic gastritis to IM, dysplasia, and early stage carcinoma and was reported to be an early event in carcinogenesis in the stomach [24-26]. Abnormal accumulation of the p53 protein, however, has not been demonstrated in IM. We detected p53 accumulation in the generative cells of FGP-IM lesions despite its sporadic expression. These observations suggest that the generative cells of FGP-IM lesions might deviate from the normal differentiation pathway and be blocked from undergoing apoptotic cell death. Thus, this classification of IM based on the link between the FGP expression seen in the generative cell zones of IM lesions and gastric carcinoma might open new opportunities for research into the carcinogenesis of gastric carcinoma.

FGP Expression in the Stomach as a Predictor of Multiple Synchronous and/or Metachronous Gastric Tumors

With recent advances in endoscopic and laparoscopic techniques, the local treatment of gastric cancer offers a better quality of life to patients with early stage gastric cancer who are free from lymph node metastasis [27-31]. However, these treatments carry an increased risk of coexisting accessory or microscopic carcinomas being missed and/or of new tumors developing in the remnant stomach [32-35]. The incidence of multiple primary gastric carcinomas has been reported to range from 5-10% in patients who undergo gastrectomy for gastric cancer [36-40]. The incidence of multiple primary gastric carcinomas increases with age and is higher in males and patients with intestinal-type tumors. Such tumors frequently occur in the lower third of the stomach and cases of mucosal cancer. However, these accessory lesions are missed preoperatively in approximately 30-40% of patients with multifocal early stage gastric cancer. Furthermore, considerable numbers of microscopic cancers could be overlooked. Therefore, we should always remember that other lesions might be present when we are treating patients with gastric cancer with local treatment, such as endoscopic mucosal resection, endoscopic submucosal dissection, or laparoscopic partial resection.

Local treatment for early stage gastric cancer is currently mainly indicated for intestinal-type carcinoma. Indicators that could be used to predict the coexistence of multiple gastric tumors and/or the metachronous growth of another gastric intestinal-type tumor would be very useful for identifying high-risk groups and would contribute to follow-up examinations after local treatment for gastric cancer.

Our previous studies have demonstrated the significant role played by the generative cells of FGP-IM in intestinal-type gastric carcinoma, in which FGP-IM acts a premalignant lesion.

We investigated the incidence of FGP-IM in gastric biopsy specimens and whether FGP-IM can be used as a predictor of coexisting accessory carcinoma and/or metachronous tumors before or after local treatment for early stage gastric cancer [41]. Fifty-nine patients with intestinal-type early stage gastric cancer or endoscopic atrophic gastritis were analyzed. Of these patients, 14 had multiple synchronous gastric carcinomas, 25 had single tumors, and 20 had endoscopic atrophic gastritis without any localized lesions. During endoscopic examinations, the lower two-thirds of the stomach were dyed with methylene blue, and 8 endoscopic biopsy samples were obtained from the stained mucosae in the anterior stomach, posterior stomach, the greater and lesser curvature of the antrum, and the lower body of the stomach. A comparison of the patients' clinicopathological features showed that the patients with multiple early stage gastric carcinomas were significantly older than those with single early stage gastric carcinomas. However, none of the other parameters differed significantly among the three groups.

The reactivity of endoscopic gastric carcinoma biopsy specimens to anti-FGP antibody is shown in **Figure 2**. Strong positive reactions were observed in the cytoplasm of the cancer cells. In 93.3% (28/30) of the multiple carcinomas and 80.0% (20/25) of the single carcinomas, the biopsy specimens exhibited positive staining for FGP. The frequency of FGP positivity in intestinal-type carcinoma corresponded well with the findings of our previous reports [11,42]. The IM glands displayed slight structural deformity, but no cellular atypia was observed. The generative cell zones of the IM lesions exhibited positive reactivity. Strong reactivity, similar to that seen in the cancer cells, was noted in the cytoplasm of the IM generative cells.

The incidence of FGP-IM is shown in **Figure 2**. The distribution of the FGP-IM lesions in the stomach was extremely characteristic in each group. The distribution was almost symmetrical in both the multiple carcinoma and atrophic gastritis groups. Although almost none of the biopsy specimens from the stomachs with atrophic gastritis contained FGP-IM lesions, all of the biopsy specimens from the stomachs with multiple carcinomas included FGP-IM lesions. Furthermore, all of the carcinomas in the multiple carcinoma group exhibited high frequencies of FGP-IM lesions, except for two in which the cancer foci were negative for FGP. On the other hand, a bimodal distribution pattern was observed

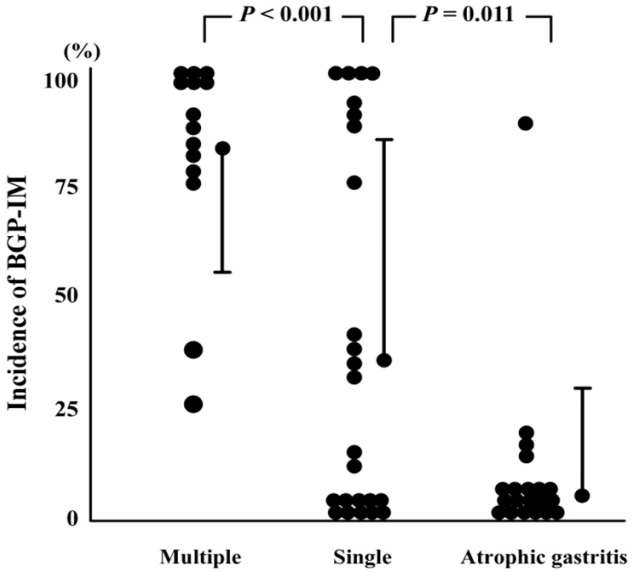


Figure 2 Distribution of the incidence of FGP-IM in the multiple carcinoma, single carcinoma, and atrophic gastritis groups.

