

Roles of interleukins in spasmolytic polypeptide-expressing metaplasia (Review)

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Abstract. Gastric cancer (GC) is a major global health burden, ranking fifth in incidence and third in cancer-related mortality. By 2040, there are expected to be ~1.8 million new cases and 1.3 million fatalities associated with GC. Spasmolytic polypeptide-expressing metaplasia (SPEM) is a central component of gastric precancerous lesions, which remodels the gastric mucosa in response to injury through a lineage of mucus-secreting cells. Interleukins (ILs) are the communication means for innate and adaptive immune cells as well as non-immune cells and tissues. Their complex network regulation contributes to the development of SPEM and is a key driver in the transformation of SPEM to GC. The present review systematically described the IL-related mechanisms underlying the formation and progression of SPEM and categorizes the roles of different ILs by family. In addition, the molecular association between IL dynamics and SPEM following *Helicobacter pylori* infection is explored, and various SPEM experimental model characteristics and IL-based therapeutic strategy advances and limitations are discussed. The clinical translation of IL-targeted therapies is limited, but the development of therapies that target pathogenesis specifically and the enhancement of IL therapy combinations with other therapeutic options may improve efficacy and reduce side effects. Increased understanding of the causes of SPEM and the mechanisms underlying GC may open up new avenues for early detection and targeted therapy.

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1. Introduction

Gastric cancer (GC) continues to have a high global burden, ranking third in terms of cancer-related mortality and fifth in terms of incidence (1,2). Annually, ~660,000 individuals die from GC, despite improvements in early detection and treatment methods (3); by 2040, it is estimated to increase to ~1.8 million new cases and 1.3 million fatalities (4). GC follows a multistage progression pattern driven by chronic inflammation, including atrophy, metaplasia, dysplasia and invasive carcinoma, termed the 'Correa pathway' proposed by Correa *et al* (5) in 1975. Current research is improving the understanding of the molecular mechanisms underlying the progression of precancerous lesions through inflammation-mediated epigenetic changes, such as microbiota dysbiosis, while therapeutic studies are investigating novel approaches to target particular pathways, such as glycosylation, in order to prevent metastasis (6,7). When a terminally differentiated cell type that is not typically found at a specific anatomical location replaces pre-existing terminally differentiated cells, this is termed metaplasia (8). In most cases, the metaplasia lineage is characterized by mucus secretion. A key characteristic of the metaplastic lineage is the remodeling of the gastric mucosa by mucus-secreting cell cohorts in response to damage (9), and mucus production is typically the distinguishing characteristic of this lineage. In the gastric mucosa, two main forms of metaplasia have been identified: i) Intestinal metaplasia (IM); and ii) spasmolytic polypeptide-expressing metaplasia (SPEM).

SPEM, also termed pseudopyloric metaplasia or mucous metaplasia, is a regenerative lesion that presents histologically as Brunner's glands or deep proventricular glands. It is

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distinguished by the expression of Trefoil factor 2 (TFF2), *Griffonia simplicifolia* lectin II (GS II) and mucin (MUC) 6 (10). SPEM formation is frequently accompanied by abnormal gastric pit hyperplasia, macrophage infiltration and glandular structure disarray. Chronic damage (such as inflammation or NSAID use) causes the gastric epithelium to ablate, which leads to the formation of SPEM during regeneration. Similar to intestinal cup cells (MUC5AC, MUC6 and MUC2), these metaplasia cells typically exhibit a distinct mucus-secreting phenotype, altering the defensive and digestive characteristics of the gastric mucosa (10,11). SPEM and IM are two distinct lineages of metaplasia cells. However, SPEM may precede IM and promote carcinogenesis via a variety of mechanisms (12). According to independent clinical studies carried out in the US, Japan and Iceland, SPEM is found in >90% of GC resection specimens, is linked to >50% of early GCs and is frequently found in the paracarcinoma or dysplasia region (13-15). Furthermore, animal models have confirmed that SPEM is an important intermediate stage in gastric precancerous lesions (16-18).

Interleukins (ILs) are potent secreted regulators of various cell types and activities. By targeting and influencing various cell signaling pathways, they aid in the development and progression of inflammatory diseases and various types of cancer. ILs also regulate processes such as cell death, proliferation, differentiation and migration, and are involved in cellular communication during homeostasis and disease (19-22). IL production and function are central regulators of SPEM development. Research has verified that the development of SPEM is closely associated with chronic inflammation and involves an imbalance in the network of pro-inflammatory/anti-inflammatory ILs, such as IL-1 β , IL-10, IL-17A and IL-33. ILs bind to high-affinity receptors on the cell membrane and activate intracellular signaling pathways, including NF- κ B, MAPK and JAK-STAT, resulting in gene transcription changes. This in turn regulates local cell proliferation, differentiation and reprogramming (23-26) and induces or alters specific cellular functions (27-29). The IL network may disturb the normal homeostasis of gastric mucosal cells by controlling local inflammation, cellular infiltration and multi-pathway interactions. This could lead to the development of SPEM or be a major factor in the transformation of SPEM into GC (30).

The present review summarized recent findings on IL-related mechanisms involved in SPEM formation and progression. Furthermore, the roles of various ILs in SPEM and the relationship between IL changes and SPEM after *Helicobacter pylori* (*H. pylori*) infection are described. In addition, the present review offered a comprehensive summary of the features of the different SPEM experimental models that are employed in IL studies. Finally, by describing the progress and limitations of ILs for therapeutic use, novel directions for future investigation are discussed.

2. Overview of SPEM

The mucosal barrier, made up of closely knit epithelial cells and a thick layer of mucus, protects the gastric epithelium from harmful agents such as ingested food, bacteria, gastric acid and digestive enzymes, stopping the stomach contents from penetrating into the underlying tissues (31).

Pepsinogen-producing chief cells, mucus-producing surface foveolar cells, neck cells and acid-producing parietal cells make up the majority of the gastric mucosal barrier (32). The chief cell is a differentiated cell lineage, and a subset of it serves as 'reserve' stem cells in the gastric mucosa. During gastric injury, parietal cells become deficient due to a variety of pathogenic factors, resulting in a compensatory proliferative response of gastric stem and progenitor cells, as well as metaplasia with zymogenic chief cells that can be recruited back into the cell cycle. Metaplasia in the stomach, which results in the structural change of its glands, is considered to be an 'adaptive' process that reacts to a range of endogenous or exogenous aggressors, including pH, hormones, chemicals and microbiota changes (33). SPEM is a type of metaplasia that occurs during the healing of gastric mucosal damage. This is due to the metaplasia cells expressing spasmodic polypeptide, also termed TFF2. Fully differentiated gastric chief cells can be reprogrammed into mucin-secreting metaplasia cells, and the presence of mature chief cells in the corpus is the source of SPEM cells via transdifferentiation. These metaplasia changes take place concurrently with or in response to parietal cell death and inflammation (34). SPEM cells are histologically localized at the base of metaplasia glands following injury, and their specificity was determined by the co-expression of molecular markers including GS II lectin, TFF2, Muc6, CD44v9 and AQP5 (35). The formation of metaplasia lineage cells, proliferation of neck cells and amplification of the small foveolar/tuft cell lineage in the gastric mucosa are characteristic pathological alterations (36,37). Additionally, excessive immune activation in the stomach can damage epithelial cells and induce the development of SPEM (38). Acute SPEM may be a healing mechanism, but when it persists in an environment of chronic inflammation, chronic SPEM is strongly associated with the development of gastric adenocarcinoma (34,38). It has been recorded that >95% of GCs are adenocarcinomas, and according to Laurén's classification, they can be divided into two types: i) Diffuse; and ii) intestinal (39). SPEM is present in almost all GC types, and research on animal models with acute oxyntic atrophy, transgenic and knockout (KO) genes, chronic infection and genetic modification indicates that SPEM is a key precancerous intermediate in the malignant transformation of gastric mucositis (9,40). Although SPEM is partially reversible, intestinal SPEM and/or IM are considered precancerous lesions that may be irreversible in the presence of chronic inflammatory stimuli (41,42). Dysplasia progression is an inevitable stage of cancer development (39). The susceptibility of gastric precancerous lesions to alterations in the expression of numerous ILs suggests that immune cells and different ILs implicated in the progression of metaplasia may be important in predicting the risk of carcinogenesis (27,39,43,44). Thus, additional identification and clarification of ILs associated with the SPEM response will greatly enhance the present understanding of gastric carcinogenesis.

3. IL family and SPEM-associated IL signaling

ILs are a subset of cytokines and a family of signaling proteins that are essential for the regulation and coordination of immune system responses. The family consists of small proteins

