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Review Article

Role of spasmolytic polypeptide-expressing metaplasia in gastric mucosal diseases

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Abstract: Spasmolytic polypeptide-expressing metaplasia (SPEM) is a trefoil factor 2-expressing metaplasia in the fundic glands that resembles the fundic metaplasia of deep antral glandular cells and arises mainly from transdifferentiation of mature chief cells as well as mucous neck cells or isthmic stem cells. SPEM participates in the regulation of gastric mucosal injury, including focal and diffuse injury. This review focuses on the origin, models, and regulatory mechanisms of SPEM and on its role in the development of gastric mucosal injury. We hope to provide new prospects for the prevention and treatment of gastric mucosal diseases from the perspective of cell differentiation and transformation.

Keywords: Gastric mucosal injury, cellular differentiation, regeneration and repair, preneoplastic metaplasia, dysplasia

Introduction

SPEM is a spasmolytic polypeptide/trefoil factor 2 (TFF2)-expressing metaplasia in the fundic glands that resembles the fundic metaplasia of deep antral glandular cells and has morphological features similar to the abnormal metaplastic cell lineage of Brunner's glands of the duodenum [1] and the expression of CD44 variant isoform 9 (CD44v9), lectin, mucin 6 (Muc6), GSII-lectin, and HE4, in addition to the characteristic expression of TFF2 [2]. SPEM arises mainly from the transdifferentiation of mature chief cells, which regain the ability to proliferate during acute or chronic injury of the gastric mucosa and then differentiate into metaplastic mucus-secreting SPEM cells [3].

Gastric mucosal injury classified as local and diffuse injury, and the SPEM cell lineage is present regardless of the type of injury [4] (**Figure 1**). Local injury is a repairable injury that does not alter the pattern of cellular differentiation, and gastric ulcers are the most common type [5]. In gastric ulcer-induced injury, SPEM represents a mucus secretion repair lineage that appears at the ulcer margin and disappears when the mucosa returns to the normal cell lineage [6]. Therefore, SPEM not only recruits repair cells to the site of mucosal injury but also reprograms gastric epithelial cells and increases the protective barrier of the epithelium, which is an important process associated with regeneration and repair after gastric mucosal injury [6, 7]. Accumulating studies have shown that SPEM represents an initializing metaplastic response to acute gastric injury and that when injury and chronic inflammation persist, focal injury progresses to diffuse injury and can perpetuate recurrent reprogramming and metaplastic patterns, which are common preneoplastic pathways associated with diffuse injury [2, 8, 9].

Diffuse injury is a type of chronic injury that alters the pattern of cell differentiation; it is commonly caused by chronic *Helicobacter pylori* infection or parietal cell loss and is closely related to the development of gastric lesions [10, 11]. In diffuse gastric injury, gastric acid-secreting parietal cells undergo atrophy, the number of parietal cells decreases, and zymo-

