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WORD COUNT 4079
TIME SUBMITTED 15-MAR-2023 10:05PM
PAPER ID 97650013

**Name of Journal:** *World Journal of Clinical Cases*
**Manuscript NO:** 82965
**Manuscript Type:** MINIREVIEWS

# Helicobacter pylori plays a key role in gastric adenocarcinoma induced by spasmolytic polypeptide-expressing metaplasia

Helicobacter pylori; Spasmolytic polypeptide-expressing metaplasia;

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**Abstract**

*Heliobacter pylori*, a group 1 human gastric carcinogen, is significantly associated with chronic gastritis, gastric mucosal atrophy, and gastric cancer. Approximately 20% of patients infected with *H. pylori* develop precancerous lesions, among which metaplasia is the most critical. Except for intestinal metaplasia (IM), which is characterized by goblet cells appearing in the stomach glands, one type of mucous cell metaplasia, spasmolytic polypeptide-expressing metaplasia (SPEM), has attracted much attention. Epidemiological and clinicopathological studies suggest that SPEM may be more strongly linked to gastric adenocarcinoma than IM. SPEM, characterized by abnormal expression of trefoil factor 2 (TFF2), mucin 6 (MUC6), and Griffonia simplicifolia lectin II (GSII) in the deep glands of the stomach, is caused by acute injury or inflammation. Although it is generally believed that the loss of parietal cells alone is a sufficient and direct cause of SPEM, further in-depth studies have revealed the critical role of immunosignals. There is controversy regarding whether SPEM cells originate from the transdifferentiation of mature chief cells or professional progenitors. SPEM plays a functional role in the repair of gastric epithelial injury. However, chronic inflammation and immune responses caused by *H. pylori* infection can induce further progression of

SPEM to IM, dysplasia, and adenocarcinoma. SPEM cells upregulate the expression of whey acidic protein(WAP) 4-disulfide core domain protein 2 (WFDC2) and CD44 variant 9 (CD44v9), which recruit M2 macrophages to the wound. Studies have revealed that IL-33, the most significantly upregulated cytokine in macrophages, promotes SPEM toward more advanced metaplasia. Overall, more effort is needed to reveal the specific mechanism of SPEM malignant progression driven by *H. pylori* infection.

**Key Words:** Gastric cancers; *Helicobacter pylori*; Intestinal metaplasia; Macrophages; Spasmolytic polypeptide-expressing metaplasia; SPEM

Li M, Hong X, Zhang W, Liang Y, Cai T, Chen Y, Pan H, Kang J, Guo S, Li H. Helicobacter pylori plays a key role in gastric adenocarcinoma induced by spasmolytic polypeptide-expressing metaplasia. *World J Clin Cases* 2023; In press

**Core Tip:** SPEM, induced by *Heliobacter pylori* infection in humans, is strongly associated with gastric adenocarcinoma. Chronic inflammation and immune responses caused by *H. pylori* infection play important roles in the malignant progression of SPEM. Recent studies suggest that CD44v9 and WFDC2 expressed by SPEM leads to M2 macrophage recruitment. Furthermore, M2 macrophages upregulate the expression of IL33, which eventually promotes malignant progression.

## INTRODUCTION

Alterations in gland cell lineages between normal and metaplastic cells, including in IM and SPEM, are key processes in *H. pylori*-induced gastric cancer. SPEM, induced by the loss of parietal cells, is a type of mucous cell metaplasia characterized by abnormal expression of TFF2 in the deep glands of the stomach. It is generally believed that SPEM cells arise following transdifferentiation of mature chief cells and represent the major reparative lineage responsible for wound healing. However, the chronic inflammation

and immune response caused by *H. pylori* infection exacerbates the transformation of SPEM into cancerous malignancies. The mechanism of how *H. pylori* causes parietal cell loss remains unclear, although it may be related to the disruption of CLDN18 in gastric epithelial cells. After parietal cell loss, SPEM emerges in the deep glands of the stomach. CD44V9 and WFDC2 secreted by the SPEM cells recruit macrophages and drive M2 polarization; thus, up-regulating inflammatory factors such as IL33 and IFN-γ to promote the progression of SPEM to IM and adenoma. Further studies on the specific association between SPEM and adenocarcinomas are needed.