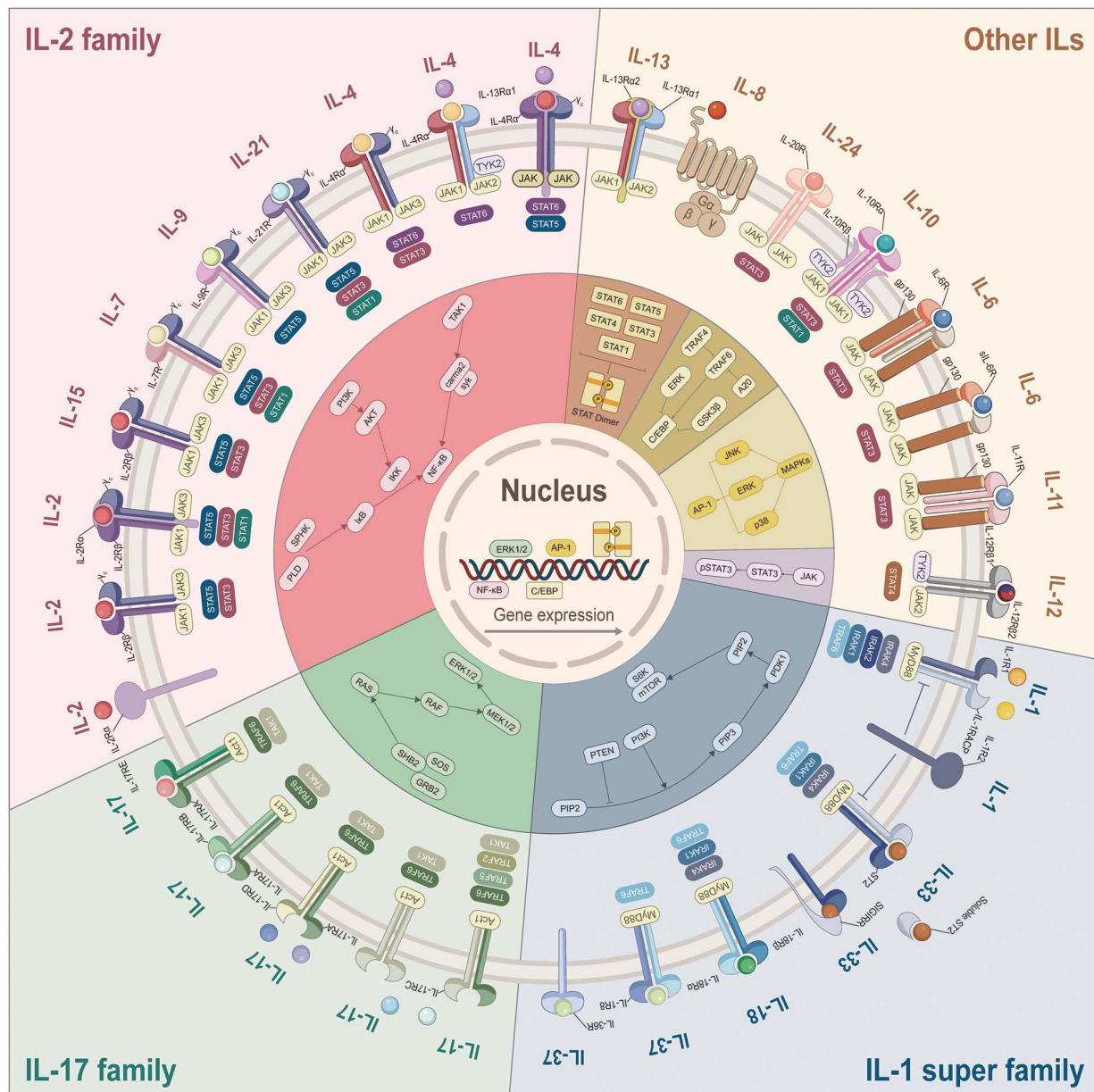
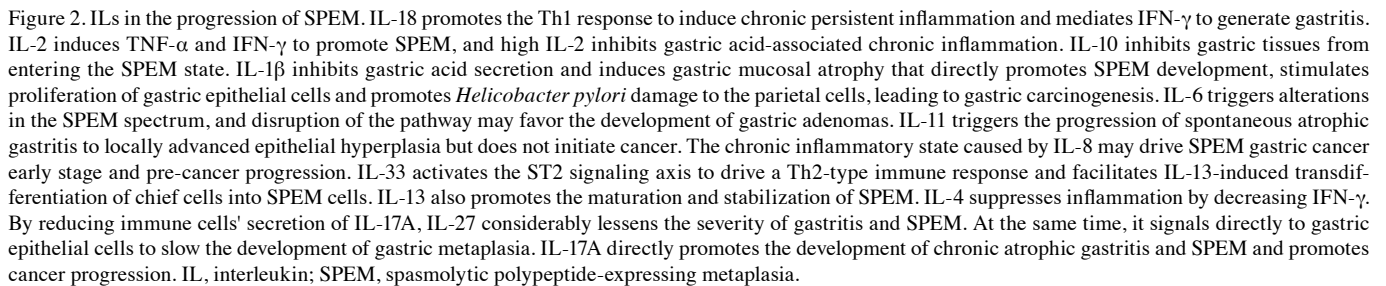


Figure 1. IL family surface receptors and intracellular signaling. The IL-2 interleukin family receptors for IL-2, IL-15, IL-7, IL-9, IL-21 and IL-4 share a common γ c subunit. IL-2 and IL-15 also share IL-2R β . All γ c cytokines activate JAK1 and JAK3. They phosphorylate various STAT proteins downstream by activating the JAK/STAT signaling pathway. The IL-2 receptor has forms with low, intermediate and high affinity and activates JAK-STAT, PI3K and MAPK signaling pathways upon its engagement in the specific receptor complexes. There are three forms of IL-4 receptors involving the IL-4R α subunit, γ c chain, IL-13R α 1 subunit and the IL-2R α subunit, which activate the PI3K and MAPK pathways. IL-4 activates intracellular pathways to produce phosphorylated STAT6, ERK and AKT. IL-6 has classical and trans-signaling properties and activates multiple intracellular pathways, including JAK1-STAT3, RAS-MAPK and PI3K-AKT. IL-1 family receptors are heterodimers consisting of ligand-sensing and signaling monomers. Cellular activation by stimulation of the polymerization of the IRAK4-MyD88 complex leads to the recruitment of IRAK1/2, further recruitment of TRAF6 and activation of MAPK/NIK, and finally activation of the IKK complex, NF- κ B, AP-1 and IRFs. IL-33/ST2 activates NF- κ B, PI3K/AKT, MAPKs and ERK1/2. The six members of the IL-17 family form homodimers and heterodimers that recruit the ubiquitin ligase Act1 to the SEFIR structural domain, triggering the downstream TRAF6-TAK1-NF- κ B pathway, as well as activating the C/EBP and MAPK pathways. IL, interleukin; IRFs, interferon regulatory factors; γ c, γ -chain; IRAK4, IL-1 receptor-associated kinase; MyD88, myeloid differentiation primary response 88; TRAF6, tumor necrosis factor receptor-associated factor 6; NIK, NF- κ B-inducing kinase; AP-1, activator protein 1; SEFIR, similar expression to fibroblast growth factor genes/IL-17 receptors; TAK1, TGF- β -activated kinase 1; C/EBP, CCAAT/enhancer-binding protein.

secreted by different cells to facilitate cellular communication and interaction (45). At least 40 ILs have been identified, a number of which can be classified into separate families or superfamilies (46). Typically, each IL interacts with a different receptor or group of closely related receptors expressed on the target cell, and when bound, the intracellular structural domain of the receptor is activated, triggering an intracellular signaling

cascade (Fig. 1). Numerous ILs are especially important for the onset and course of SPEM, and their pleiotropic effects depend on a number of factors, including dose dependency, receptor heterogeneity, cellular source diversity and signaling pathway complexity (21). In the present review, the cytokine signals associated with SPEM were systematically categorized (Fig. 2), including the IL-1 superfamily, IL-2 family, IL-6



IL-1. IL-1 is a polypeptide synthesized and secreted by lymphocytes and monocyte macrophages and has various functions, such as participation in immune response, thermogenesis and mediation of inflammation (47). Within a 430 kilobase region, the IL-1 gene cluster on chromosome 2q comprises three related genes, IL-1A, IL-1B and IL-1RN, which encode IL-1 α , IL-1 β and IL-1 receptor antagonist (IL-1Ra) (27). IL-1 α and IL-1 β are alarm cytokines (also termed alarm proteins), both of which initiate and amplify local inflammation via the IL-1 receptor (IL-1R) (48). Additionally, IL-1 β directly stimulates the development of SPEM by strongly suppressing the secretion of gastric acid and causing the atrophy of the gastric mucosa. When pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns activate the pattern recognition receptor, IL-1 β is produced as an inactive precursor (pro-IL-1 β). The cleavage of pro-IL-1 β into its active form by caspase-1 proteolysis requires the activation of inflammasomes, which are then released extracellularly (47).

IL-18. IL-18, a member of the IL-1 superfamily, is a pleiotropic pro-inflammatory cytokine that is important in gastric mucosal inflammation and immunomodulation (27,51). IL-18 signaling begins with a ligand binding to the receptor IL-18R α (also termed IL-1R-related protein). When IL-18 binds to IL-18R α , IL-18R β /IL-18RACp is recruited into the complex and activates downstream signaling pathways such as NF- κ B. IL-18 can dominate the gastric mucosal response to *H. pylori* infection by promoting T helper (Th) 1 responses and inducing chronic persistent inflammatory changes (52). Initially, it was referred to as an IFN-inducing factor that could stimulate the production of IFN- γ by splenocytes, hepatic lymphocytes and Th1 cells, as well as increase the cytotoxicity of natural

Table I. SPEM-related cytokine signaling.

First author/s, year	Cytokines	Receptor	Targeted cells	Measurement of SPEM	Related signaling pathways	Promotes or suppresses SPEM	Mouse model	Methods	(Refs.)
El-Zaatari <i>et al</i> , 2013	IL-1 β	-	Epithelial mucous cells	Histopathology scoring (0-3) and biomarkers to determine lineages	IL-6/pSTAT3	Promote	C57BL/6 and Gli1 ^{+/LacZ}	Immunofluorescence, RT-qPCR, flow cytometry and western blot	(31)
Lee C <i>et al</i> , 2017	IL-10	IL10R α and IL10R β	Epithelial cells	Calculated the number of PCs and determine lineage using biomarkers	-	Unknown	Tamoxifen- induced C57BL/6	H&E staining, immunofluorescence, RNA-seq and multi- plex immunoassay	(25)
Buzzelli JN <i>et al</i> , 2019	IL-11	IL-11R α	Epithelial cells	Histopathology scoring (0-5) and biomarkers to determine lineages	gp130-JAK- STAT3	Promote	K19-IL11Tg	RT-qPCR, immunoblotting, ELISA, immunofluorescence, immunohisto- chemistry, flow cytometry and AB-PAS staining	(104)
Howlett M <i>et al</i> , 2012	IL-11	IL-11R α	Epithelial cells	Histological examination and biomarkers to determine lineages	IL-11/STAT3	Promote	Wild-type C57BL/6 and HK $\beta^{-/-}$	Immunohisto- chemistry, immuno- blotting, RT-qPCR and PAS Staining	(103)
Howlett M <i>et al</i> , 2009	IL-11	IL-11R α	Epithelial cells	Histological examination and biomarkers to determine lineages	IL-11/STAT3/ ERK1/2	Promote	gp130 ^{757E/F} , IL-11R ^{-/-} , HK ^{-/-} , K19- C2mE and K19-Wnt/ C2mE	H&E/alcan blue/ periodic acid-Schiff staining, qPCR, immunohisto- chemistry and immunoblotting	(105)
Petersen CP <i>et al</i> , 2018	IL-13	IL13R α 1	Chief cells	Biomarkers to determine lineages	IL-33/ST2 axis and IL-13/ IL13 α 1	Promote	L635-treated C57BL/6	FACS analysis, immunofluorescence, RNA-seq, RT-qPCR	(63)
Noto CN <i>et al</i> , 2022	IL-13	IL4R α	Epithelial cells	Histopathology scoring (0-4) and biomarkers to determine organoid lineages	IL-33/ST2 axis and IL-13/IL4R α	Promote	Gastric orga- noids, Tx A23 xlfng ^{-/-} , Tx A23 andTx A23 x Il13-Yfp	H&E/toluidine blue staining, immunofluorescence, RNA-seq, flow cytometry and RT- qPCR	(144)

Table I. Continued.