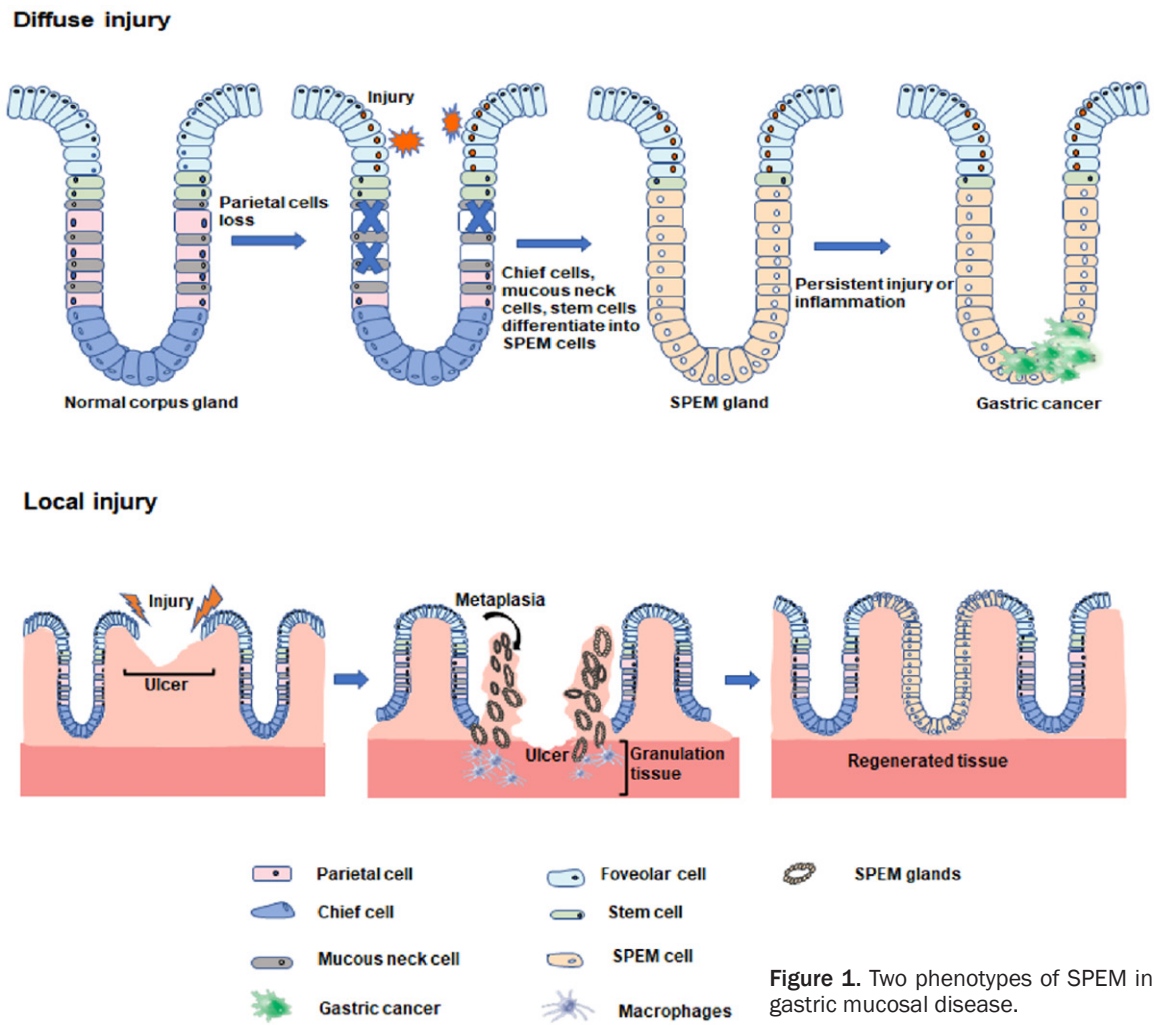

Figure 1. Two phenotypes of SPEM in gastric mucosal disease.

gen-secreting chief cells also decrease and are replaced by TFF2-expressing metaplasia, resulting in the production of SPEM cell lineages [12]. In the area of the fundic gland, which contains both SPEM and intestinal metaplasia (IM), SPEM appears in the area of the deep fundic gland, while IM can be observed in the lumen of the gland, and IM may have developed from SPEM [13]. The transition from SPEM to IM indicates that metaplasia has passed the transition point of preneoplastic metaplasia and may progress to dysplasia and adenocarcinoma [14, 15].

In conclusion, SPEM is an adaptive change and repair mechanism made by gastric epithelial cells in response to injury that regulates gene transcription and changes cell phenotype and tissue structure, thereby producing differentiation and transformation in cells [16]. SPEM represents not only a repair system during focal injury of the gastric mucosa [6] but also the possibility of further development into IM or even gastric cancer during diffuse injury [17]. Focal injury can transform into diffuse injury in the presence of chronic injury and persistent inflammation, but even chronic metaplasia can reverse some types of diffuse injury [9, 18]. Therefore, the aim of this paper is to summarize the role of SPEM in gastric mucosal injury diseases and provide a preventive direction for gastric mucosal diseases.

Sources, regulators, and related models of SPEM

Mature chief cells are located at the base of the gland following mitosis, are reprogrammed to transdifferentiate into SPEM cells in response to the repair of gastric injury and are

