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Recent advances in spasmolytic polypeptide expressing metaplasia research

Yang RR *et al.* Advances in SPEM research

Abstract

Gastric cancer remains a leading cause of global cancer mortality, with limited advances in its prevention and treatment owing to an incomplete understanding of its pathogenesis. Among the key precancerous lesions, spasmolytic polypeptide-expressing metaplasia has emerged as a critical driver in gastric carcinogenesis. This review summarizes the recent advances in the mechanistic roles of spasmolytic polypeptide-expressing metaplasia in gastric mucosal diseases. By elucidating these pathways, this review sought to provide novel insights that could inform future strategies for early intervention and prevention of gastric cancer.

Key Words: Gastric adenocarcinoma; Spasmolytic polypeptide-expressing metaplasia; Signaling pathway; Research progress; Pathogenesis

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Core Tip: Gastric cancer is one of the most common cancers worldwide, with exceptionally high morbidity and fatality rates. A thorough investigation of the pathophysiology of spasmolytic polypeptide-expressing metaplasia (SPEM) is required. SPEM serves as a critical nexus between mucosal repair and gastric carcinogenesis and is a valuable target for early detection and intervention. To gain a deeper understanding of SPEM, this review summarizes its recent mechanistic roles in gastric mucosal diseases. By elucidating these mechanisms, this review aims to provide deeper insights into the research and prevention of SPEM-related diseases.

INTRODUCTION

Spasmolytic polypeptide-expressing metaplasia (SPEM) is an adaptive metaplastic cell lineage that develops in the gastric mucosa in response to injury. Although traditionally regarded as a reparative program, its strong association with gastric cancer

development has led to SPEM redefinition as a critical precursor lesion and an important target for its prevention. Gastric cancer is a major global health burden and ranks as the fifth most common malignancy worldwide in terms of both incidence and mortality[1]. Its development often follows the classic Correa cascade, a multistep progression from normal gastric mucosa to invasive carcinoma through chronic gastritis, atrophic gastritis, intestinal metaplasia (IM), and dysplasia stages[2]. Throughout this process, persistent atrophy and inflammation drive the development of metaplastic lesions such as SPEM and IM, which are recognized as precancerous conditions. Consequently, SPEM is regarded as a key target for the prevention and control of gastric cancer.

The stomach epithelium exhibits considerable self-renewal capacity and cellular plasticity, enabling periodic differentiation and dedifferentiation of gastric epithelial cells, a property that inherently increases the susceptibility to carcinogenesis[3]. Under acute or chronic inflammatory conditions, parietal cell loss from the normal gastric mucosa marks the onset of oxyntic atrophy, which is a prerequisite for the emergence of SPEM[4]. Beyond parietal cell loss, depletion of chief cells has also been identified as an initiating factor in gastric mucosal injury[5,6].

SPEM concept emerged from observations of aberrant epithelial lineages in *Helicobacter pylori* (*H. pylori*)-infected mice[7], and is now recognized as an adaptive, repair-oriented cellular conversion. SPEM is characterized by the expression of trefoil factor 2 (TFF2) and mucin 6 (MUC6)[8,9]. In contrast, IM is generally regarded as the outcome of transdifferentiation toward an intestinal phenotype, featuring the presence of MUC-containing goblet cells, paneth cells, and absorptive enterocytes, along with TFF3 and MUC2 expression[10]. SPEM is typically located deep in the fundic gland. In contrast, IM is present in the gland lumen, and evidence suggests that IM likely evolves from SPEM[4,11]. Consequently, SPEM and IM detection in clinical specimens is crucial for risk stratification and early intervention in gastric cancer.

MECHANISM OF SPEM AND ITS ORIGIN

The cellular origin of SPEM, which is central to understanding its initiation, is the subject of active investigation and debate. While the predominant model centers on the transdifferentiation of mature chief cells, emerging evidence suggests alternative cellular sources that highlight the plasticity of the gastric epithelium. Cell differentiation is the developmental mechanism by which a cohort of multipotent progenitors gives rise to diverse specialized cell lineages, each with unique morphological and functional properties[3]. In the stomach, tissue repair after injury involves reprogramming fully differentiated cells back into a less-differentiated proliferative state to replenish lost cells. Pathologists refer to this stereotypical cycle of cellular phenotypic changes as paligenosis.