First author/s, year	Cytokines	Receptor	Targeted cells	Measurement of SPEM	Related signaling pathways	Promotes or suppresses SPEM	Mouse model	Methods	(Refs.)
Meyer AR <i>et al.</i> , 2020	IL-13	-	Chief cells	Histological examination and biomarkers to determine lineages	IL-33/ILC2s/IL- 13 axis	Promote	Wild-type C57BL/6 and IL-13- tdTomato reporter	ELISA, immunostaining, flow cytometry and FACS analysis	(36)
Busada JT <i>et al.</i> , 2021	IL-13	-	-	Biomarkers to determine lineages	IL-33/ILC2s/IL- 13 axis	Promote	Adrenalecto- my and castration C57BL/6J IL-13- tdTomato reporter	qRT-PCR, H&E staining, flow cytometry and scRNA-seq	(38)
Contreras- Panta EW <i>et al.</i> , 2024	IL-13	-	SPEM cells	Histological examination and biomarkers to determine lineages	IL-13/STAT6	Promote	IL-13- tdTomato reporter	Flow cytometry, scRNA-seq, RT-qPCR, H&E staining, immunofluorescence and immunoblotting	(39)
O'Keefe- RN <i>et al.</i> , 2023	IL-13	IL13R α	ILC2s, Tuft cells and stem cells	Biomarkers to determine lineages	ILC2-tuft cell circuit	Promote	BAC(Dcl1: CreERT2), CreERT2- negative Ros 26DTA (TC ^{WT})	Flow cytometry, scRNA-seq, RT-qPCR and immunofluorescence	(138)
Miska J <i>et al.</i> , 2018	IL-13	IL4R α	Epithelial and immune cells	Histopathology scoring (0-4) and biomarkers to determine organoid lineages	IL-4/IL-13- independent hits and Tet3- mediated epigenetic dysregulation	Promote	CTLA4KD IL4/IL13 ⁺ and CTLA4KD IL4/IL13 ⁺	Genetic ablation, flow cytometry, RT-qPCR, H&E staining and immunofluorescence	(149)
Bockerstett KA <i>et al.</i> , 2018	IL-17A	IL17RA	PCs	Histopathology scoring (0-4) and biomarkers to determine lineages	IL-17A/IL17RA	Promote	TxA23 and BALB/c	H&E staining, immunofluorescence and flow cytometry	(34)
Bockerstett KA <i>et al.</i> , 2020	IL-27	IL27RA	CD4 ⁺ T cells	Histopathology scoring (0-4) and biomarkers to determine lineages	IL-27/IL27RA	Suppress	TxA23 and TxA23 x Ebi3 ^{-/-}	Flow cytometry, scRNA-seq, qRT-PCR, H&E staining and immunofluorescence	(43)

Table I. Continued.

First author/s, year	Cytokines	Receptor	Targeted cells	Measurement of SPEM	Related signaling pathways	Promotes or suppresses SPEM	Mouse model	Methods	(Refs.)
Petersen CP <i>et al</i> , 2018	IL-33	ST2	ILC2s, M2 macrophages	Biomarkers to determine lineages	IL-33/ST2 axis	Promote	L635-treated C57BL/6	FACS analysis, immunofluorescence, RNA-seq, RT-qPCR	(63)
Jeong H <i>et al</i> , 2021	IL-33	ST2	Immune cells	Histological examination and biomarkers to determine lineages	IL-33/ST2 axis, NF-κB	Promote	Wfdc2 ^{-/-} and C57BL/6	FACS analysis, immunofluorescence, H&E staining, RNA-seq and RT-qPCR	(186)
Buzzelli JN <i>et al</i> , 2015	IL-33	ST2	Immune regulatory cells	Biomarkers to determine lineages	ERK1/2	Promote	C57BL/6 wild-type	Flow cytometry, RT-qPCR, immunofluorescence, immunohisto- chemistry and immunosorbent assay	(60)
De Salvo C <i>et al</i> , 2021	IL-33	ST2L/IL- 1R4	Immune cells, M2 macrophages	Histopathology scoring and biomarkers to determine lineages	IL-33/ST2 axis	Promote	SAMP x IL33 ^{-/-} and C57BL/6J wild-type	H&E/staining, AB- PAS blue staining, RT-qPCR, western blot, BrdU staining, immunohisto- chemistry and flow cytometry	(62)
Zeng X <i>et al</i> , 2023	IL-33	ST2	Immune cells	Histological examination	ROS/NRF2- HO-1/NFκB axis	Promote	GRIM-19 ^{-/-}	H&E staining, RT-qPCR, western blots, cytokine ELISA plate array, immunohisto- chemistry and flow cytometry	(28)
Li W <i>et al</i> , 2024	IL-33	ST2	ILC2s	Histological examination and biomarkers to determine lineages	IL-33/ILC2s/ IL-13 axis	Promote	RAG1 knockout and wild type C57BL/6 mice	Flow cytometry, immunofluorescence and immuno- histochemical staining	(72)

IL-, interleukin; SPEM, spasmodytic polypeptide-expressing metaplasia; PC, parietal cells; gp130, glycoprotein 130; pSTAT3, phosphorylated STAT 3; RT-qPCR, reverse transcription-quantitative PCR; AB-PAS, Alcian blue-periodic acid Schiff; RNA-seq, RNA sequencing; scRNA-seq, single cell RNA-seq; BrdU, 5-bromo-2'-deoxyuridine; GRIM-19, gene-related to melanoma-19.

killer (NK) cells and stimulate the production of IFN- γ in conjunction with IL-12 (53). The production of IFN- γ causes the death of gastric epithelial cells that express the IFN- γ receptor and is directly linked to the pathological process of SPEM (54). Although the link between IFN- γ and subsequent neoplasia remains uncertain, studies have shown that IFN- γ is crucial during the SPEM stage of precancerous lesions (55). Current studies have typically focused on IL-18-related gene polymorphisms. Research has demonstrated that IL-18RAP gene polymorphisms serve a notable role in the development of gastric precancerous lesions by controlling the IFN- γ production pathway, and may be linked to precancerous lesions or susceptibility to GC in GC high-risk populations (51,53). However, according to a different study, there was no meaningful association between the progression of gastric precancerous lesions and IL-18 promoter polymorphisms (56). Therefore, there is a lack of direct evidence that IL-18 serves a key role in gastric precancerous lesions and SPEM progression.

IL-33. IL-33, a member of the IL-1 superfamily, is a cytokine involved in tissue homeostasis, pathogenic infections, inflammation, allergies and the type 2 immune response. Through its receptor ST2 (ST2L; also termed T1/ST2, IL1RL1, T1, Der4, Fit1 or IL-33R), IL-33 forms a heterodimeric complex with IL-1 receptor accessory protein (IL-1R3). IL-33 is extensively found on the surfaces of Th2 cells, group 2 innate lymphocytes (ILC2s), mast cells and macrophages (57,58). IL-33 serves as an intranuclear transcriptional regulator, an extracellular alarmin and an immune regulation mediator. Under healthy conditions, IL-33 translocates to the nucleus and is involved in regulating gene expression (59). When necrosis or cell damage compromises the epithelial cell barrier, cells release IL-33, which also acts as an alarm protein (60,61). The immune defense and repair systems are coordinated by extracellular IL-33, which also initiates adaptive immune responses. Increased extracellular IL-33 activates expanded tissue ILC2 and Treg and promotes the recruitment and survival of immune cells (such as eosinophils, AAM, Th2 cells and basophils). These cells and signals feed back to the tissue to promote remodeling and limit inflammation. In the gastric mucosa, IL-33 is mainly secreted by damaged epithelial cells, a subset of mucous foveolar epithelial cells and M2-type macrophages (60,62,63). When there is acute inflammation and a loss of gastric mucosal parietal cells, macrophages infiltrate and gastric pit epithelial cells release IL-33 to synchronize immune defense and repair processes. IL-33 also promotes epithelial proliferation through activation of the MAPK pathway (ERK1/2, JNK and p38) (64). The IL-33/IL-13 axis is critical for gastric metaplasia and gastric epithelial repair, and several studies have linked reduced IL-33 in TFF2-deficient mice to defective metaplasia development and delayed downstream gastric epithelial repair (60,65,66). Following parietal cell loss, IL-33 stimulates the ST2 signaling axis, triggers a Th2-type immune response, promotes the release of cytokines such as IL-13 and causes the transdifferentiation of gastric chief cells into SPEM cells (63). IL-33- or ST2-KO mice are unable to form SPEM after L635-induced acute injury, suggesting that appropriate ILs are required to promote transdifferentiation as part of the gastric epithelial repair process (63,67).

IL-33 also enhances ILC2 activity by upregulating GATA3 signaling, drives the gastric mucosal Th2 response and synergistically promotes goblet cell proliferation with IL-25 (68). Furthermore, IL-33 activates ILC2 in combination with IL-25 released by Tuft cells, increasing type II cytokines such as IL-4, IL-5, IL-9 and IL-13 (57,63,69). Among these cytokines, IL-13 and IL-4 mediate M2 macrophage activation through the co-receptor IL-4R α (70). M2 macrophages and eosinophils in turn produce IL-13 and IL-33, self-sustaining the feed-forward cycle and stimulating mast cell activity (71,72). The resulting downstream release of IL-13 facilitates the progression of SPEM. A series of IL-33-mediated signaling events that promote SPEM progression are centrally involved, and persistent inflammation of the gastric mucosa can further lead to additional IM and carcinogenesis (68). Long-term and high levels of IL-33 cause M2 macrophage polarization, eosinophil proliferation and severe infiltration into the stomach mucosa, resulting in the maintenance of Th2-driven chronic inflammation (73). This increases the risk of cancer and promotes metaplasia to transform into GC (60,62,64,68). Given that IL-33 stimulates epithelial proliferation and metaplasia whilst also inducing and maintaining chronic Th2-driven inflammation, it is a key mediator of SPEM/intestinal SPEM manifestations.