responsible for the secretion of pepsin and other digestive enzymes [3, 12, 19-21]. Transdifferentiation of chief cells to a SPEM phenotype is a highly elaborate regulatory process not only involving disruption of chief cell secretory architecture and changes in transcription factors [22] but also possibly serving as an acute reparative lesion in injury models, such as those established with DMP-777, L-635, or high-dose tamoxifen (HDT) and models of acid-induced ulcers [23]. However, some scholars have proposed that chief cells are not the only source of SPEM and that SPEM also arises from mucous neck cells or isthmic stem cells. During chronic inflammation, mucous neck cells also exhibit plasticity and contribute to the development of SPEM [3, 7, 23-25]. Single-cell RNA sequencing analysis of gastric body epithelium showed that both mucous neck cells and chief cells can transform into SPEM in the setting of chronic inflammation, a finding that not only broadens the understanding of the origin of SPEM but also reveals additional epithelial plasticity in metaplasia [26]. To gain insight into the molecular mechanisms driving gastric metaplasia and its progression to tumors, researchers have developed many mouse models that successfully mimic metaplasia before tumorigenesis [27]. In these mouse models, the metaplastic lineage is dominated by SPEM. Based on the induction factors and regulatory mechanism of SPEM, there are several main mouse models: 1) the acute drug-induced SPEM model, 2) the gene and transcriptional manipulation-induced SPEM mouse model [28], and 3) the chronic *Helicobacter* infection-induced SPEM model. These models are summarized in **Table 1**.

Acute drug-induced SPEM model

Modeling of the chronic *Helicobacter* infection model takes more than 6 months and is slow, and asynchronous metaplasia may occur during mass induction. Therefore, researchers developed acute drug-induced models, mainly using DMP-777, high-dose tamoxifen, and L635. DMP-777 is a proton carrier that is specific for the apical acid secretory membrane of parietal cells, leads to the rapid ablation of parietal cells and induces SPEM development, which is reversible and does not produce proliferative SPEM after the cessation of DMP-777 treatment [29]. DMP-777 is also a neutrophil elastase inhibitor that forms a murine gastric SPEM lineage that is inflammation-free [24]. High-dose tamoxifen rapidly induces apoptosis in gastric parietal cells and zymogen-secreting chief cell metaplasia in mice, with scattered proliferative SPEM cells observable within 3 days, and these effects are reversible after tamoxifen discontinuation [25, 30]. The loss of oral omeprazole gastric parietal cells was eliminated before tamoxifen or DMP-777 treatment [24, 31], but tamoxifen caused more inflammation. L635 is an analog of DMP-777, but the lack of elastase inhibition by L635 leads to a significant inflammatory response, and the inflammatory environment can lead to a shift in SPEM from slow metaplasia to extended proliferative metaplasia [3]. It has been shown that L-635-treated mice develop SPEM lineages with similar phenotypes 6-12 months after *H. felis* infection [32]. The acute drug-induced SPEM model is less time-consuming, and lesions are reversible compared to other models, which contradicts the concept that metaplasia is irreversible. Therefore, we can hypothesize that the mechanism of drug-induced SPEM may be the response to acute injury and the process of regeneration, and acute drug administration can directly induce rapid parietal cell death, synchronously induce metaplasia, and bypass the chronic immune mechanism, which provides an important experimental basis for the successful and efficient study of specific stages of metaplasia.

Gene and transcriptional manipulation to induce SPEM mouse models

Mouse models of the oxyntic atrophy phenotype can be generated by gene-targeted overexpression or deletion. The Cre-loxP system is an important method for achieving cell- or tissue-specific deletion of the target gene, and a generated transgenic mouse line (Atp4b-Cre) provides a valuable tool for studying gastric parietal cell differentiation, survival, and physiological function [33]. Slc26a9 is strongly expressed in gastric parietal cells in mice and humans and is extremely important for the function of parietal cells [34-37]. Published studies by our group have confirmed that $Slc26a9^{fl/fl}$/Atp4b-Cre mice generated by parietal cell-specific Slc26a9 knockout have parietal cell loss at 1 month of age, oxyntic atrophy at 2 months of age, and metaplasia (SPEM) and