in the single-carcinoma group; i.e., about a quarter of the group displayed a high frequency of FGP-IM lesions, but about half of the group did not have any FGP-IM lesions at all. The incidence of FGP-IM in the stomachs with multiple carcinomas, single carcinomas, and atrophic gastritis was 83.2% ± 22.8%, 36.5% ± 41.3%, and 7.1% ± 18.0%, respectively. The incidence of FGP-IM was significantly higher in the stomachs with multiple carcinomas than in those with single carcinomas or atrophic gastritis, and it was significantly higher in the stomachs with single carcinomas than in those with atrophic gastritis.

One of the major problems with the local treatment of gastric cancer is that metachronous carcinomas can arise in other parts of the stomach. A recent molecular biological study has suggested that high microsatellite instability in gastric tumors is associated with synchronous and/or metachronous gastric cancer, whereas there was no difference in proliferative ability, the carcinogenic pathway (p53 or K-ras), or the expression of various mismatch repair genes between synchronous/metachronous and single gastric tumors, although the mechanism underlying this relationship remains unclear [43]. However, the application of molecular genetics to the screening and surveillance of patients with gastric cancer is still in its infancy. Arima et al. reported that metachronous recurrence was found in 6 of 76 endoscopically treated patients, and it was encountered significantly more frequently in patients in which multiple synchronous lesions were detected during the initial treatment. In addition, Arima et al. stressed the importance of performing frequent periodic endoscopic examinations during the follow-up period after endoscopic treatment for detecting gastric mucosal recurrence [34]. The early detection of metachronous cancer has beneficial effects on the outcomes of any subsequent treatment, for which minimally invasive therapy, including endoscopic treatment, can be used. The necessity of frequent endoscopic follow-up, however, affects the quality of life of patients and increases medical costs. Therefore, the ability to reliably identify patients who are at high risk of metachronous recurrence is very important for determining the endoscopic follow-up schedule after the initial endoscopic treatment. As metachronous recurrence was detected significantly more frequently in patients with multiple synchronous lesions [28,29,34], predictors of metachronous recurrence might correspond with indicators of multiple synchronous gastric carcinomas.

Wittekind et al. analyzed the cases of 61 patients with synchronous gastric carcinomas and suggested that multiple primary tumors often arose from precancerous lesions, leading to them displaying similar genetic alterations [40]. It is generally accepted that IM in the stomach increases the risk of gastric cancer [12-15]. However, it has been suggested that only 0.1-0.2% of IM lesions are involved in the carcinogenesis of intestinal-type gastric cancer worldwide [44]. Therefore, IM lesions that are significantly correlated with the carcinogenesis of intestinal-type cancer should be selected for use as markers of such cancer. Our previous studies revealed that the frequency of FGP positivity in both cancer and the adjacent IM was significantly higher in intestinal-type carcinoma than in the diffuse type. Also, we found that FGP-IM exhibited a much stronger correlation with gastric carcinoma than the conventional type of IM, and FGP-IM samples were demonstrated to be in a proliferative state significantly more often than FGP-negative IM samples. Furthermore, p53 mutations were only detected in FGP-IM, suggesting that FGP-IM is a precancerous condition that can lead to intestinal-type carcinoma [10,11,22,42,45]. Thus, our findings indicate that FGP-IM is an excellent marker of the early stages of gastric carcinogenesis.

We also clearly demonstrated that the incidence of FGP-IM was significantly higher in stomachs with multiple gastric carcinomas than in those with single carcinomas or atrophic gastritis. The finding that some stomachs with single carcinomas had a high incidence of FGP-IM might be suggestive of the coexistence of microscopic intestinal-type carcinomas or the possibility of metachronous recurrence in the future. Subjecting endoscopic biopsy specimens to immunohistochemical assays of FGP expression in IM lesions is an easy and reliable way of assessing the FGP-IM status of the stomach, and thus, could be used to predict the risk of metachronous gastric carcinoma in patients with synchronous gastric carcinoma. These results suggest that analyzing FGP expression in IM lesions in biopsy specimens would contribute to the pre- and postoperative assessment of multiple and metachronous gastric tumors.

Our study demonstrated that FGP-IM was even detected in stomachs with endoscopic atrophic gastritis that were free from malignant lesions, suggesting that FGP-IM is not a pathological entity that is associated with changes in the carcinogenic microenvironment in the gastric mucosa. Therefore, FGP could serve as a potential predictor of the risk of the development of multiple and/or metachronous carcinomas. It might be possible to follow-up new lesions using this method, and follow-up studies would provide better information on whether FGP-IM positivity is a good predictor of metachronous recurrence after local treatment for gastric cancer.

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