Chief cell transdifferentiation via paligenosis

The cellular origin of SPEM has not been fully determined; however, the most widely accepted explanation is that it arises from the transdifferentiation of mature chief cells[12], also known as pyloric metaplasia, which is histologically defined by the luminal proliferation of MUC5AC-positive cells, concurrent with parietal cell loss and replacement of chief cells by basally emerging SPEM cells[7]. Through an evolutionarily conserved process termed “paligenosis”, mature gastric chief cells can be reprogrammed, re-enter the cell cycle, and transform into SPEM cells (Figure 1)[13].

A preliminary exploration of the process of chief cell transdifferentiation into SPEM cells has been reported. This process begins with the dedifferentiation of chief cells, which is marked by the key molecular event of muscle, intestine, stomach expression 1 (MIST1) downregulation[14]. This process begins with the disruption of normal cellular morphology *via* the activation of the lysosomal and autophagic pathways. It has been proposed that a related process, termed “cathartocytosis”, may occur in parallel with autophagy. Although mechanistically distinct, cathartocytosis enables the cell to rapidly expel excess material, such as endoplasmic reticulum membranes and secretory granule contents[15].

In the early stages of pathogenesis, activating transcription factor 3 is upregulated, which induces autophagy and lysosomal activity to dismantle the characteristic structures of differentiated chief cells[16]. Chief cell reprogramming is initiated by sulforaphane (Sfn)[17] and is accompanied by MIST1 downregulation[14] and upregulation of aquaporin 5 (AQP5)[18] and SRY-Box transcription factor 9 (SOX9)[19]. Notably, SFN loss in chief cells abrogates SOX9 expression. SOX9 itself is also known to promote metaplasia in Barrett's esophagus[20].

In the later stages, transdifferentiated cells begin to produce cytoplasmic granules expressing TFF2 or MUC6, a process facilitated by interleukin (IL)-13[3,21]. The concurrent shrinkage of zymogen granules and the upregulation of MUC granule formation are likely associated with the generation of reactive oxygen species (ROS). ROS function as inducible upstream signals in pathogenesis and are essential for normal progression. Furthermore, both acute and chronic inflammation can increase cellular ROS levels[22]. In response to oxidative stress, cells activate the CD44v9-xCT pathway[23]. Ultimately, downregulation of DNA damage induced transcript 4 (DDIT4) allows SPEM cells to reactivate mechanistic target of rapamycin (mTOR) complex 1 signaling, thereby acquiring a proliferative phenotype[24,25].

The microenvironment and alternative cellular origins

SPEM development is influenced by factors beyond epithelial cells, particularly dynamic interactions with the underlying mesenchyme (stroma). However, the specific role of the stroma in the progression of precancerous gastric lesions remains unclear. Evidence suggests that telocytes, a specialized type of mesenchymal cell, may drive metaplastic progression by secreting signaling molecules, such as Wnt and bone morphogenetic protein (BMP), thereby providing critical microenvironmental support for epithelial cells undergoing phenotypic changes[26]. The Wnt pathway is known for its key role in gastric development and regeneration, whereas BMP signaling has been implicated in the differentiation of both gastric and intestinal epithelial cells[27,28].

Furthermore, fibroblasts have been identified as the key promoters of direct carcinogenesis in SPEM cells[29].

Besides the stromal influences, the SPEM cellular origin is an area of active research. An alternative hypothesis posits that neck and progenitor cells located in the glandular isthmus also give rise to SPEM[30-32]. This suggests that chief cells are not the only cells capable of undergoing paligenosis. Notably, parietal cell precursors, which are derived from isthmus stem cells, highly express the orphan nuclear receptor gene estrogen-related receptor gamma. Deficiency in estrogen-related receptor gamma leads to impaired parietal cell differentiation, a disruption that may indirectly facilitate SPEM development[33].

ROLE OF SPEM IN GASTRIC INFLAMMATION, ATROPHY, AND DYSPLASIA

SPEM emerges in inflammatory, atrophic, and precancerous lesions as an initial response to diffuse gastric injury, representing the reprogramming of the epithelium towards a proliferative, reparative state[34]. Morphologically, SPEM is characterized by the transdifferentiation of zymogen-secreting chief cells into mucus-producing cells, which constitutes a key mucosal repair mechanism[35]. Although this response is initially adaptive, persistent inflammatory insult can lead to repeated repair cycles, thereby increasing the risk of neoplastic progression.