Table 1. Pathologic phenotypes of gastric metaplasia in mouse models

Mouse model	SPEM	SPEM for Proliferation Capacity	Intestinal metaplasia	Foveolar hyperplasia	Inflammatory infiltrate	Invasive glandular production
Acute drug-induced SPEM model						
Oral DMP-777 Treatment [29]	Yes	No	No	Yes	No	No
Oral high-dose tamoxifen treatmen [25, 30]	Yes	No	No	Yes	Yes	No
Oral L-635 treatment [32]	Yes	Yes	No	Yes	Yes	No
gene and transcriptional manipulation mice induce SPEM model						
Slc26a9$^{fl/fl}$/Atp4b-Cre mice [38]	Yes	Yes	Yes	Yes	Yes	Yes
KLF4-deficient mice [39, 40]	Yes	No	No	Yes	No	No
Runx3 deficient mice [43]	Yes	Yes	No	No	No	No
H/K-IFN-γ transgenic mice [47]	Yes	Yes	No	Yes	Yes	Yes
H/K-noggin transgenic mice [49]	Yes	No	No	Yes	No	No
Amphiregulin-deficient mice [14]	Yes	Yes	Yes	Yes	Yes	Yes
Gastrin-deficient mice [31]	Yes	No	No	No	No	No
Insulin-gastrin transgenic mice [63]	Yes	Yes	No	Yes	Yes	Yes
IL33-deficient mice or IL13-deficient mice [15, 83]	No	No	No	No	No	No
Claudin 18-deficient mice [111]	Yes	Yes	No	No	Yes	Yes
Mist1-Kras mice [9, 115]	Yes	Yes	Yes	Yes	Yes	Yes
Chronic Helicobacter infection model						
H. felis or *H. Pylori* infection [3]	Yes	Yes	No	No	Yes	Yes

IM with significant expression of spasmolytic peptides at 6 months of age [38], indicating that Slc26a9 is essential for parietal cell function and maintaining gastric cell homeostasis.

Moreover, Kruppel-like factor 4 (KLF4) can regulate cell proliferation and differentiation, and significant oxyntic atrophy, foveal hyperplasia, and TFF2 metaplasia occurs at birth in KLF4-deficient mice [39, 40]; this phenotype is similar to that of mice infected with *H. felis*, but no IM, dysplasia, or invasive lesions occur in the gastric mucosa, a phenotype equivalent to that of benign metaplasia without an inflammatory response [41]. The gastric tumor suppressor Runx3 is highly expressed in chief cells and is an important factor in chief cell differentiation [42]. Runx3-knockout mice mainly exhibit hyperplasia of gastric epithelial cells, loss of chief cells, and significant SPEM lineage populations [43]. Although no glandular dysplasia or invasiveness has been reported, adenocarcinoma can persist following N-methyl-N-nitrosourea treatment [44, 45]. H/K-IFN-γ transgenic mice are formed by targeted transfection of mouse IFN-γ into gastric parietal cells using H/K ATPase β-subunit promoter fragments [46]. The gastric mucosa of this mouse model showed significant inflammation, oxyntic atrophy, SPEM, dysplasia at 3 to 5 months of age, cystic gland dilatation with age, occasional breakthrough to the submucosa, and antral polyps or tumors after 12 months [47].

However, in H/K-noggin transgenic mice, in which the H+/K+-ATPase β subunit gene promoter is specifically expressed by parietal cells and regulates noggin expression in the mouse gastric epithelium, noggin expression inhibits bone morphogenetic protein (BMP) signaling in the stomach [48] and has anti-inflammatory effects, and its deletion promotes the development of SPEM [48, 49]. In addition, noggin overexpression increases the chronic inflammatory response to *H. pylori* infection and accelerates the progression of dysplasia [50].

Paracrine factors such as epidermal growth factor receptor (EGFR) ligands, transforming growth factor-α (TGF-α), amphiregulin (AR), and heparin-binding EGF-like growth factor (HB-EGF) are produced by gastric parietal cells and can affect gastric lineage differentiation and transformation [51, 52]. Epidermal growth factor (EGF)-like growth factor is induced during acute gastric injury and is involved in the repair of acute gastric mucosal injury [53]. In a rat gastric epithelial cell line (RGM1), EGFR induces the expression of HB-EGF and EGFR tyrosine phosphorylation, followed by a significant increase in HB-EGF and AR transcription in RGM1 cells [53]. However, different EGF receptor ligands have different effects on the development and regulation of SPEM, and TGFα-deficient mice exhibit SPEM similar to wild-type mice [54]. AR-deficient mice spontaneously developed SPEM and exhibited dysplastic changes at 1 year of age [14]. The loss of AR can lead to SPEM acceleration and amplification. In addition, hepatocyte growth factor (HGF) activators (HGFAs) sense mucosal injury and are activated, promote HGF activation and participate in gastric mucosal repair [55-58]. Gastric mucosal lineage changes were observed in HGFA-deficient mice and wild-type mice after DMP-777 treatment, and HGFA promoted foveal cell proliferation and mucosal cell proliferation in acute oxyntic injury without affecting the occurrence of SPEM, but a lack of HGFA signaling delayed the recovery of SPEM cells to normal gastric gland cells [59].