## THE CHARACTERISTICS OF SPEM:

***1. SPEM is induced by the loss of parietal cells in combination with additional signals***

Initially, it was believed that the loss of parietal cells (oxyntic atrophy) alone was a sufficient and direct cause of SPEM[16]. Studies examining the predisposing factors of SPEM in mice have demonstrated that SPEM develops after parietal cell loss and chronic Helicobacter infection or acute injury due to treatment with DMP-777, L-635, or high-dose tamoxifen[17,18,19]. SPEM caused by *H. pylori* infection is discussed separately in the following sections. Here, SPEM induced by drug treatment in a mouse model is discussed. Three drugs, DMP-777, L-635, and tamoxifen, have frequently been used to study the progression of SPEM in mice because they induce acute parietal cell loss of mucous glands, which leads to the development of trefoil factor (TFF) 2–expressing metaplasia (SPEM)[16,19,20,21,22]. DMP-777, a parietal cell-specific protonophore, can partition into the apical acid secretory membranes of parietal cells, leading to acute death after acid secretion[4,23]. DMP-777 is also a potent neutrophil elastase inhibitor, does not elicit a significant inflammatory response to the acute parietal cell loss. L-635 is an analog of DMP-777 with the same ability to specifically kill parietal cells without inhibiting the inflammatory response[4,23]. Tamoxifen, a selective estrogen-receptor modulator, is widely used in chemotherapy and to treat osteomalacia. However, one study found that treatment of normal mice with a single >3 mg/20 g body weight dose of tamoxifen led to >90% apoptosis of all gastric parietal cells, and expression of

mucous neck cell marker TFF2 which occurred at the base of mucous glands[19,24,25,26]. SPEM is induced by these drugs, causing the loss of parietal cells and altering the orderly differentiation of gastric mucosal cell lineages. However, the mechanism by which this occurs remains unclear (Table 1). In addition, SPEM was found in a rodent animal model that had received preoperative nitrite carcinogen administration and developed post-gastrectomy syndrome[27]. Parietal cells secrete several epidermal growth factor (EGF) receptor ligands, including transforming growth factor (TGF)-α, amphiregulin (AR), and heparin-binding EGF–like growth factor (HB-EGF)[28,29,30,31], which regulate differentiation and epithelial cell function. Therefore, altering the levels of these EGF receptor ligands may contribute to the emergence of SPEM. Previous studies using AR knockout and TGF-α knockout mice showed that the loss of TGF-α did not influence the induction of SPEM and loss of AR caused an acceleration and augmentation in the induction of SPEM[4,32]. Additionally, the AR-null mouse model represents the first mouse model for the spontaneous development of fundic SPEM with progression to IM and neoplasia. An increasing number of trials are underway to decipher the precise mechanism of the progression from parietal cell loss to SPEM. Additional signals, such as cytokines secreted by immune cells, are also important for the progression of SPEM. As the necessities of th2 cytokine induction in the stomach, IL-33 signaling pathway has been proved indispensable for the development of metaplasia after parietal cell loss. Interestingly, IL33 KO (IL33 knockout), ST2 KO (IL33 receptor knockout,ST2, knockout), and IL13 KO (IL13 knockout) mice treated with either L-635 or DMP-777 did not develop metaplasia following acute parietal cell loss. IL-33 signaling drives M2 macrophage polarization, which is associated with progression toward more advanced metaplasia[33,34]. Although the association between the immune phenotype and SPEM remains unclear, there is growing evidence that some immune factors lead to the development of SPEM. For example, interferon-γ(IFN-γ), the most abundant cytokine detected in the highly complex cytokine milieu of atrophic gastritis, contributes to the emergence of SPEM [35]. An investigation showed that IFN-γ causes gastric epithelial cells expressing the IFN-γ receptor to die and

promotes the progression from gastritis caused by anti-parietal T-cells to atrophic gastritis and SPEM[33]. Overall, After the loss of parietal cells, inflammatory factors, as additional signals, are crucial for the production of SPEM.,Specifically, IL13, IL33 and their receptor ST2 have been found to play an indispensable role. In addition, overexpression of IFN-γ also causes parietal cell death and induces SPEM. At present, it is not clear why parietal cell loss induces SPEM, but the absence of AR secreted by parietal cells may be the key factor (Table 2).