IL-2 family (common γ -chain)

IL-2. IL-2 is a pro- and anti-inflammatory cytokine produced primarily by activated T cells that regulates immune response and anti-tumor immunity. The IL-2 receptor consists of three subunits: i) IL-2R α (CD25); ii) IL-2R β (CD122); and iii) common γ -chain (γ c; CD132). The IL-2R $\alpha\beta\gamma$ c heterotrimer is constitutively expressed on Tregs and ILC2s and has the highest affinity for IL-2. In the context of chronic or acute inflammation, mucosal cells proliferate at an accelerated rate to promote the repair of damaged epithelium (74). *H. pylori*-associated gastritis is closely related to IL-2, and the DMP-777 model shows that parietal cell deficiency is sufficient to trigger SPEM, but inflammation is critical for further differentiation and the development of SPEM (75,76). Studies into the inflammatory component in mice have shown that the progression of SPEM to developmental abnormalities requires a Th1-dominated inflammatory response (77,78). Th1 cells characteristically secrete IFN- γ and IL-2 (79). Th1 cells in *H. pylori*-infected individuals produce large amounts of IL-2, which induces T cell differentiation and immune memory (80,81). IL-2 is considered to provide a pathological basis for gastric carcinogenesis and SPEM by suppressing the secretion of gastric acid and modifying Th1 immune responses. A previous study found that the Th1-specific cytokines IL-2 and IFN- γ directly inhibit acid secretion in mice, which can lead to gastric atrophy and promote the development of precursor lesions to GC (82). However, there is no direct experimental evidence that indicates that IL-2 is directly related to SPEM differentiation and maturation. Instead, IL-2 primarily mitigates tissue damage by reducing gastric acid secretion and thus acid-related chronic inflammation (83). In summary, IL-2 serves an important role in SPEM progression by regulating the intensity of inflammation and the immune microenvironment, but its specific signaling pathways and interactions with other cytokines still need further exploration.

IL-4. IL-4 is an important immunomodulatory cytokine involved in the cascade transduction of several cytokines. Its signaling is initiated through two heterodimeric receptor complexes: i) Type I (IL-4R α / γ c) specifically bound to IL-4; and ii) type II (IL-4R α /IL-13R α 1) bound to both IL-4 and IL-13, activating STAT6, JNK or IRS2 signaling pathways that drive macrophage polarization towards the alternative activation phenotype (M2a) (70,84). Activated JAK phosphorylates IL-4R α tyrosine residues, creating binding sites for STAT6, which dimerizes and translocates to the nucleus to activate gene transcription (85). IL-4 also maintains immune homeostasis by balancing M1/M2 macrophage polarization via STAT1/3 and STAT6 synergistic regulation (84,86). In gastric mucosal inflammation, IL-4 acts as an anti-inflammatory factor to inhibit inflammation and atrophy by reducing IFN- γ . It inhibits the secretion of pro-inflammatory cytokines, such as IL-1, IL-6 and TNF- α , and regulates lymphocyte differentiation and the tumor microenvironment (84). Due to the structural similarity of the surface receptors, in a variety of diseases IL-4 acts predominantly in conjunction with another type II cytokine, IL-13 (84). IL-4 and IL-13 activate macrophages by alternating, a process that is also an important step in the progression of SPEM (70,86-88). IL-4 also serves a central role in the Th2 cell phenotype, with studies revealing that sequential activation of STAT5 and STAT6 enhances the subsequent response to IL-4, ultimately leading to Th2 T cell differentiation (89,90). Studies have shown that IL-4 also inhibits the growth of GC cells, and a notable increase in serum IL-4 levels has also been reported in patients with GC (85,91,92). IL-4 is considered to be associated with the repair of epithelial damage in the early stages, and the mechanism of its association with cancer progression in the late stages has not yet been demonstrated. Furthermore, a study demonstrated that IL-4 notably increased M2 macrophage differentiation in a diabetic mouse model, indicating that it may serve a similar role in gastric mucosal injury repair (57).

IL-6 family

IL-6. IL-6, a pleiotropic cytokine, is secreted by immune cells (such as monocytes, macrophages and lymphocytes) and non-immune cells (such as endothelial cells, intestinal epithelial cells, tumor-associated fibroblasts and tumor cells) (93-95). IL-6 regulates inflammatory mediators and endocrine responses, and serves as a link between innate and adaptive systems in host defense mechanisms (96). IL-6 signaling necessitates binding to the specific receptor IL-6R or IL-11R, which then binds to the common signal transduction receptor subunit glycoprotein 130 (gp130), causing its recruitment and homodimerization, eventually leading to the activation of the JAK/STAT and SHP2/Ras/MAPK/ERK1-2/activator protein 1 (AP-1) signaling cascades (97-99). In gastric mucosal lesions, IL-6 regulates gastric mucosal homeostasis by regulating TFF1 and mucosal proliferation, inflammation, angiogenesis and apoptosis-related mediators, and its signaling regulates gastric mucosal homeostasis by balancing SHP2/Ras/ERK and STAT3. Elevated IL-6 levels were noted in chronic inflammatory conditions, and the downregulation of TFF1 tumor suppressor activity was caused by the absence of ERK/AP-1 signaling downstream of gp130. This, in turn, results in the

activation of constitutive and oncogenic STAT3, which inhibits apoptotic processes and promotes cellular proliferation and inflammatory responses. These factors ultimately lead to the development of mucosal atrophy, metaplasia, TFF2-associated changes in the SPEM lineage, aberrant cell proliferation and the progression to dysplasia and submucosal invasion (98). When IL-6 family signaling pathways are interfered with, increased STAT3 signaling may promote the growth of gastric adenomas, while increased SHP2/ERK2 signaling may result in chronic mucosal inflammation (100). Therapeutic strategies targeting the IL-6/JAK/STAT3 axis, such as the JAK inhibitor WP1066, have been shown to inhibit STAT3 phosphorylation and reduce pro-inflammatory factors (IL-6, IL-11 and IL-1 β) and growth factor expression, thereby blocking tumor proliferation and inducing apoptosis (101). Nonetheless, there is insufficient evidence to support a causal role for IL-6 in cancer progression, implying that this IL may serve a protective rather than pathogenic role in the stomach (102).

IL-11. IL-11 belongs to the IL-6 family and is a pleiotropic cytokine. It is a key mediator of inflammation in the gastrointestinal tract, influencing the activity of numerous immune cell populations such as macrophages, mast cells, dendritic cells (DCs) and lymphocytes (103). IL-11 initiates signal transduction by binding to IL-11 receptor α , which recruits the signal transduction receptor gp130. By extending stem cell survival, decreasing apoptosis and promoting mitosis, IL-11 can impact epithelial homeostasis and is crucial for gastric injury, mucosal repair and cancer progression (104). Chronic IL-11 elevation causes severe fundus damage, including inflammation, metaplasia, loss of chief and parietal cells and increased proliferation, all of which are closely linked to chronic atrophic gastritis in humans (103). IL-11 has been shown to mediate the hyperactivation of STAT3 by gp130 in a gp130^{F/F} mouse model of gastric tumorigenesis (105,106). Overexpression of IL-11 in the stomach caused by mutations in the gp130-JAK-STAT3 pathway can cause spontaneous atrophic gastritis to progress to locally advanced epithelial hyperplasia, but not dysplasia or cancer (104). Furthermore, alongside IL-11-induced gastric atrophy, there is a modest influx of polymorphonuclear cells, accompanied by elevated expression of IL-1 β and IL-33 (103). IL-33 modulates Th1/Th2 cytokine balance in epithelial cells (107), whereas IL-1 β regulates the expression of HK-ATPase α subunit 64 and suppresses gastrin-dependent acid secretion (108,109). Notably, IL-11 can directly activate GC cells, thereby driving the development of an invasive phenotype (110), and is upregulated in both mouse and human GC as well as preneoplastic mucosa (111).

IL-10 family. IL-10 is an important anti-inflammatory cytokine and serves a key role in immunomodulation by inhibiting the synthesis of pro-inflammatory cytokines such as IL-1 β , IL-6, IL-12 and TNF- α (112-114). IL-10 activity is mediated by heterodimeric IL-10 receptors (IL-10R1 and IL-10R2) (112). By preventing macrophage-mediated inflammatory responses and limiting pro-inflammatory signaling pathways such as NF- κ B, IL-10 facilitates tissue repair (112,113). In a tamoxifen-induced SPEM model of gastric mucosa, IL-10 expression was notably reduced 3 days after administration and coincided with a histological loss of ~90% of parietal cells in the gastric mucosa. IL-10 levels were restored after

10 and 21 days, accompanied by histological normalization, suggesting that it may be involved in mucosal repair by modulating parietal cell function (25). Deficits in IL-10 can also result in the development of precancerous microenvironments and chronic inflammation (42). In addition, intracellular IL-10 levels are significantly elevated in patients with advanced GC (115). IL-10 present in tumor-associated macrophages creates an immune-evasive microenvironment (116), and elevated IL-10 levels are associated with GC metastasis and poor prognosis (117). The regulatory mechanism of IL-10 on SPEM-related carcinogenesis is still being investigated (42); however, IL-10 is regarded as a key target for intervention in gastric metaplasia and carcinogenesis (25,118).

IL-12 family. IL-27, a heterodimeric cytokine composed of p28 and EBI3, has a receptor consisting of IL-27R α and gp130 and is widely expressed in immune cells such as T cells (43). Studies have shown that IL-27 serves a key regulatory role in chronic gastritis and gastric mucosal metaplasia. IL-27-deficient mice progress more rapidly during gastric carcinogenesis, as evidenced by earlier and faster development of severe gastric atrophy, metaplasia and inflammatory infiltrates, whereas exogenous IL-27 treatment notably reduces the severity of gastritis, atrophy and SPEM (43,119). IL-27 protective effects are primarily twofold: i) Reduces immune cell secretion of IL-17A; and ii) Transmits signals directly to gastric epithelial cells, slowing the progression of gastric metaplasia and possibly promoting reparative metaplasia (120). Rapid disease progression and notable variations in the degree of STAT signaling pathway activation in gastric epithelial cells are linked to increased Th17 cell proportion and pro-inflammatory cytokine levels (IL-6, G-CSF, MIP-2 and IL-5) in IL-27-deficient models (119,121,122). Notably, IL-27 largely controls metaplasia linked to chronic inflammation and has no discernible impact on metaplasia brought on by acute injury (122). Based on this evidence, IL-27 may serve a crucial protective role in preventing gastric carcinogenesis and SPEM by regulating immune cell activity and epithelial cell response.