Gastrin secretion, which is increased with parietal cell loss, regulates glandular homeostasis [50, 60, 61], epithelial cell proliferation and vesicular hyperplasia [62]. Gastrin-knockout mice treated with DMP-777 exhibited accelerated SPEM development [31]. Insulin-gastrin (INS-GAS) transgenic mice also have high circulating levels of gastrin and initially exhibit elevated serum gastrin levels and increased numbers of parietal cells, but increased acid secretion is lost with gastric atrophy as these mice age [63]. This mouse developed SPEM and submucosal lesions at 20 months of age and had accelerated SPEM progression during *H. felis* infection, further leading to the development of gastric cancer [63].

Chronic H. pylori infection-induced SPEM models

For mice with chronic *H. felis* or *H. pylori* infection, parietal cell loss occurs after six months, principal cells differentiate into a highly proliferative SPEM lineage [3], and SPEM-related dysplasia persists for up to 1 year after inflammation, but IM with characteristic goblet cells has not been observed in humans [64-66]. Lesions similar to those of metaplasia due to *H.*

pylori infection in humans can be observed in mice infected with *H. felis* or *H. pylori* [63-65, 67]. Lineage studies of SLFN4 in *H. pylori*-infected mice have shown that bone marrow-derived SLFN4+ cells migrate into the stomach via Hh signaling after *H. pylori* infection, polarize into myeloid-derived suppressor cells (MDSCs) among gastric epithelial cells, and acquire the ability to inhibit T-cell proliferation 4-6 months after *H. pylori* infection, which is consistent with oxyntic atrophy and SPEM [68]. In the *H. pylori*-infected human stomach, SLFN12L affects cell migration in a manner similar to SLFN4 in cells of myeloid origin [68]. In addition, SLFN4+ cells in the mouse stomach highly express miR-130b, which is required for MDSC function and is able to regulate suppressive functions of T cells and promote *H. pylori*-induced metaplasia [69]. Upregulated miR-130b targets Cyld (cylindromatosis gene, encoding a deubiquitinating enzyme), which negatively regulates NF-κB, and the NF-κB signaling pathway is a key pathway in *H. pylori*-induced gastritis and metaplasia [70]. NF-κB directly binds to the miR-130b promoter to induce its upregulation, thus forming a positive feedback loop, thereby promoting the development of SPEM [69, 71].

Highly proliferative SPEM has long been considered a precancerous lesion in gastric carcinogenesis [72], and for further study, many researchers currently use organoids formed in a gastric epithelial cell culture system to characterize changes in epithelial cells after chronic *H. pylori* infection. In a study by the Wataru Shibata group, chronic inflammation induced by *H. pylori* infection was found to increase the number of cells expressing tissue stem cell markers and the expression of genes involved in intestinal phenotypes, and the upregulation of these genes and the increase in the number of stem cells were abolished with the eradication of *H. pylori*, as determined by analysis of the formal classifications [73]. Thus, stemness or metaplastic phenotypes are acquired following chronic inflammation through genetic/epigenetic changes in gastric tissue stem cells [74].

Role of SPEM in gastric mucosal diseases

Role of SPEM in gastric ulcer regeneration and repair (gastric focal injury diseases)

Gastric ulcer repair is an extremely complex process involving tissue re-epithelialization and regeneration, which includes inflammatory infiltration, cell proliferation, and granulation tissue formation [75]. In response to mucosal injury following gastric ulcer development, the glands surrounding the ulcer expand, epidermal growth factor (EGF) expression increases, and granulation tissue begins to proliferate, which is followed by re-epithelialization at the wound base [75-77]. The ulcer-associated cell lineage (UACL) formed here was identified as SPEM, and its marker was CD44v9. SPEM is associated with increased expression of CD44 (particularly CD44v9) on the cell surface and plays an important role in the repair of gastric injury [6, 7, 78].

CD44-deficient mice have impaired ulcer repair, which is characterized by insufficient epithelial gland regeneration, ulcer persistence, and the loss of epithelial proliferation [7]. CD44v9-expressing gastric xenografts were transplanted into the gastric epithelium of CD44-deficient mice in an orthotopic organoid transplantation model, which resulted in epithelial cell proliferation and regeneration [7]. The appearance of CD44v9 at the ulcer margin is associated with proliferation, as CD44 orchestrates progenitor proliferation within both normal and metaplastic gastric epithelium [14, 31, 66, 79]. In addition, CD44v9 also protects against reactive oxygen species (ROS) during gastric ulcer repair, interacts with the glutamate-cysteine transporter xCT, stabilizes proteins and promotes effective regeneration after injury [80, 81].