***2. SPEM cells may arise from different types of cells besides mature chief cells and professional progenitors***

There are two hypotheses regarding the derivation of SPEM cells: 1) These metaplastic cells arise from cryptic professional progenitors that enter an abnormal differentiation state stimulated by the environment; and 2) SPEM cells originate from transdifferentiation of mature chief cells. Increasing experimental evidence from human and rodent models supports the latter hypothesis. In 2010, Nam *et al* performed lineage tracing of chief cells using Mist1CreER/+mice, in which Mist1 was chief cell-restricted expression, to examine to origin of SPEM lineages. Initially, complete separation of TFF2 immune-stained mucous neck cells and X-gal stained Mist1-expressing chief cells were observed in the fundus. After the 10-day period after tamoxifen treatment, basal glandular cells labeled with antibodies against TFF2 were observed, which concomitantly showed β-galactosidase enzymatic activity, indicating that these SPEM cells were derived from mature, Mist1-expressing chief cells[16]. In 2017, Radyh *et al* successfully induced SPEM in mice using a non-genetic approach by intraperitoneal injections of 5-fluorouracil, which blocked gastric cell proliferation, and tamoxifen. In this study, a similar magnitude of gastric intrinsic factor(GIF)$^+$ cell loss and GIF$^+$GSII$^+$ SPEM cell increase was observed at the gland base, indicating that SPEM developed in the absence of cell proliferation; therefore, it did not arise from stem cells. Then, histological analysis were used to investigate gastric resection specimens from 10 patients with adenocarcinoma and found normal zymogenic chief cells that were transitioning into SPEM cells only in the gland bases, rather than the proliferative stem

cell zone[36]. Recent studies have shown that SPEM is derived from mature chief cells. Caldwell *et al* used a GIF-green fluorescent protein(GIF-GFP) marker to trace the cell lineage of mice during the development of acute metaplasia after L-635 treatment, and performed co-immunofluorescence staining for various gastric lineage markers. These results demonstrated that SPEM cells predominantly transdifferentiated from GFP-expressing chief cells, rather than proliferating isthmal progenitor cells, thereby providing pivotal evidence for cell lineage contributions from differentiated gastric chief cells[37]. In contrast, Hata *et al* identified G protein-coupled receptor 30(GPR30), the G-protein-coupled form of the estrogen receptor, as a chief cell-specific marker of mice to trace the gland cell lineage during the development of SPEM[38]. This study found no evidence of lineage expansion from GPR30$^{+}$ chief cells after treatment with tamoxifen and suggested that GSII+GIF+ SPEM may not be a sign of chief cell dedifferentiation, but represent a regenerative expansion of neck cells in response to chief cell depletion. Although the hypotheses regarding the origin of SPEM remain divisive, more studies are investigating the mechanism of SPEM cell differentiation, with the mainstream belief being that SPEM cells arise from transdifferentiation of mature chief cells.

***3. SPEM plays a functional role in repairing gastric epithelial injury***

The complex process of tissue repair in gastric ulcers involves re-epithelialization and regeneration[39]. Ulcer-associated cell lineages (UACL) greatly contributes to epithelial regeneration, proliferation, and differentiation into intestinal crypts of the injured gastric tissue[39,40]. Recent studies have claimed that SPEM is always localized to the base of the ulcer margin in the stomach mucosa, in a position similar to that of the UACL after severe gastric injury[41]. Data from numerous pathologists have demonstrated that SPEM also represents the major reparative lineage responsible for wound healing. Engevik *et al* determined the quality of ulcer repair with advancing age in mice and found that the emergence of SPEM within the ulcerated region in young mice coincided and disappeared when the mucosa returned to its normal compendium

of cell lineages, a response that was absent in aged mice with a weaker capacity for repair injury[42]. This study suggests that SPEM might secrete the growth factors and cytokines necessary for wound repair in ulcers and is correlated with age. Therefore, further research performed by Aihara *et al* revealed that TFF2 expression by SPEM has a central role in gastric injury and repair[43]. TFF2 was upregulated and sustained in mice with gastric ulcers induced by acetic acid application, and promoted gastric healing after injury through anti-apoptotic and motogenic (cell migratory) activities[44,45,46,47]. Gastric ulcer healing was strongly delayed in TFF2 knockout mice, suggesting that TFF2 is markedly involved in the initial closure of an ulcer[43]. The development of SPEM is also followed by the expression of CD44 variant isoform 9 (CD44v9), which contributes to defense against reactive oxygen species (ROS); therefore, promoting tumor growth[48,49,50]. CD44v9 expression emerged at the ulcer margin during gastric ulcer repair, and was rarely expressed as the gastric epithelium healed. While CD44 KO mice demonstrated loss of epithelial repair ability, CD44 KO mice transplanted with CD44v9-expressing gastric organoids demonstrated epithelial repair comparable to that of the normal group[51]. These data suggested that CD44 contributes to gastric ulcer repair.