Inflammation is the primary trigger for this cascade, with *H. pylori* infection being the predominant risk factor. *H. pylori* activates the expression of numerous inflammatory mediators, promoting immune cell infiltration, oxidative stress, and aberrant epithelial proliferation[36]. A critical virulence factor for its survival and pathogenicity is lipopolysaccharide[37]. Lipopolysaccharide can downregulate protective cytokines, such as IL-33, impair mucosal repair[38], and induce excessive ROS accumulation, leading to DNA damage and epithelial cell death[39].

The gastric epithelium responds to such injuries through cellular plasticity, a fundamental adaptive process that balances damage and repair. Plasticity is a prerequisite for SPEM development. The nature of the epithelial response depends on

the injury pattern. Localized injury often results in altered differentiation, marked by Tff2 expression and Sox9 upregulation[40], whereas diffuse injury typically triggers the full SPEM program. Notably, SPEM predominantly arises following oxyntic gland atrophy and loss of parietal cells[41]. While epithelial cells exhibit varying sensitivities to inflammatory signals, interferon-gamma (IFN- γ) has been established as a key driver that induces parietal cell atrophy, initiating the sequence of events leading to metaplasia[42,43].

Inflammation is a requisite driver for the progression of SPEM towards a more aggressive phenotype[44]. *H. pylori* can exploit this process to expand its ecological niche within the gastric mucosa[45]. Within the inflammatory milieu, the immune cells and their secreted cytokines are central to SPEM development. For instance, the activation of IL-33 and M2-type macrophages at the injury site is critical for SPEM progression[44,46,47].

At the molecular level, lineage markers upregulation, such as TFF2 and MUC6[34], along with CD44v9, helps mitigate ROS-induced oxidative stress[48]. Changes in CD44v9 expression are also linked to the downregulation of miR-148a, a potential regulator of cell fate determination[49]. Epidermal growth factor receptor (EGFR) signaling pathway role in gastric mucosal differentiation is well-established; however, the specific functions of its ligands - including transforming growth factor- α , amphiregulin, and heparin-binding epidermal growth factor-like growth factor - in SPEM remain understudied[50]. A recent study using a mouse model of acute parietal cell atrophy induced by DMP-777 demonstrated that SFN promotes mucosal repair by activating the EGFR/extracellular signal-regulated kinase pathway, thereby mediating the transdifferentiation of chief cells into SPEM cells, a process accompanied by upregulation of the AQP5 water channel[17].

When the gastric mucosa develops IM, which is characterized by the appearance of intestinal goblet cells[51], SPEM can persist in the basal layer of the incomplete IM. This subtype is associated with a high risk of gastric carcinogenesis. SPEM is widely considered a key precursor of gastric cancer. Persistent SPEM cells, under the combined

pressure of a chronic inflammatory microenvironment, genetic alterations, and epigenetic dysregulation, can progressively accumulate oncogenic mutations, ultimately leading to invasive carcinoma[52,53].

In summary, SPEM is a crucial repair response to gastric mucosal injury that aims to restore epithelial integrity through cellular reprogramming. However, when driven by persistent insults such as *H. pylori* infection, glandular atrophy, and microenvironmental dysregulation, this reparative mechanism can become dysregulated. Instead of restoring homeostasis, they may initiate a pathogenic sequence that begins with metaplasia and progresses to precancerous lesions and cancer.

RELATED MODELS OF SPEM

Owing to the inherent limitations in studying the pathogenesis and interventions directly in humans, mouse models have become indispensable for investigating spasmodic SPEM and gastric precancerous progression. Their physiological relevance to humans, coupled with established genetic tools and cost-effectiveness, makes them a tractable and widely adopted system. Its key advantages include experimental controllability and phenotypic uniformity. Through genetic engineering, researchers can precisely manipulate gene expression or cell lineages *in vivo*, enabling the systematic observation of gastric mucosal changes and establishing clear causal links between molecular perturbations and histological phenotypes. Commonly utilized SPEM models fall into three categories: (1) The *H. pylori* infection-induced SPEM model, which recapitulates chronic inflammation-driven pathogenesis; (2) Acute chemical injury-induced SPEM models, which probe SPEM origins during repair and regeneration; and (3) Genetically engineered models that directly test molecular mechanisms by activating or deleting specific genes. The models used are listed in Table 1[8,54-73].