Mucosal damage repair following gastric ulcer development is closely associated with the development of SPEM, which constitutes a major repair lineage for wound healing following injury [82] and reacts to immune responses following gastric injury [6, 7, 15, 83]. Interleukin 33 (IL-33) is an important driver of SPEM development [83-85] and is a gastric alarmin that acts as a secretory signal [86]. Macrophages infiltrate during acute inflammation and the loss of gastric mucosal parietal cells, and IL-33 is released from gastric foveolar epithelial cells to orchestrate immune defense and repair mechanisms [2]. IL-33 release and signaling lead to upregulation of type II cytokines [2, 83, 87], including IL-4, IL-5, IL-9, and IL-13. Among these cytokines, IL-13 and IL-4 mediate M2 macrophage activation through the coreceptor IL-4Rα [88]. IL-33 is required for promoting Th2 inflammatory responses and M2a polarization

in recruited macrophages and drives the development of SPEM [89, 90]. Exogenous treatment of mice with IL33 results in the recruitment of inflammatory cells to gastric epithelial cells, which induces significant inflammatory responses and SPEM development [86, 91]. However, IL33KO, ST2KO, and IL13KO mice showed severe parietal cell loss and decreased Mist1 expression after L635 treatment, but chief cells failed to complete transdifferentiation, and parietal cell loss alone could not induce chief cell transdifferentiation [15, 83]. Therefore, IL-13 and IL-33 were identified as promoters of SPEM, supporting the central role of cytokines and the immunoregulatory epithelium in the acute injury response, which has an important role in mucosal injury repair after gastric ulcer development [15].

In addition, Sonic Hedgehog (Shh), a secreted protein that regulates gastric ulcer healing, contributes to gastric mucosal recovery after injury [92-94] and plays a very important role in regulating epithelial cell regeneration and differentiation [95]. Shh also regulates immune responses, particularly macrophage recruitment [94]. Shh acts as a macrophage chemotactic agent through a smoothened-dependent mechanism in myeloid lineage cells, leading to expression of the chemokine receptor CCR2 on M2 macrophages [96], thereby linking metaplasia induction and the combined response to injury to the coordination of cytokine signaling by IL-33 and IL-13, which in turn regulates the development of SPEM and is essential for the regeneration and repair of damaged gastric epithelial cells [7].

The role of SPEM in gastric precancerous lesions and gastric cancer (gastric diffuse injury diseases)

The persistence of oxyntic atrophy and inflammation can lead to IM and SPEM [97-100]. IM was initially thought to be a preneoplastic metaplasia leading to intestinal-type gastric cancer [98]. However, recent studies have identified SPEM as a possible preneoplastic metaplasia, and IM can develop a more proliferative phenotype [13]. SPEM can be observed before cancer development and in gastric biopsies from most patients with gastric stump cancer and is strongly associated with early gastric cancer [101, 102]. The spread of SPEM from the initially emerging lesser curvature region to the greater curvature was observed as inflammation persisted [66], promoting the development of SPEM in mice and ultimately leading to dysplasia and cancer development [63, 66]. Therefore, SPEM represents an important precursor lineage for the development of dysplasia preceding gastric cancer [103]. Understanding the SPEM signaling pathway in gastric cancer provides an important theoretical basis for the prevention and treatment of early gastric cancer.

Slc26a9, which is a member of the Slc26a family of anion transporters [104], is a Cl - uniporter expressed by gastric mucosal cells and glands in mice and humans and plays an important role in parietal cell function and survival [34-37]. Slc26a9$^{fl/fl}$/Atp4b-Cre mice with specific knockout of the Slc26a9 gene in parietal cells progressively develop parietal cell loss, fundic gland hyperplasia, hypochlorhydria, and hypergastrinemia, and these steps are critical processes in the formation of a precancerous environment [38, 105]. Our group confirmed that Slc26a9 deletion can dysregulate stem cell and progenitor cell differentiation and lead to SPEM development, further promoting cell proliferation, inhibiting apoptosis, activating the Wnt pathway, and ultimately leading to the development of spontaneous precancerous lesions and gastric cancer. More importantly, our recent study showed that overexpression of Slc26a9 repaired SPEM (Liu et al., unpublished data), indicating that Slc26a9 plays a key regulatory role in protection of the gastric epithelium. In addition, some mouse models of gastric acid deficiency, such as AE2-/-, nhe4-/-, nhe2-/-, and kcne2-/-, show the loss of parietal cells, and the transformation of the gastric mucosa into SPEM has also been observed in these models [106-109]. However, whether gastric acid deficiency can transform from SPEM into tumors needs to be confirmed by more studies.