***4. The progression from normal gastric mucosa to SPEM is dynamic and consecutive***

The mature chief cell, differentiated from mucous neck cells migrating toward the bottom of the glands, expresses not only pepsinogen but also GPR30, helix-loop-helix (bHLH) transcription factor Mist1, and GIF[52]. Unlike chief cells, SPEM, is a type of mucous cell metaplasia characterized by the expression of TFF2, MUC6, CD44v9, and GSII[10]. Immunohistochemistry is widely used to monitor different cell locations, proliferation states, and survival stages, based on differences in expression levels and reveals the dynamic and consecutive transformation of glandular molecular expression profiles during metaplasia[53]. Dual immunofluorescence staining for TFF2 and GIF in Hp-infected Mongolian gerbils revealed that SPEM exhibits TFF2 and GIF double-staining at the bases of glands in the earlier stages. However, over the time of infection, GIF staining progressively decreased and single staining was observed with anti-

TFF2[3]. Similarly, in resection and gastric tissue microarray (TMA) samples obtained from SPEM lesions from the USA and Republic of Korea, TFF2+/MIST1+ and TFF2+/MIST1- SPEM cells were observed coincidentally[14]. Lennerz described these samples as exhibiting hybrid-SPEM and established SPEM because MIST1 expression was restricted to the chief cell compartment in the normal oxyntic mucosa[14]. This suggests that the transdifferentiation of master cells is a continuous process, in which the characteristics of chief cells are gradually reduced and the cell expression profile is transformed from mature master cells to SPEM. Single-cell RNA sequencing of two SPEM phenotypes (Tff2+Muc6+Gif+ and Tff2+Muc6+Gif-) revealed that Gif+ and Gif- TFF2-expressing mucinous cells exhibit nearly indistinguishable transcriptomes[54]. Different metaplastic cells exhibit overwhelming overlap in physical location within the gastric unit, implying that Gif expression is gradually lost during the development of SPEM, and they share an ontology rather than a separation into unique subsets[54]. Therefore, it is conceivable that a pathological definition of SPEM includes cells that do not express mature chief cell transcripts, such as Gif in the murine stomach.

## THE LINK BETWEEN *H. PYLORI* INFECTION AND SPEM

*H. pylori* infection is not only a predisposing factor for SPEM but also causes chronic inflammation and immune response which promotes SPEM development. *H. pylori* infection is the major predisposing factor for gastric cancer, as it causes parietal cell loss and induces the development of SPEM. Additionally, in the presence of ongoing inflammation, metaplasia evolves and expands[16,21,23,27,34].

### *1. The presence of SPEM promoted the colonization and spread of H. pylori*

*H. pylori* attaches to the gastric epithelium primarily through the binding of two bacterial adhesins, BabA11 and SabA,12 to the glycosylated receptors Lewis B (Leb) and sialyl-Lewis X (sLex), respectively[55]. sLex extends deep into the metaplastic neck and gland base, and accompanies SPEM progression in the stomach. Therefore, *H. pylori* can access deeper regions along the gastric corpus units, which protects *H. pylori* from the harsher, more acidic environment near the gastric lumen[56]. This mechanism allows H

pylori to advance the infected area throughout the stomach by binding to the expanded sLex. Furthermore, because H pylori interacts with the injured corpus epithelium and may lead to an accumulation of mutations within metaplastic cells, increased expression of sLex indicates poor prognosis in gastric adenocarcinoma[57].

***2. Chronic inflammation and immune response caused by H. pylori infection exacerbates SPEM malignant transformation***