Animal models are indispensable for investigating the pathogenesis and identifying potential therapeutic targets. However, these models cannot fully recapitulate the complexity of human diseases; therefore, their findings require validation in clinical

studies. For instance, although *H. pylori* infection can successfully establish a mouse model of SPEM, lesions have also been identified in humans[57]. However, mouse models offer a tractable platform for the systematic study of the multistep pathogenesis. Crucially, studies in mice have demonstrated that SPEM is reversible[68]; direct evidence in humans remains limited, although eradicating *H. pylori* may halt its progression, particularly in the early stages[73]. The reversibility of IM is still debated. Therefore, advancing gastric cancer prevention requires an integrated strategy. Mouse models provide mechanistic insights and identify therapeutic candidates, as demonstrated by the signal transducer and activator of transcription 3 (STAT3) inhibitor STA-21, which limits early metaplasia[74]. These findings must then be validated in clinically relevant human models, such as patient-derived gastric organoids, to confirm their efficacy, as exemplified by luteolin reversing premalignant lesions (SPEM/IM)[75], and to accelerate clinical translation.

EFFECT OF CYTOKINES ON THE INDUCTION OF METAPLASTIC PHENOTYPES

Cytokines play a pivotal role in shaping the tumor microenvironment, orchestrating the initiation and progression of SPEM, and significantly promoting gastric cancer development[76]. Chronic inflammation represents the initial step in diffuse gastric cancer[77] with common etiologies including autoimmune responses (accompanied by the involvement of multiple cytokines) and *H. pylori* infection, both of which lead to parietal cell atrophy and SPEM[42,78,79]. Inflammatory cytokines act as auxiliary signals following parietal cell loss and are critical for SPEM induction and progression[80]. *H. pylori* infection³ elicits the release of numerous cytokines, such as IL-1 β , IL-6, IL-17, IFN- γ , and tumor necrosis factor- α (TNF- α)[81]. These include² pro-inflammatory cytokines (IL-1 β , TNF- α , IL-6, IFN- γ) and anti-inflammatory cytokines (IL-10, IL-18). An imbalance between these subsets disrupts inflammatory processes, thereby contributing to metaplasia and tumorigenesis[82]. As a key component of type I immune responses, IFN- γ fosters an inflammatory milieu and serves as a major driver of SPEM development[42,43]. IL-17A, a canonical pro-inflammatory cytokine primarily

secreted by T helper 17 (Th17) cells, is regulated by IL-23, a critical factor for Th17 cell differentiation and maintenance. IL-10, released by regulatory T (Treg) cells, inhibits Th17-induced inflammation; the Th17/Treg balance sustains gastric mucosal immune homeostasis while potentially promoting persistent inflammation[76,83]. *H. pylori* modulates immune escape mechanisms and polarizes dendritic cells (DCs) to secrete IL-23, which induces and maintains Th17 cells. The subsequent secretion of IL-17 and IL-21 by Th17 cells amplifies the Th17 response *via* IL-21-mediated positive feedback[84]. Additionally, IFN- γ and IL-17A directly induce gastric epithelial cell death, which is essential for subsequent parietal cell atrophy and SPEM progression[42,79]. TNF- α , a pro-inflammatory cytokine secreted by macrophages, activates multiple inflammation-related downstream signaling pathways and enhances gastric cancer cell metastasis[85,86]. While the precise mechanism of IL-1 β in gastric cancer remains elusive, existing data indicate that IL-1 β acts as a key mediator of inflammatory responses, contributing to gastric precancerous lesions and suppressing gastric acid secretion, thereby facilitating gastric cancer development[81,87]. IL-6, a pleiotropic cytokine that acts primarily *via* the IL-6/STAT3 pathway, contributes to both inflammation and gastric cancer progression and promotes M2 macrophage polarization[88,89]. M2 macrophages play critical roles in gastric cancer progression and participate in angiogenesis, tumor invasion, metastasis, and therapeutic resistance[78]. DCs secrete IL-18, which acts directly on T cells to promote Treg differentiation, suppress immune responses, and facilitate persistent *H. pylori* infection[90]. IL-10, mainly secreted by macrophages and DCs, functions as an immunosuppressive cytokine that fosters an immunosuppressive microenvironment that favors the formation and progression of precancerous lesions, such as SPEM, and even creates conditions for further gastric cancer development[91].