IL-17 family. The IL-17 cytokine family consists of six members [IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25) and IL-17F] (123-125). IL-17A (also commonly referred to as IL-17) has been extensively studied and serves a crucial role in host defense against microbes and in the development of inflammatory diseases (126-130). IL-17 is derived from a wide range of sources, including adaptive immune cells (such as CD8⁺ T cells and $\gamma\delta$ T cells) and innate immune cells or myeloid cells (NK cells, macrophages, DCs, neutrophils and eosinophils) (126,131-135). The receptor for IL-17A consists of two protein monomers: i) IL-17 receptor A; and ii) IL-17 receptor C. The IL-17 receptor complex is expressed on numerous cell types, including various types of epithelial cells (34). IL-17A promotes inflammation by upregulating cellular adhesion molecules such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, activating downstream signaling pathways (including NF- κ B, MAPKs and JAK2/STAT3), and stimulating the production of cytokines and chemokines (including IL-1, IL-6 and monocyte chemoattractant protein-1) (123,136). IL-17A is a primary cause

of mural cell atrophy and metaplasia in chronic atrophic gastritis. Overproduction of IL-17A in the setting of chronic inflammation directly causes parietal cell apoptosis and accelerates the process of gastric mucosal atrophy and metaplasia, whilst neutralization of IL-17A successfully inhibits the aforementioned pathological alterations (34,137). Patients with gastro-IM have increased IL-17 levels, indicating that a prolonged Th17 response may occur prior to cancer formation. The gastric epithelium may undergo physiological and morphological changes as a result of a persistent inflammatory state or immune response in the gastric region. This increases the risk of tumor transformation due to atrophy and decreased gastric acid levels (72). By upregulating the matrix metalloproteinases MMP2/MMP9, disrupting the extracellular matrix and activating the JAK2/STAT3 signaling pathway, IL-17A promotes the formation of the tumor microenvironment by increasing the migration and invasion of cancer cells (132). According to clinical evidence, patients with GC had significantly higher serum IL-17A levels, which may indicate that the protein could be used as a diagnostic marker (133). In summary, cytokine networks control the proinflammatory and procarcinogenic effects of IL-17A, which is pleiotropic in gastric mucosal inflammation, metaplasia and carcinogenesis.

IL-25. IL-25, also termed IL-17E, is a member of the IL-17 cytokine family. IL-25 is an important regulator of the type 2 immune response, and its increased expression is closely related to the metaplasia microenvironment after parietal cell loss (138). Its receptor is expressed on the surface of ILC2 cells, and when the gastric mucosa is severely injured, surface mucus cells produce IL-33 and IL-25, which stimulate ILC2 to secrete IL-13 together (Fig. 3). IL-13 is an important driver of the reprogramming of chief cells into SPEM cells and the development of pyloric metaplasia. Cluster cells further activate ILC2 by secreting IL-25, forming a signaling loop (138,139). Notably, IL-25 also indirectly triggers epithelial cell proliferation by inducing IL-13 production in ILC2 (139). The IL-25/ILC2 axis is implicated in the development of metaplasia, but it also facilitates the malignant progression of metaplasia to tumor cells. According to the aforementioned findings, inhibiting IL-25 signaling or ablation of tuft cells or ILC2 has notable therapeutic potential in both the early (gastric metaplasia) and advanced stages of the tumor trajectory.

Other ILs

IL-8. IL-8, also termed CXCL8, belongs to the CXC chemokine family. By binding to the G protein-coupled receptors CXCR1 and CXCR2, it activates downstream signaling pathways that contribute to angiogenesis, the inflammatory response and the growth of tumors (140). Its expression is influenced by inflammatory factors (such as TNF- α and IL-1 β), environmental stress (including hypoxia and chemotherapy) and hormones (including androgens and dexamethasone), and is associated with a poor cancer prognosis (140-142). IL-8 was first identified for its neutrophil chemotactic and degranulation effects, but its pro-inflammatory properties and link to tumor metastasis are especially important in GC (143). The chronic inflammatory state caused by IL-8 may accelerate the progression of early pre-cancerous lesions in GC, but no study has directly demonstrated a link between IL-8 and SPEM.

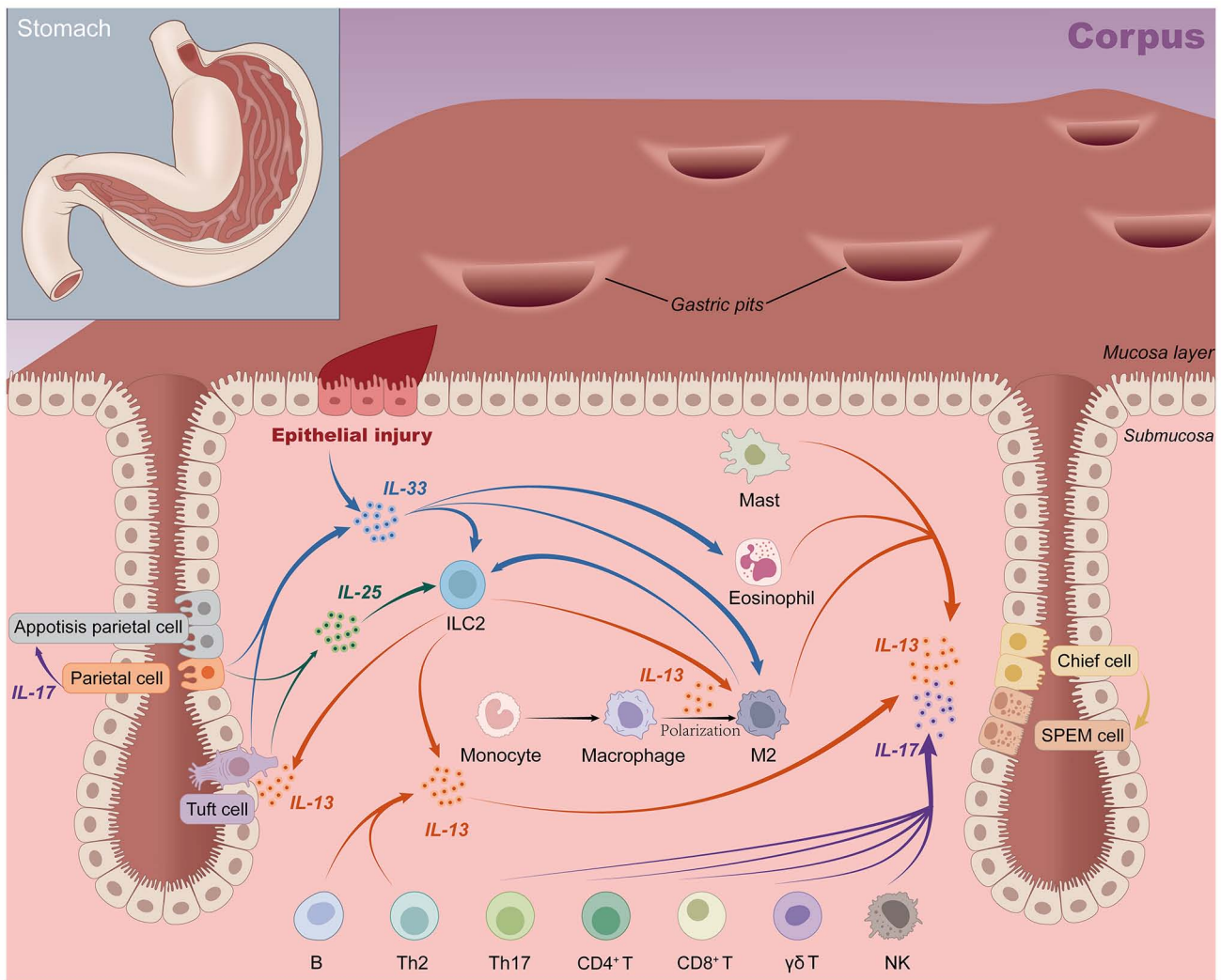


Figure 3. IL-33, IL-25, IL-13 and IL-17 are associated with the onset and progression of gastric epithelial metaplasia as SPEM. Epithelial injury and parietal cell apoptosis lead to the release of IL-33, which causes macrophage polarization toward M2. IL-25 released by tuft cells along with IL-33 also contributes to the potential induction of ILC2 activation and proliferation. M2 macrophages and eosinophils in turn produce IL-13 and more IL-33. B cells, Th2 cells and mast cells also produce IL-13. The development of SPEM is aided by the downstream release of IL-13 and IL-17, which are produced by various T cells and NK cells. IL, interleukin; SPEM, spasmolytic polypeptide-expressing metaplasia; NK, natural killer; Th, T helper cell.

IL-13. IL-13 is the central cytokine of the Th2 immune response, mediating local tissue effects in gastritis such as chemokine secretion, goblet cell proliferation, mucus production and smooth muscle changes (84). There are six immune cell types that secrete IL-13, and in autoimmune gastritis models, mast cells produce the majority of them. They also penetrate the gastric mucosa during chronic inflammation (138,144,145). Another key source of IL-13 is ILC2s, which are also found in inflammatory stomach tissue. IL4R α , IL13R α 1 and IL13R α 2 are three heterodimeric receptors that deliver IL-13 signaling (146,147). The process involves JAK signaling transducers (including JAK1 and JAK3) and the activator of transcription (STAT) pathway (63,144). The most important of these is STAT6, where IL-13 induces STAT6 phosphorylation and gene transcriptional regulation to propel chief cell transdifferentiation toward the SPEM phenotype (39,144,147). The gastric epithelium expresses IL-4R α , and IL-13 affects epithelial cells directly, which leads to the expansion of mucus neck cells and the development of SPEM. Furthermore, IL-13 can directly control chief cells through IL-13R α . In gastric

metaplasia, its importance is mainly associated with mucus hypersecretion, a specific feature of SPEM. IL-13 is a core effector molecule of the IL-33/ILC2s/IL-13 axis (Fig. 4), and after chemically-induced acute parietal cell loss, ILC2 is the major source of IL-13. In conjunction with amphipysin and IL-4, IL-13 promotes the recruitment of eosinophils and the activation of M2-type macrophages, as well as the induction and growth of SPEM (36,39). By contrast, ILC2 depletion or ablation notably inhibits metaplasia induction, cell proliferation and macrophage infiltration (36,38). Mice lacking the IL-33 receptor (ST2) are unable to develop SPEM following L635 induction. However, exogenous recombinant IL-13 aids in the redevelopment of SPEM, and neutralizing IL-13 notably reverses the metaplasia in gastritis mice (62,144). This suggests that IL-13 serves an important role in the pathogenesis of SPEM, with IL-33 acting only as its upstream inducer (63,148).