Stomach tight junction protein 18 (stCldn18) expression is reduced in gastric cancer, and its loss promotes the development of progressive gastric tumors in mice [110]. Studies in stCldn18-knockout mice showed that SPEM could develop in juvenile mice and that long-term stCldn18 deficiency activated the expression of CXC chemokine ligand 5 and promoted

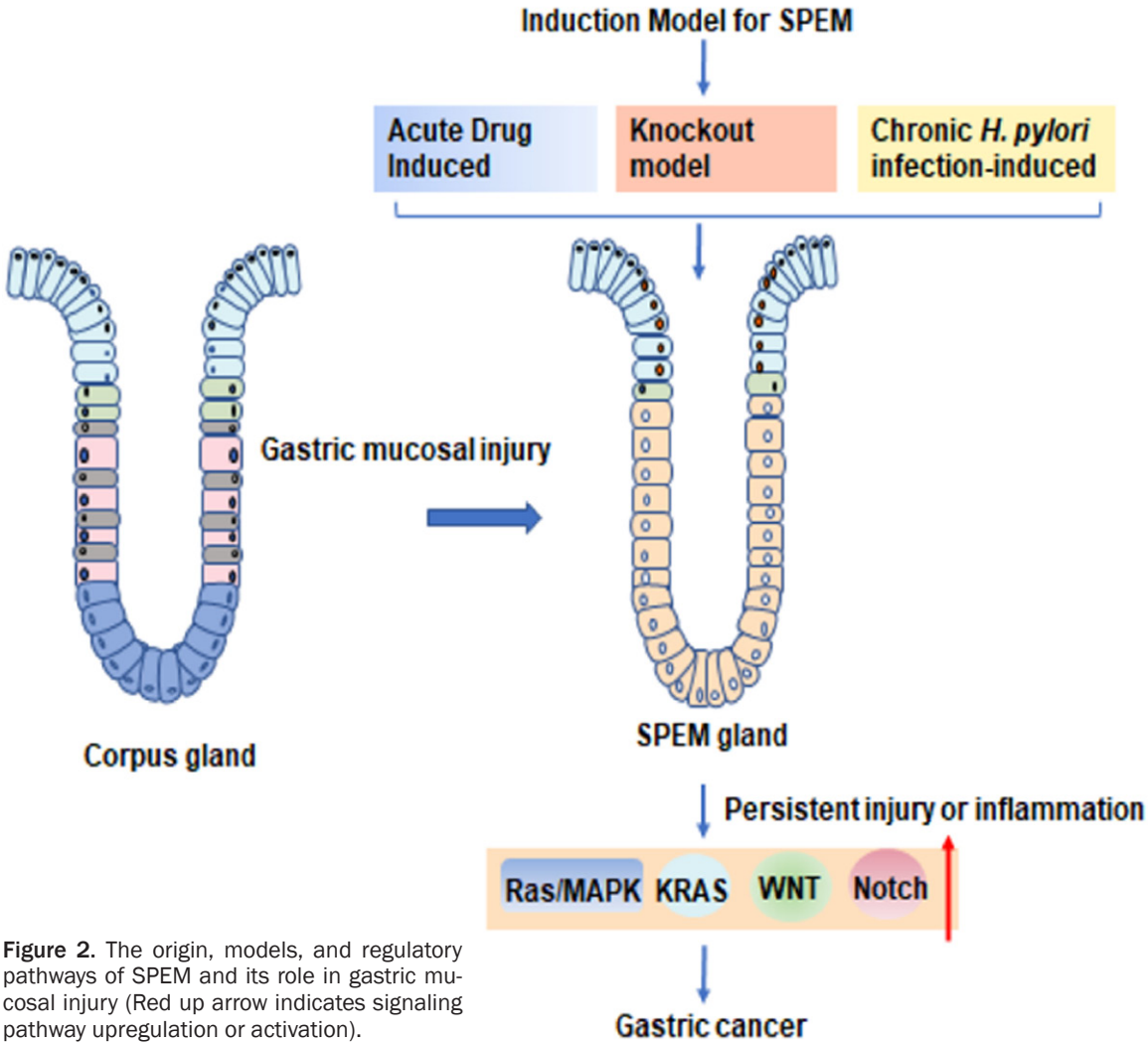

Figure 2. The origin, models, and regulatory pathways of SPEM and its role in gastric mucosal injury (Red up arrow indicates signaling pathway upregulation or activation).