Notably, IL-33, a member of the IL-1 family, plays a crucial role in driving SPEM as emphasized in recent studies[21,77,92,93]. IL-13 is also important for the maturation and proliferation of SPEM cells[21]. Type II immune responses have been implicated as key contributors to epithelial metaplasia, with IL-33 identified as a critical inducer and

type II cytokines (IL-4 and IL-13) as major drivers[77,78]. IL-33 release and signaling trigger the upregulation of type 2 inflammatory cytokines, including IL-4 and IL-13[94]. IL-13 not only serves as a key regulator of SPEM cell generation but also promotes the maturation and proliferation of SPEM lineages[21,93]. Type 2 innate lymphoid cells play a vital role in the IL-33/IL-13 axis by initiating the release of IL-13 and IL-4, activating mast cells, and promoting M2 macrophage polarization[78] (Figure 2).

Other IL-1 family members also modulate SPEM activity. IL-36 triggers the expression of pro-inflammatory cytokines, such as IL-12, fostering a chronic inflammatory environment that perpetuates a cycle of mucosal damage and repair, thus sustaining SPEM. It can also enhance the invasive and metastatic potential of gastric cancer. Conversely, IL-38 effectively counteracts the pro-inflammatory effects of IL-36[95,96]. Given their shared family affiliations, it is plausible that IL-36 and IL-33 act synergistically to coactivate the IL-13 pathway, thereby promoting the transdifferentiation of chief cells and contributing to the initial formation of SPEM.

Besides cytokine networks, the Hippo pathway effector Yes-associated protein (YAP) is implicated in metaplastic progression. Analysis of human gastric tumor tissue revealed that nuclear YAP and HE4 expression was upregulated in metaplastic regions[97]. Both YAP and HE4 were highly expressed in SPEM and IM, suggesting that YAP activation may promote the development of these precancerous lesions, potentially through the positive regulation of SPEM-related genes such as HE4. Immune regulation also plays a counterbalancing role. In autoimmune gastritis, IL-27 has been identified as an inhibitor of CD4⁺ T cell-mediated inflammation in the gastric mucosa, thereby exerting a protective effect against gastritis and SPEM[46].

MicroRNAs (miRNAs) are endogenously expressed noncoding RNAs that post-transcriptionally regulate gene expression by binding to target mRNAs through sequence complementarity. They ⁵ play pivotal roles in a wide array of biological processes, including cell development, differentiation, and proliferation[98-101]. The dysregulation of specific miRNAs has been implicated in gastric carcinogenesis. In SPEM, miRNAs, such as miR-21, miR-155, and miR-223, were upregulated, whereas

miR-148a was downregulated. Downregulation of miR-148a may be a key event in the initiation of chief cell reprogramming[102]. During IM, lesions are influenced by other miRNAs, including miR-1, miR-30, miR-194, and miR-490[103].

A notable example is miR-30a, which is highly expressed in mucus neck cells and chief cells of normal gastric tissue in both mice and humans. However, its expression is significantly downregulated in mouse models of SPEM and IM (induced by DMP-777 or L635), including in human clinical samples of these lesions. This downregulation was observed in both GSII-positive SPEM and GSII-negative IM tissues. Reduced miR-30a levels have also been observed in human gastric cancer cells, suggesting its potential role as an early biomarker and therapeutic target to prevent gastric carcinogenesis[101,104].

Furthermore, downregulation of miR-7 has been identified as an early event in the metaplasia-carcinoma sequence. In SPEM tissues, decreased miR-7 expression was associated with the upregulation of TFF2[105]. From a therapeutic perspective, a study found that 18 β -glycyrrhetic acid suppresses proliferation, induces cell cycle arrest, and promotes apoptosis in gastric cancer cells. This compound acts by regulating the miR-328-3p/STAT3 signaling pathway and promoting autophagic flux, highlighting a potential novel pharmacological strategy for gastric cancer treatment[100].

SPEM-RELATED SIGNALING PATHWAYS

Research into the molecular mechanisms of SPEM has revealed a highly interconnected regulatory network, with key signaling pathways - including STAT3, nuclear factor kappa B (NF- κ B), mTOR, and Wnt/ β -catenin - synergistically driving the phenotypic transformation of gastric epithelial cells to promote SPEM development and maintenance (Figure 3).