Existing research on the role of IL-13 in the progression of SPEM to malignancy takes two opposing perspectives. A previous study suggested that IL-13 mainly promotes the maturation and stabilization of SPEM. By activating

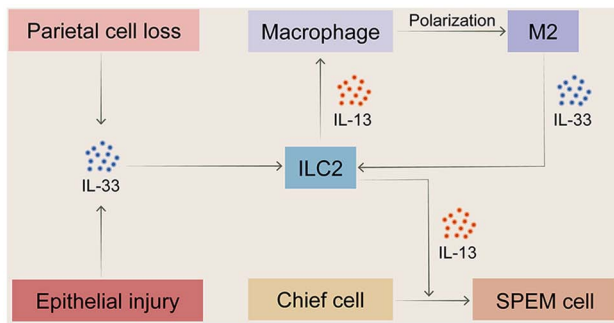


Figure 4. IL-33/ILC2s/IL-13 axis regulates the development of spasmolytic polypeptide-expressing metaplasia. When mucosal damage or parietal cell loss occurs, IL-33 is released and interacts with the IL-33 receptor (ST2) on type II innate lymphocytes (ILC2s). IL-13 signaling downstream of IL-33 promotes SPEM formation and the selective activation of macrophages to M2. Activated macrophages generate IL-33, which may further increase IL-13 release and aid in chief cell transdifferentiation into SPEM cells. IL, interleukin; SPEM, spasmolytic polypeptide-expressing metaplasia.

the IL-13/STAT6 axis, it causes STAT6 phosphorylation in SPEM cells and boosts mucin production, resulting in a mature and proliferative SPEM cell phenotype (39). Another study reported the potential pro-cancer mechanism of IL-13; ILC2-derived IL-13 promotes the growth and secretion of IL-25 by gastric mucosal tufted cells, which in turn triggers ILC2 activity. This creates an IL-13/IL-25 feedback loop and speeds up the development of cancer from SPEM (138). Simultaneously, TNF^+ Tregs release IL-13, which activates STAT3, directly promoting the malignant biologicals of cancer cells (149). In addition, the increase of the Th2 response and IL-4/IL-13 in chronic inflammatory environments can trigger Tet3-mediated epigenetic disorders. This process causes changes in gene expression programs, which initiate epithelial transformation and differentiation of precancerous cells (149). In conclusion, interventions targeting IL-13 may be expected to alleviate gastrointestinal tumor precursors and possibly reverse the development of gastric metaplasia.

IL-32. IL-32 was first discovered in 1992 in NK cells activated by IL-2 (150). Due to its then unknown function, it was termed the N-terminal and four kringle structural domain of the hepatocyte growth factor protein (NK4) (151,152). Of the nine IL-32 isoforms that have been identified, IL-32 α is the most widely expressed, IL-32 γ has the highest biological activity and IL-32 β has the highest genetic homology to humans (153). IL-32 is mainly expressed by NK cells, monocytes, epithelial cell lines and T cells. The structure of IL-32 is unique in that it lacks any specific cell surface receptors involved in extracellular signaling and is hypothesized to exert its effects through a number of intracellular molecular interactions (154). The expression of IL-32 is highly increased in the gastric mucosa of patients with GC and is rare in healthy gastric mucosa, but the increased levels of IL-32 are mainly confined to the cytoplasm of gastric epithelial cells in patients with gastritis and GC (152). Internal infection causes the synthesis and secretion of various pro-inflammatory and anti-inflammatory cytokines, resulting in the formation of a tumor microenvironment in GC cells. These microenvironments are constantly involved in the synthesis of IL-8, which has a biological effect by triggering the synthesis of IL-32 (154). It not only promotes the

development of inflammation, but also induces the expression of a number of potent inflammatory cytokines. Further studies are needed to investigate the different pathways regulated by IL-32 and its role in SPEM.

4. ILs and *H. pylori* infection SPEM

H. pylori is a spiral, flagellated, microaerophilic, gram-negative bacillus that colonizes the gastric mucosa and is the leading cause of chronic gastritis, peptic ulcers and cancer (75). Although most *H. pylori* live freely in the mucous layer, a small portion can adhere to mucosal epithelial cells (125). Its interaction with the epithelial cells of the gastric body triggers an immune response that leads to the production of several cytokines and the establishment of chronic inflammation (68). In this process, ILs induce the inflammatory process by recruiting neutrophils, lymphocytes, macrophages and DCs (155). As a major carcinogen, *H. pylori* is widely recognized to be associated with mucosal barrier disruption (156). During *H. pylori* infection, the gastric epithelium enlarges the mucous cell compartment at the expense of parietal cells and chief cells, thereby reducing acid secretion (13,31). *H. pylori*-dependent activation of different signaling cascades induces upregulation of pro-inflammatory ILs and induces morphological rearrangement of epithelial cells, leading to chronic gastritis, which progresses from atrophy to antispasmodic polypeptide expression and IM, dysplasia and ultimately to cancer (125). Patients with *H. pylori* infection have a much higher prevalence of SPEM compared with patients without the infection, and 6 months after *H. pylori* eradication therapy, SPEM declines as inflammation improves (157).

Following *H. pylori* infection, chronic inflammation progressively worsens and alters the dynamics of ILs (Fig. 5). *H. pylori* cytotoxins (VacA, CagA, CagL and GGT) and PAMPs (flagella and lipopolysaccharide) in the gastric mucosa activate antigen-presenting cells. These cells in turn activate Th1 and Th17 cells through the production of IL-12 and IL-23, respectively (68). The IL-2 and IFN- γ released by Th1 cells promote B-cell differentiation and the secretion of anti-*H. pylori* IgG, while the IL-32 generated by epithelial cells causes inflammation and chemokines (68). Cytotoxin-associated antigen A (CagA) is commonly acknowledged as the primary virulence determinant of *H. pylori* among the aforementioned virulence factors. It is delivered to the epithelial cytoplasm through the type IV secretion system and regulates multiple signaling pathways to exert its pathogenic effects. IL-6 expression is strongly linked to *H. pylori* infection, and CagA⁺ *H. pylori* stimulates transcriptional activator-3 and signaling transducer by altering the gp130 signaling switch, causing aberrant activation that leads to aberrant proliferation and gastric epithelial cell metaplasia (100). IL-18 and IL-1 β activate Treg cells in CagA⁺ *H. pylori*-infected individuals, modifying the immune response and resulting in a persistent infection. Bacterial density and the virulence factor have a direct relationship with IL-8 expression levels. *In vitro* studies have demonstrated that CagA and/or cytotoxin-associated gene pathogenicity island activate the NF- κ B pathway, leading to increased IL-8 or IL-32 levels and anti-apoptotic responses. The gastric sinusoidal mucosa of patients with CagA⁺ *H. pylori* produces increased levels IL-8 and IL-1 α , which attracts inflammatory cells

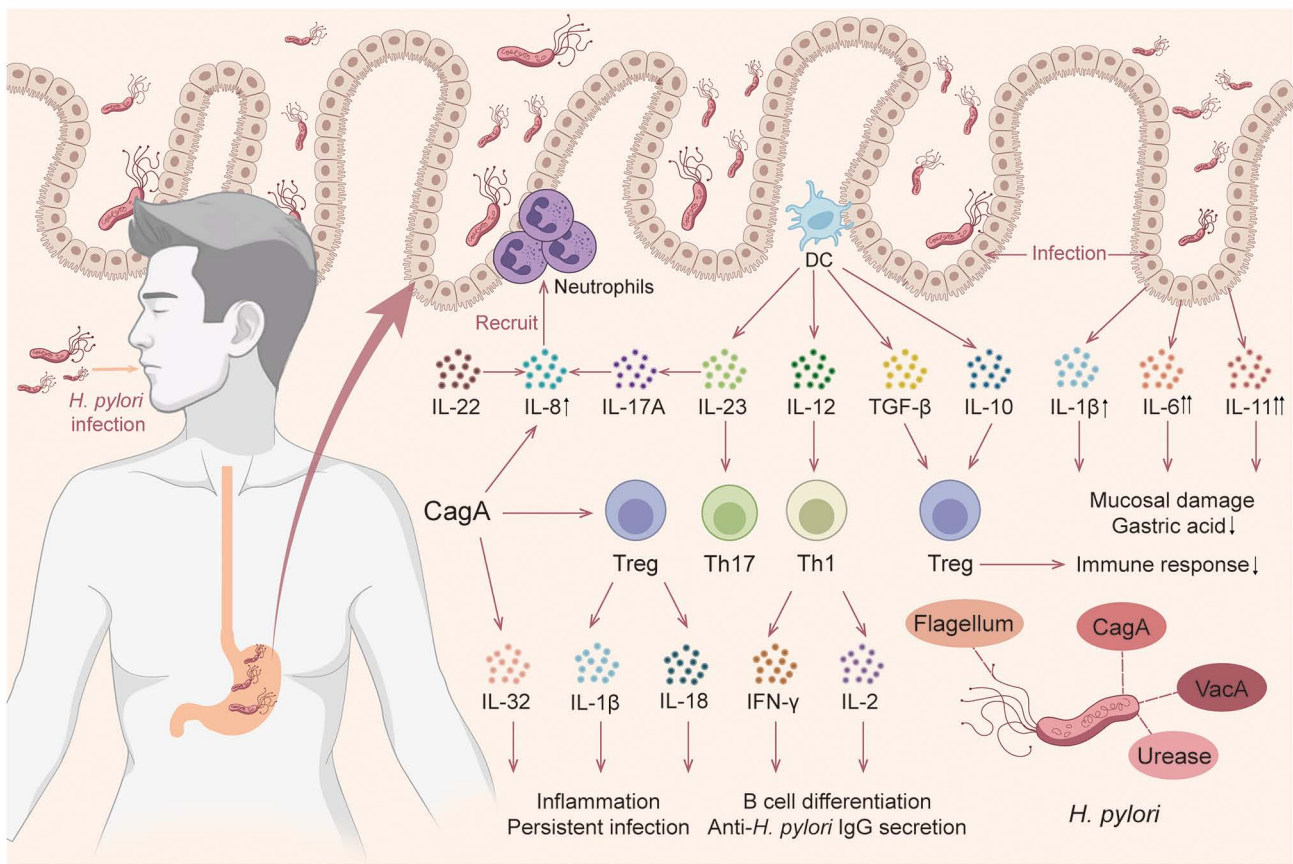


Figure 5. Dynamics of *H. pylori* infection and ILs. After infection, IL-8 expression activates and recruits neutrophils to the gastric mucosa to establish an innate immune response against *H. pylori* infection. Dendritic cell secretion produces IL-12 and IL-23 to activate Th1 and Th17 cells, respectively and Th1 cells release IL-2 and IFN- γ , which stimulate B-cell differentiation and anti-*H. pylori* IgG secretion. Synergistic IL-17A is increased by IL-23, and when combined with IL-22, it causes IL-8 secretion and intensifies the inflammatory response. The virulence factor CagA triggers upregulation of IL-8 or IL-32. Treg cells are activated by IL-18 and IL-1 β to modulate the immune response and lead to persistent infection. Infection leading to massive production of IL-1 β , IL-6 and IL-11 may exacerbate mucosal damage, inhibit gastric acid secretion and promote chronic inflammation. DC-produced IL-10 and TGF- β inhibit host immune response through Treg differentiation. Below right is the structure of *H. pylori*. IL, interleukin; SPEM, spasmolytic polypeptide-expressing metaplasia; Th, T helper cell; Treg, T regulatory cell; CagA, Cytotoxin-associated antigen A; DC, dendritic cell; *Helicobacter pylori*, *H. pylori*; VacA, vacuolating cytotoxin A.

locally and promotes mucosal damage and chronic inflammation (79,143,158). In summary, the intricate relationship between virulence factors and host immune cells ultimately triggers transcription factors and inflammatory pathways, which in turn increases the synthesis of additional cytokines.