SPEM appears to be a traumatic stress mechanism to repair the gastric mucosa in the event of acute injury. After the injury is repaired, the gastric glands return to normal. One study, using a tamoxifen-induced SPEM mouse model, showed that SPEM cells are able to re-differentiate into chief cells following recovery from injury without chronic inflammation[58]. However, the continuous expansion of *H. pylori* infection causes chronic inflammatory infiltration, which changes the expression of SPEM and leads to the development of dysplasia or IM. SPEM development as a result of *H. pylori* infection is focused on as it is the most common situation of SPEM development in humans. Gastric epithelial cells adhere to each other through tight junctions (TJs), sealing intercellular spaces to maintain epithelial barrier function and mucosal homeostasis[59,60,61]. The stomach-type claudin-18 (stCLDN-18) is the predominant claudin expressed in the stomach, resisting H+ and pepsin leakage [62]. One study found that *H. pylori* infection in mice resulted in focal loss, attenuation, and disruption of CLDN18 in gastric epithelial cells and showed parietal cell loss and SPEM characteristics[10]. Further study using stCLDN-18 gene knockout mice showed that stClDN-18 deficiency causes gastric tumor emergence *via* cytokine, stemness, and Wnt signaling–activated pathways[63]. Once *H. pylori* or inflammation attenuates the expression of stCLDN18, adenocarcinoma progression occurs spontaneously[10]. This could be attributed to the SPEM development; however, the detailed mechanisms are unclear. To identify the commonalities and differences between SPEM lineages induced by three different methods, Weis *et al* used three different mouse models of parietal cell loss, chronic inflammation with *Helicobacter felis* infection, acute inflammation with L-

635 treatment, and without inflammation following DMP-777 treatment[20]. The RNA transcripts showed that while markers such as whey acidic protein(WAP) 4-disulfide core domain protein 2 (WFDC2, also named HE4) and clusterin (Clu) are expressed in all three phenotypic SPEM lineages, cytokines such as cystic fibrosis transmembrane conductance regulator (CFTR) ,which is expressed only in intestinal metaplasia in humans,are only upregulated in metaplasia associated with chronic inflammation. These data indicate that distinct heterogeneity is present in three different SPEM mice models, but inflammatory infiltration leads to the evolution of metaplasia toward a more proliferative lineage. Overall, inflammation is a key factor in the progression of SPEM to a more aggressive metaplastic phenotype. Another important factor related to *H. pylori* infection that promotes SPEM toward gastric cancer is the immune response. MicroRNAs (miRNAs) are critical post-transcriptional regulators of gene expression[64,65]. miRNA sequencing, which investigated mice infected with *H. felis*, showed that several miRNAs were highly expressed in normal chief cells but downregulated in SPEM cells, and a decrease in miR148a in chief cells induced upregulation of CD44 variant 9 (CD44v9), one of the transcripts expressed at an early stage of SPEM development[66]. These results suggest that miR-148a regulates early reprogramming of chief cells and the process of transdifferentiation into SPEM[66]. CD44v9 plays a critical role in wound repair and recruits macrophages, key immune cells, and secretes cytokines, chemokines, and pro-angiogenic factors that are necessary for repair. Marked infiltration of macrophages was observed around the SPEM, and were positive for the M2 marker and hemoglobin scavenger receptor CD163, suggesting M2 polarization[34,67,68]. Although M2 macrophages are linked to repair and are anti-inflammatory, they have been shown to promote neoplasia[69]. The occurrence and development of SPEM are closely related to macrophages. Firstly, L635-treated macrophage-depleted mice demonstrated a significant reduction in SPEM cell numbers, indicating that macrophage infiltration may promote the production of SPEM cells[70]. Secondly, after SPEM induction, WFDC2 secreted by SPEM cells has been confirmed to induce M2 macrophage polarization and up-regulate the secretion of IL33 by

macrophages to advance SPEM[70,71]. Studies of mouse models and human metaplastic tissues indicate that M2-macrophages promote the progression of metaplasia toward a more proliferative and advanced phenotype[34]. Petersen *et al* used RNA sequencing to analyze macrophages from the stomach corpus of mice with SPEM and identified an M2a-polarized macrophage population. Additionally, IL-33, an IL-1 family member, was the most significantly upregulated cytokine in macrophages, which drives M2 macrophage polarization associated with the progression toward more advanced metaplasia[34,71]. Another study investigating the function of IL-33 and IL-33 receptor ST2 showed that IL-33/ST2 promoted the malignant progression of gastric cancer cells[72]. In addition, Jeong *et al*. observed a similar phenomenon; WFDC2, a small secretory protein highly expressed in fibrosis, lung cancer, and stomach cancer in humans, was able to induce M2 macrophage polarization and IL33 production in mice. Wfdc2-knockout mice treated with DMP-777, L-635, or high-dose tamoxifen showed remarkable resistance to SPEM development. However, M2 macrophage polarization, IL33 production, and SPEM development were observed after treatment with recombinant WFDC2[70] (Figure 1). Therefore, after the SPEM induced, WFDC2 secreted by SPEM has been confirmed to induce M2 macrophage polarization and up-regulate the secretion of IL33 by macrophages to advance SPEM[70,71].However, whether high WFDC2 gene expression affects the poor prognosis of SPEM through the WFDC2 protein or other pathways remains controversial. We found that upregulation of WFDC2 gene expression was accompanied by WFDC2 protein reduction in SPEM murine models with chronic *H. pylori* inflammation (data not shown). Similarly, a previous report showed that serum WFDC2 Levels were not altered in patients with gastric cancer[73]. These studies suggest that *H. pylori* infection, leading to the loss of parietal cells, induces SPEM emergence and upregulation of CD44V9 and WFDC2 expression under chronic inflammation and immune responses. CD44V9 and WFDC2 recruit M2 macrophages and release IL33 to advance SPEM malignant progression, which may be the potential mechanism of gastric cancer (Figure 2).