Wnt signaling pathway

Wnt proteins are secreted glycoproteins whose core effector, β -catenin, plays crucial roles in cell adhesion and gene transcription[106,107]. The Wnt signaling pathway plays

a pivotal role in gastric development and homeostasis. *H. pylori* infection can upregulate AQP5 *via* its virulence factor cytotoxin-associated gene A, which in turn leads to aberrant activation of the Wnt/ β -catenin pathway. This activation not only drives the progression of gastritis but also serves as a key mechanism inducing host cell dedifferentiation and SPEM formation[57,108].

During this process, ROS act as key signaling molecules. On one hand, ROS can further activate the Wnt/ β -catenin pathway to mediate hyperproliferation[109]. Conversely, chief cells can employ the peroxisome proliferator-activated receptor gamma co-activator-1 α -xCT-glutathione peroxidase 4 axis to regulate mitochondrial activity and manage ROS levels; a failure in ROS clearance impedes SPEM development and promotes cell death[22]. Telocytes within the microenvironment secrete signaling molecules such as Wnt5a, Bmp4, and Bmp7[26]. Substantial ¹ evidence indicates that sustained activation of the Wnt/ β -catenin pathway is closely associated with gastric cancer development, progression, and invasiveness of gastric cancer. The drug nitazoxanide effectively mitigates SPEM by inhibiting this pathway, providing an experimental basis for its potential as a therapeutic strategy[57,110].

mTOR signaling pathway

The mTOR signaling pathway is involved in the development of pathogenesis. Its activity is regulated by key factors including Ddit4 and the transcription factor Sox9, which coordinate cell cycle progression to drive cellular reprogramming[25,111]. YAP, which is specifically activated during SPEM, is a central regulator of gastric regeneration and tumorigenesis. It modulates the activity of the mTOR complex 1 *via* its target gene *Ddit4*, thereby promoting SPEM formation *via* a pathogenesis program[24,25,97].

R-spondin 3, a Wnt signaling enhancer known to regulate stem cell behavior in various organs[112,113], transiently activates YAP to promote regeneration after acute injury. However, during chronic *H. pylori* infection, sustained R-spondin 3

overexpression synergizes with signaling pathways such as mTOR and cytokines such as IL-33, driving glandular hyperplasia and the development of precancerous lesions and demonstrating long-range regulatory capabilities[114].

NF-κB signaling pathway

The NF-κB signaling pathway serves as a central regulator of innate and adaptive immunity and is extensively involved in controlling cell proliferation, apoptosis, migration, invasion, and inflammatory responses. It is primarily activated *via* the canonical pathway and plays a key role in gastric mucosal lesion development[115]. Studies have shown that deletion of the mitochondrial protein gene associated with retinoid-IFN-induced mortality 19 in parietal cells triggers SPEM formation *via* the ROS-NF-κB axis. This process depends on IκB degradation and p65 nuclear translocation, mediated by the IKK kinase complex, in which the catalytic subunit IKKα serves as a core signaling component. The resulting aberrant NF-κB activation induces the release of inflammatory factors such as IL-6 and TNF-α, and cooperates with the NLR family pyrin domain-containing 3/IL-33 pathway to promote SPEM development[116,117]. Additionally, miR-130b plays a central role in driving gastric metaplasia by activating the NF-κB pathway[118]. The Mongolian gerbil *H. pylori* infection model further confirmed that SPEM lesion formation is closely associated with sustained activation of the NF-κB pathway[119].

STAT3 signaling pathway

STAT3 is a key transcription factor linking chronic inflammation to gastric tumorigenesis. Upon *H. pylori* infection, cytokines, such as IL-6 and IL-11, bind to their receptors and trigger STAT3 phosphorylation at tyrosine 705. Phosphorylated STAT3 (p-STAT3) ⁶ dimerizes and translocates to the nucleus, where it activates the transcription of genes involved in proliferation, apoptosis, and invasion. STAT3 signaling evolves from transient activation in early infection to sustained activation in tumors, driving the progression of gastric mucosal lesions and correlating with poor prognosis[120-122].