Overproduction of IL-1 β during *H. pylori* gastric infection can lead to mucosal damage, chronic inflammation and increased risk of tumorigenesis by inhibiting gastric acid secretion, inducing GC-related gene methylation and promoting angiogenesis (48,159). IL-2 gene polymorphisms are associated with an increased risk of developing GC, and they may also promote gastric mucosal atrophy by increasing inflammatory responses (75). Notably, high IL-2 production may enhance the immune response to *H. pylori* eradication, reducing gastric mucosal inflammation. In the gastric mucosa of patients infected with *H. pylori*, studies have revealed a marked upregulation of IL-6 and IL-11 expression. This is associated with persistent phosphorylation of STAT3 and ERK1/2, which leads to abnormal proliferation of the gastric epithelium and the development of SPEM (100,160,161). IL-8 is considered to be one of the most important cytokines associated with the immune response and inflammatory process against *H. pylori*. Increased expression of IL-8 was detected

in patients with *H. pylori* infection and gastric diseases (27). Infection can cause gastric mucosal epithelial cells to secrete IL-8 by activating EPK and MAPK chemoattracting inflammatory cytokines to the local gastric mucosa and promoting *H. pylori* adhesion to the mucosa, eventually leading to chronic inflammation and continuous circulation (143). *H. pylori*-infected gastric stromal cells control the secretion of IL-23 by DCs and monocytes, which in turn stimulates the expression of IL-17 and Th17 cell differentiation (162). In addition, bacterial infection induces the transformation of naive T cells or tissue-resident T cells in gastric tissue into Th17 cells, which recruit inflammatory cells by secreting IL-17A (163). By triggering the ERK 1/2 MAP kinase pathway, IL-17 can also trigger the release of IL-8, which chemoattracts neutrophil infiltration and intensifies the inflammatory response (125). In addition, IL-17A can also synergize with IL-22 to enhance neutrophil recruitment and further aggravate chronic inflammation after *H. pylori* infection (163). Treg cells secrete TGF- β 1 and IL-10 to inhibit the Th17-mediated inflammatory response, and the imbalance between the two impacts gastric inflammation (114,162). IL-10 is also secreted by gastric mucosal tissue and protects the mucosal barrier by regulating mucosal homeostasis and preventing excessive inflammatory

reactions caused by *H. pylori* (25,112). IL-17A inhibits Th1 differentiation and inhibits *H. pylori*-induced gastric mucosal damage (136). However, it also activates NF- κ B signaling and increases IFN- γ levels in the gastric mucosa, which promotes cancer (163). By activating the NF- κ B pathway, infection raises the expression of pro-inflammatory cytokines (IL-1 β , IL-6, IL-8 and TNF- α), which increases the risk of damaged DNA and tumorigenesis (164). Chronic inflammation and immune responses caused by infection recruit M2 macrophages, which release IL-33, accelerating the progression of SPEM to malignancy (60,156). These mechanisms suggest that *H. pylori* disrupts the IL network via multiple pathways, leading to chronic inflammation, SPEM and malignant transformation.

5. SPEM models in IL research

Animal models and gastric organoids are the two most common types of SPEM models used in IL research. There are three types of animal models: i) Drug-induced models; ii) transgenic mouse models; and iii) *H. pylori* infection models (Table II). Specific drugs cause SPEM by directly inducing parietal cell death, making it an ideal model for studying specific stages of the metaplasia process due to its rapid and precise action. The drugs commonly used to induce SPEM are DMP-777, L635 and tamoxifen. As a leukocyte elastase protease inhibitor, DMP-777 was administered for 10-14 days to induce gastric oxidative atrophy and metaplasia, accompanied by mild inflammation (165). Its analog L635 rapidly induces parietal cell loss in an inflammatory environment, and treatment for 3 days can trigger inflammatory infiltration and proliferative SPEM (advanced SPEM). Alterations in its lineage are strikingly similar to those seen following 6-12 months of *H. pylori* infection (166-168). Tamoxifen, as a chemotherapeutic drug, can rapidly induce SPEM formation through a selective estrogen receptor-independent pathway within 3 days following oral or intraperitoneal injection (169). The drug causes proton leakage by damaging cells rich in proton pumps and mitochondria (such as parietal cells), reducing mitochondrial phosphorylation efficiency and interfering with intracellular pH homeostasis. Its resulting loss of parietal cells can be reversed by the proton pump inhibitor omeprazole, confirming that its action is dependent on active acid secretion (170). Therefore, tamoxifen-induced SPEM is considered a reversible precursor of precancerous lesions (42,165,169,170). In the autoimmune transgenic TxA23 mouse model, CD4⁺ T cells cause chronic gastritis by targeting H⁺/K⁺ ATPase and inducing apoptosis of gastric parietal cells. This mimics a number of aspects of human atrophic gastritis and metaplasia, including chronic inflammation and parietal cell atrophy, mucus neck cell proliferation, SPEM and, eventually, gastric intraepithelial tumors (34). Focal SPEM lesions were observed in 2-month-old mice, while extensive and severe SPEM lesions were observed in 12-month-old mice. SPEM was also highly proliferated in *H. felis*-infected mice. A total of 6 months after *H. pylori* infection, mice showed acid secretion atrophy and TFF2-expressing metaplasia (9). The detection methods for mouse model establishment include histological analysis and marker detection. Histological analysis identified the morphological features (such as focal lesions and glandular structural abnormalities) and inflammation of the metaplastic

glands by H&E staining. When inflammation occurs, different types of metaplastic glands can form in nearby focal lesions, creating a complex glandular assembly made up of a variety of intestinal or gastric cell lineages that co-positively test for different cell lineage markers. Cell lineage markers, such as HE4, TFF2, MUC6, CD44v9 of SPEM and TFF3, MUC2, tail-type homeobox 1/2 or α -defense 5 of IM, were used to identify the lineage. Together with the identification of associated ILs, Ki67, CD44, MUC1, MUC5AC, p53, VEGF and other biomarkers, it can be used to assess the malignant potential of SPEM (74).

Gastric organoids, also referred to as gastroids, are 3-dimensional spheroids made by researchers from glands that have separated from the stomach corpus mucosa. These gastroids allowed the examination of the direct effects of ILs on gastric epithelial cells (144). Gastric glands were isolated from the target mice, and Matrigel was used to cultivate whole gastric glands. They were placed in 24- or 48-well plates, and cultured gastric organoids were treated with recombinant IL (Table SI). Typical images were captured of organoids aged 10 days following a 7-day IL treatment (34,39,138), and microphotographs were used to examine changes in gastroids. Organoid diameter, relative organoid diameter, organoid size, survival rate, Muc6 expression level, AQP5/MUC6 double positive rate, structural departure from normal tissue, height deviation from normal tissue, growth arrest, mortality and structural collapse were among the statistical indicators. This model is a crucial tool for studying the onset and progression of SPEM as it closely resembles the cellular makeup and behavior of the normal organism, making it easier to add ILs from exogenous sources.

6. Therapeutic implications and future prospects

At present, SPEM detection in clinical practice has not yet been popularized, but there is a growing interest in the importance of metaplasia in precancerous lesions. Endoscopy, tissue biopsy and biomarker detection are the most effective diagnostic methods for gastric precancerous lesions (74). To lower the risk of inflammatory cancer transformation and enhance the quality of life of patients, the recommended management strategies include routine gastroscopy monitoring, *H. pylori* eradication, lifestyle modifications and medication interventions. The therapeutic potential of ILs has gained interest from basic and translational cancer researchers. A growing number of ongoing clinical trials have highlighted their value as therapeutic agents and targets (171-175). Among these, IL-13 and its receptor were found to be promising targets for treatment in order to prevent and/or reverse the development of metaplasia in atrophic gastritis (144). IL-13 and IL-4Ra neutralizing antibodies (lebrizumab, dupilumab) have been used in clinical settings, and antagonizing the IL-33/IL-13 signaling pathway has become a prospective treatment paradigm to reduce the progression of metaplasia and tumor transformation (144,176). By controlling the cytokine environment and CD4⁺ T cell infiltration, systemic IL-27 administration prevents gastric injury and aids in the recovery of acid glands (43). Non-small cell lung cancer, myelodysplastic syndrome and chronic myeloid leukemia have been treated with IL-1 neutralization strategies (such as canakinumab and anakinra) and the IL-6 antibody

Table II. Mouse models of SPEM induced by different approaches of IL research.