## CONCLUSION

The Working Group Meeting of the International Agency for Research on Cancer with the World Health Organization has classified *Helicobacter pylori* (*H. pylori*) as a group 1 human gastric carcinogen. *H. pylori* colonizes the gastric mucosa of more than half of the world's population [1]. Epidemiological studies in humans and experiments in rodents have shown that *H. pylori* infection, the accompanying immune response, and chronic inflammation are closely related to the occurrence and progression of gastric adenocarcinoma[2,3,4,5]. Alterations in gland cell lineages between normal and metaplasia cells, including intestinal metaplasia (IM) and spasmolytic polypeptide-expressing metaplasia (SPEM), are key processes in *H. pylori*-induced gastric cancer. Gastric cancer is one of the most common and deadly cancers worldwide, leading to the death of nearly 1 million of people every year[6]. Approximately 95% of gastric cancers are adenocarcinomas derived from the glandular epithelium of the gastric mucosa[7]. This theory (called the Correa pathway) was first proposed by Professor Correa in 1975 and was updated in 1992[8]. The progression was later recognized as normal gastric mucosa → superficial gastritis (later renamed non-atrophic gastritis, NAG) → multifocal atrophic gastritis (MAG) without IM → IM of the complete (small intestine) type → IM of the incomplete (colonic) type → low-grade dysplasia (low-grade noninvasive neoplasia) → high-grade dysplasia (high-grade noninvasive neoplasia) → invasive adenocarcinoma[8]. Among these stages, IM is of great interest to pathologists because the intestinal mucosa containing goblet cells is found in the stomach. Follow-up studies focused on IM suggest that it is a useful biomarker for gastric cancer risk. However, recent studies have revealed the existence of a second metaplastic lineage, spasmolytic polypeptide-expressing metaplasia (SPEM)[9]. SPEM, characterized by abnormal expression of spasmolytic polypeptide (SP) / trefoil factor 2 (TFF2) in the deep glands of the stomach, is a type of mucous cell metaplasia caused by acute injury or inflammation. SPEM also expresses mucinous molecular markers, such as mucin 6 (MUC6) and Griffonia simplicifolia lectin II (GSII)[10]. This underappreciated type of mucous metaplasia has been described with various names, including pseudo-pyloric

metaplasia, mucous metaplasia, or antralization of the corpus. Numerous studies have reported that SPEM may have a stronger link to gastric adenocarcinoma than intestinal metaplasia, and is a neoplastic precursor of gastric adenocarcinoma in humans[3,4,11]. Epidemiological studies in the United States, Japan, and Iceland showed that SPEM, typically located in the mucosa adjacent to the carcinoma or areas of dysplasia, was associated with > 90% of resected gastric cancers and > 50% of early gastric cancers[9,11]. Additionally, a clinicopathological study in patients from Korea suggested that TFF2 expression plays a role in gastric cancer invasion[12]. Previous studies have reported that SPEM and IM often co-exist in people with atrophic gastritis caused by chronic *H. pylori* infection[13,14]. Notably, SPEM and IM are two different lineages of metaplastic cells. SPEM are cells marked by the expression of TFF2 and MUC6, while the characteristic markers of IM are TFF3, MUC2 and CDX2[15]. The current mainstream view is that the progression of SPEM leads to IM. According to immunocytochemical evidence, SPEM expressing TFF3 and MUC2 has been reported; therefore, intermediates of intestinalized SPEM may exist that reflect evolution of metaplastic phenotypes[13]. However, one study also found MIST1 and CDX2 double positive SPEM cells, indicating that IM may not come from a single pathway of SPEM progression[14].

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