epithelial-mesenchymal transition downstream of the Wnt signaling pathway [111], thereby inducing the formation of gastric tumors [112]. In addition, the Notch and Wnt signaling pathways can synergistically regulate the proliferation and differentiation of gastric stem cells, and the upregulation of Notch is involved in the development of SPEM and gastric cancer in stCldn18-knockout mice [112].

Although mutations in Ras are observed in only approximately 10% of gastric cancers [66, 98], increased Kras activity is found in more than 40% of intestinal-type gastric cancers [113, 114]. After tamoxifen treatment of Mist1-Kras mice, Kras was activated in gastric chief cells and chief cells differentiated into SPEM, and transformation from SPEM to IM and then to invasive metaplasia was observed [9, 115]. Thus, Ras signaling activation is involved in the development of omnidirectional metaplasia. In addition, activation of the Ras/MAPK pathway can lead to rapid gastric mucosal atrophy, foveolar epithelial hyperplasia, and SPEM formation [116]. During this process, the BMP pathway can participate in the development of metaplasia through Smad phosphorylation [48] and synergize with MAPK activation, which in turn regulates the development of SPEM [117, 118]. MAP kinase (MEK) is an intermediate link in the Ras/MAPK pathway, and reversal of the SPEM lineage cells to normal gastric mucosal cells has also been observed in mice expressing Kras signaling changes and in *H. pylori*-infected gerbils treated with MEK inhibitors [9]. Therefore, searching for key targets and inhibitors during the transformation of SPEM into IM and then gastric cancer is the most effective approach to identify strategies to reverse metaplasia and prevent the occur-

rence of gastric cancer. Many studies have reported proteins that could be targeted to interfere with SPEM progression, such as WAP 4-disulfide core domain protein 2 (WFDC2), also called human epididymis protein 4, a small secreted protein that is upregulated in tissues and gastric juice of premalignant metaplasia and gastric cancer [119, 120]. WFDC2 promotes SPEM by upregulating IL33 expression, and Wfdc2 knockdown inhibits the progression of SPEM and precancerous dysplasia [85]. In addition, tristetraprolin (TTP) is an RNA-binding protein encoded by the gene Zfp36 [121] and exhibits decreased expression in gastric cancer samples [122]. TTP regulates the induction of SPEM by abnormal gastric inflammatory lesions, and its overexpression inhibits gastric inflammation and SPEM development [123]. Therefore, therapeutic approaches to increase TTP expression may be effective for the treatment of SPEM-associated gastric neoplastic diseases.

Conclusions

SPEM not only occurs at the edges of gastric ulcers during focal injury and recruits repair cells to the site of mucosal injury, increasing the barrier protection function of the epithelium but also progresses to dysplasia and tumors when diffuse injury and inflammation persists. Therefore, SPEM is not only a cellular system that represents repair during acute gastric mucosal injury but is also a precancerous lesion. In this article, the origin, models, and regulatory pathways of SPEM and its role in gastric mucosal injury were reviewed (**Figure 2**). We hope to provide basic, systematic and summative knowledge for this field, advocate for more research on the role of SPEM in gastric mucosal diseases, and provide new targets for clinical diagnosis and treatment.

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Disclosure of conflict of interest

None.

Abbreviations

AR, amphiregulin; BMP, bone morphogenetic protein; CD44v9, CD44 variant isoform 9; Cyld, cylindromatosis gene; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; HGFAs, hepatocyte growth factor activators; HB-EGF, heparin-binding EGF-like growth factor; INS-GAS, insulin-gastrin; IM, intestinal metaplasia; IL-33, interleukin 33; KLF4, Kruppel-like factor 4; Muc6, mucin 6; MEK, MAP kinase; MDSCs, myeloid-derived suppressor cells; RGM1 cells, rat gastric epithelial cell line; ROS, reactive oxygen species; stCldn18, stomach tight junction protein 18; SPEM, spasmolytic polypeptide-expressing metaplasia; Shh, sonic hedgehog; TFF2, trefoil factor 2; TGF-α, transforming growth factor-α; UACL, ulcer-associated cell lineage.

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