Concurrently, high expression levels of IL-6, p-STAT3, and Ki67 have been observed in SPEM lesions[123]. Aberrant STAT3 activation interacts with multiple regulatory mechanisms; for example, the inhibition of BMP signaling exacerbates inflammation and promotes SPEM through STAT3 upregulation[124]. In the DMP-777 mouse model, evidence suggests that SFN may engage the STAT3 pathway during the later stages of carcinogenesis[17]. Activated Ras is involved in the development of metaplasia in Mist1-Kras mouse principal cells[69]. IL-13 directly promotes SPEM cell proliferation and maturation *via* the STAT6 pathway[21].

Th17 cells play a significant role in autoimmune diseases, functioning in balance with Treg cells[125,126]. Tregs are lymphocytes that negatively regulate immune responses[127]. Inflammation is primarily mediated by ⁴IFN- γ -producing CD4+ T cells (Th1) and IL-17-producing CD4+ T cells (Th17)[128]. In autoimmune gastritis, STAT3 is a downstream signaling protein required for Th17 cell differentiation, and inhibition of STAT3 restores the Th17/Treg balance, thereby reducing inflammation and limiting early chemotactic changes[74]. A recent study has elucidated the immunosuppressive role of Tregs. Tregs secrete the anti-inflammatory cytokine, IL-13, which subsequently activates the STAT3 signaling pathway in gastric cancer cells through p-STAT3. This IL-13-driven p-STAT3 activation enhances the self-renewal capacity[129]. Furthermore, STAT3 acts synergistically with other oncogenic drivers. It cooperates with activated Ras to promote pathogenic sequences involved in gastric mucosal atrophy, hyperproliferation, and SPEM formation[130]. Its sustained activation can also be fueled by non-inflammatory stimuli such as the accumulation of deoxycholic acid during progression to IM[131].

Luteolin, a natural flavonoid compound widely present in various medicinal plants, has been shown to effectively block activation of the STAT3/lipocalin 2 oncogenic signaling axis in a tamoxifen-induced mouse model in preclinical studies. Luteolin curbs the progression of metaplastic lesions *in vivo* by directly binding to STAT3 and inhibiting tyrosine phosphorylation. Luteolin curbs the progression of metaplastic

lesions at the model level[75]. This demonstrates that targeted disruption of STAT3 signaling is a viable strategy for intercepting the metaplasia-carcinoma sequence.

Clinical translation strategies for SPEM

The complex, intricate molecular network governing SPEM unveils a strategic roadmap for clinical intervention. Moving beyond a one-size-fits-all approach, we propose a precision defense framework aimed at intercepting the metaplasia-carcinoma sequence at its most vulnerable points. Based on the current understanding of SPEM's multi-pathway regulatory networks, a stratified interventional framework has emerged. For early detection, the integrated assessment of TFF2/MUC6/CD44v9 protein expression profiles with characteristic miRNA signatures (miR-148a/miR-30a/miR-21) in the gastric mucosa or body fluids enables precise risk stratification of premalignant lesions. Therapeutically, beyond fundamental *H. pylori* eradication[55], targeting key pathway nodes shows promise as inhibitors of the IL-33/IL-13 axis and STAT3 signaling hub (*e.g.*, luteolin), along with EGFR/extracellular signal-regulated kinase pathway agonists (*e.g.*, SFN), providing targeted chemoprevention against the inflammation-metaplasia cascade. Additional potential targets include the Wnt/ β -catenin pathway (modulated by nitazoxanide in preclinical studies), mTOR signaling, and the YAP-DDIT4 axis in cellular dedifferentiation. Implementation requires biomarker-guided patient stratification using markers such as CD44 and p-STAT3. Synthetic lethality strategies that leverage ROS metabolic characteristics and combination therapies represent promising research directions for establishing a comprehensive SPEM management system.

CONCLUSION

Based on the synthesis of recent advances regarding the cellular origins of SPEM and its key signaling pathways - such as NF- κ B, YAP, STAT3, and Wnt/ β -catenin - it must be noted that current investigations into these pathways remain incomplete, with a limited number of experimental studies. Nevertheless, these pathways collectively regulate the

initiation and progression of SPEM, underscoring the need to prioritize signaling pathway research in future investigative strategies. Accumulating evidence has demonstrated that SPEM is not merely an adaptive repair response of the gastric mucosa to injury, but more importantly, a precancerous lesion that actively promotes gastric carcinogenesis. As a dynamic biological process at the crossroads of regeneration and cancer, SPEM represents a crucial target for early-stage targetable interventions. Therefore, deepening our understanding of SPEM mechanisms is essential for the early detection and prevention of gastric cancer.

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