Model type	IL	Mouse type	Method	Drug	Dosage	Frequency	Time of administration	SPEM	P/I SPEM	IM	Inflammatory response	Invasive glands	Markers	(Refs.)
DMP-777-induced	IL-13	C57BL/6	Intraperitoneal injection	DMP-777	350 mg/kg	Once daily	1, 3, 7 and 14 days	Yes	No	No	No	No	GS II, CD44v9, p120	(160)
	IL-13	C57BL/6 and IL13KO	Oral gavage	DMP-777	350 mg/kg	Once daily	8 days	Yes	No	No	No	No	GS II, CD44v9, GIF	(59)
	IL-33	C57BL/6 and Wfdc2 ^{-/-}	Oral inoculation	DMP-777	350 mg/kg	Once daily	7 or 14 days	Yes	No	No	No	No	GS II, CD44v9, GIF	(159)
	IL-13	C57BL/6	Oral gavage	L-635	350 mg/kg	Once daily	3 days	Yes	Yes	No	Yes	No	GS II, GIF, GIF	(36)
L-635-induced	IL-13	IL-13-td and Tomato	Oral gavage	L-635	350 mg/kg	Once daily	3 days	Yes	Yes	No	Yes	No	GS II, AQP5, CD44v9TFF2	(39)
	IL-13	C57BL/6 and IL13KO	Oral gavage	L-635	350 mg/kg	Once daily	3 days	Yes	Yes	No	Yes	No	GS II, CD44v9, GIF	(59)
	IL-13	C57BL/6	Orally injection	L-635	350 mg/kg	Once daily	2-4 days	Yes	Yes	No	Yes	No	GS II, CD44v9, p120	(160)
	IL-13	C57BL/6	Intraperitoneal injection	L-635	350 mg/kg	Once daily	1, 2, and 3 days	Yes	Yes	No	Yes	No	GS II, CD44v9, p120	(160)
Tamoxifen-induced	IL-33	C57BL/6 and IL33KO and ST2KO	Oral gavage	L-635	350 mg/kg	Once daily	3 days	Yes	Yes	No	Yes	No	GS II, CD44v9, p120	(59)
	IL-33	C57BL/6 and Wfdc2 ^{-/-}	Oral inoculation	L-635	350 mg/kg	Once daily	3 days	Yes	Yes	No	Yes	No	GS II, CD44v9, GIF	(159)
	IL-33	C57BL/6	Oral gavage	L-635	350 mg/kg	Once daily	3 days	Yes	Yes	No	Yes	No	GIF, GS II	(68)
	IL-10	C57BL/6	Intraperitoneal injection	Tamoxifen	3 mg/20 g	Once daily	3 days	Yes	No	No	No	No	GS II, VEGF-β	(25)
IL-13	gp130 ^{+/+}		Intraperitoneal injection	Tamoxifen	50 mg/kg	Two doses	3 days apart	Yes	No	No	Yes	No	GS II, GIF, TFF2	(121)

Table II. Continued.

Model type	IL	Mouse type	Method	Drug	Dosage	Frequency	Time of administration	SPEM	P/I SPEM	IM	Inflammatory response	Invasive glands	Markers	(Refs.)
Transgenic and auto-immune	IL-13	gp130 ^{FF}	Intraperitoneal injection	Tamoxifen	250 mg/kg	Once daily	3 days	Yes	No	No	Yes	No	GS II, GIF, TFF2	(121)
	IL-25	gp130 ^{FF}	Intraperitoneal injection	Tamoxifen	50 mg/kg	Two doses	3 days apart	Yes	No	No	Yes	No	GS II, GIF, TFF2	(121)
	IL-25	gp130 ^{FF}	Intraperitoneal injection	Tamoxifen	250 mg/kg	Once daily	3 days	Yes	No	No	Yes	No	GS II, GIF, TFF2	(121)
	IL-27	TxA23 x Ebi3 ^{-/-}	Intraperitoneal injection	Tamoxifen	5 mg/20 g	Once daily	3 days	Yes	No	No	Yes	No	GS II, VEGF- β , CD44v9	(105)
	IL-33	C57BL/6 and Wfdc2 ^{-/-}	Intraperitoneal injection	Tamoxifen	250 mg/kg	Once daily	3 days	Yes	No	No	Yes	No	GS II, CD44v9, GIF	(159)
Transgenic	IL-13	TxA23	Transgenic	-	-	-	4 months	Yes	Yes	No	Yes	No	GS II, GKN3	(125)
	IL-17A	TxA23	Transgenic	-	-	-	2-12 months	Yes	No	No	Yes	No	VEGF- β , CD44v9	(125)
	IL-27	TxA23	Transgenic	-	-	-	2-12 months	Yes	No	No	Yes	No	GS II, VEGF- β , CD44v9	(105)
	IL-33	SAMP1/YitFc	Transgenic	-	-	-	4 weeks	Yes	No	No	Yes	No	GS II, CD44v9, GIF	(58)
Surgical	IL-33	PC-specific GRIM-19 KO	Transgenic	-	-	-	2-10 weeks	Yes	No	No	Yes	No	GS II, GIF	(28)
	IL-13	C57BL/6J	Adrenalectomy and castration	-	-	-	2 months	Yes	No	No	Yes	No	GS II, CD44v9	(38)

Table II. Continued.

Model type	IL	Mouse type	Method	Drug	Dosage	Frequency	Time of administration	SPEM	P/I SPEM	IM	Inflammatory response	Invasive glands	Markers	(Refs.)
<i>Helico-bacter</i> infection	IL-1 β	C57BL/6 and Gli1 ^{-/-}	<i>Helico-bacter felis</i> (CS1 strain); oral gavage	Bru-cella broth with <i>H. felis</i>	10 ⁸ <i>H. felis</i> cells in 100 ml	once daily	3 days	Yes	No	No	Yes	Yes	GS II	(31)

IL, interleukin; SPEM, spasmolytic polypeptide-expressing metaplasia; P/I SPEM proliferative/intestinalized SPEM; IM, intestinal metaplasia; gp130, glycoprotein 130; GS II, *Griffonia simplicifolia* lectin II; KO, knockout; GIF, gastric intrinsic factor; AQP5, aquaporin 5; TFF2, trefoil factor 2; p120, p120 catenin; GKN3, gastrophilic 3; GRIM-19, gene-related to melanoma-19; PC, parietal cell; IL13KO, IL-13 knockout; Wfdc2^{-/-}, whey acidic protein four-disulfide core domain 2 knockout; IL33KO, IL-33 knockout; ST2KO, suppression of tumorigenicity 2 knockout.

siltuximab (177,178). Furthermore, IL-2 monotherapy has shown early success in treating melanoma, renal cell carcinoma and gastrointestinal tract cancer, and may be useful in reducing the risk of tumor transformation and metaplasia (179). Innovative IL-12 therapies (such as oncolytic viruses, nanoparticles and CAR-T cells) can enhance the therapeutic potential of gastrointestinal cancer through precise delivery (180,181).

Current clinical trials related to GC focus on innovative applications of engineered ILs (Table SII). The safety of Bempegaldesleukin, a polyethylene glycolized non- α IL-2 variant, which extends half-life and reduces toxicity by blocking the IL-2R α subunit binding site via a PEG residue, has been validated (ClinicalTrials.gov Identifier: NCT02983045, <https://clinicaltrials.gov/ct2/show/NCT02983045>). The comparable drug THOR707 (SAR444245) enhances anti-tumor activity through selective activation of intermediate affinity IL-2R (ClinicalTrials.gov Identifier: NCT04009681, <https://clinicaltrials.gov/ct2/show/NCT04009681>). In addition, ALKS 4230, which uses an IL-2/IL-2R α circular replacement structure to optimize receptor targeting, is in phase I/II studies (ClinicalTrials.gov Identifier: NCT03861793, <https://clinicaltrials.gov/ct2/show/NCT03861793>). VG161 is a recombinant human IL-12/15/PD-L1B triple factor tumor lysing HSV-1 injection that induces systemic anti-tumor immunity via local cytokine release (ClinicalTrials.gov Identifier: NCT06008925, <https://clinicaltrials.gov/ct2/show/NCT06008925>). Recombinant human nsIL12 tumor solubilizing adenovirus injection (BioTTT001) in combination with SOX chemotherapy and teraplizumab is being evaluated for synergistic efficacy against peritoneal metastasis of GC (ClinicalTrials.gov Identifier: NCT06283121, <https://clinicaltrials.gov/ct2/show/NCT06283121>). The engineered modification breaks through the limitations of traditional IL therapy and provides a novel direction for GC immunotherapy.

However, IL therapy is challenged by its short half-life and narrow therapeutic window, leading to suboptimal efficacy and unpredictable side effects (21). Common adverse reactions such as influenza-like symptoms (including fever, chills and fatigue) are short but notably affect the quality of life of patients. Severe side effects included capillary leak syndrome, hypotension, fluid retention, hepatotoxicity (liver function damage and elevated enzyme levels), bone marrow suppression (increased risk of anemia, infection and bleeding) and cardiovascular complications (arrhythmia and fluid excess) (45). IL therapy is difficult to develop and is not considered suitable as a standalone treatment for clinical conditions. The pleiotropic nature of ILs contributes to the aforementioned issues by causing dose-limiting toxicity or inadequate efficacy (46,182). Future research must elucidate the mechanism of IL-mediated SPEM in order to develop novel therapies and investigate IL modification strategies, such as targeted delivery mechanisms, PEGylation, fusion construction, affinity regulation and synergy with other immunotumor drugs (177,183-185). The emergence of more effective immunotherapy and improved understanding of the tumor microenvironment provide novel methods for the treatment of cancer using the IL network (74,137). Furthermore, patients with advanced disease are currently included in the majority of trials, which may not be the optimal setting for IL-based therapies. Future research should focus on identifying and treating gastric metaplasia

with a tendency to become cancerous (28,41,186). Specific directions may include: i) Developing more personalized IL modification strategies for patients with early-stage SPEM, ii) designing combination trials of IL therapy in patients with high-risk gastric metaplasia to halt malignant progression, and iii) exploring the efficacy of IL-targeted therapies in well-defined SPEM cohorts with targeted design. Further research to target early precancerous lesions, combined with tumor microenvironment regulation, deepen the understanding of the pathogenesis of SPEM and provide direction for targeted therapy to alleviate the progression of GC is warranted.

7. Conclusion

The present review described the role of various ILs and their expression products in the formation and progression of SPEM. IL effects are complex and multifactorial. It was summarized that certain ILs, such as IL-2, IL-4, IL-6, IL-8, IL-18 and IL-32, have not yet been studied to confirm a direct relationship with SPEM but are closely related to IM and GC development, which require further investigation. M2 macrophages promote SPEM progression in the context of inflammation and parietal cell atrophy, and the establishment of a chronic inflammatory environment through pro-inflammatory IL recruitment is also a potential direction for research. Studies have focused on the role that these ILs may serve in GC-associated with angiogenesis, metastasis and chemotherapy resistance, which are key factors influencing carcinogenesis and tumor progression, quality and patient survival. Although there are still a number of challenges to overcome in the development of IL- or IL-targeted therapies, the development of biologics and small-molecule inhibitors that selectively target pathogenesis could improve therapeutic efficacy and minimize side effects. With the discovery of specific markers, the understanding of SPEM origin and cancer progression will be improved, which may contribute to the simple and accurate diagnosis of early developmental abnormalities. These results provide a research direction for the pathogenesis of SPEM and open up new avenues for future diagnosis and treatment.

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Authors' contributions

Conceptualization, literature investigation, writing the original draft, writing, review and editing, and visualization were performed by TZ, MJ and XZ. WG, SZ and HL made

substantial contributions to writing, reviewing and editing. HL and MJ were responsible for conceptualization (substantial contribution to the design of the work), supervision and project administration. Data authentication is not applicable. All authors read and approved the final manuscript, and agree to be accountable for all aspects of the work.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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