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Review article

Could the inhibition of IL-17 or IL-18 be a potential therapeutic opportunity for gastric cancer?

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ABSTRACT

Chronic inflammation is recognized as a key tumor-promoting factor in a number of epithelial cancers, including gastric cancer (GC). The production of pro-inflammatory cytokines in the tumor microenvironment by both the innate and the adaptive immune response can activate signaling pathways that are associated with increased cell survival and proliferation of cancer cells. Among the cytokines that have most commonly been linked to inflammation-associated cancers, are the Th17 cell-associated cytokines IL-17A, IL-23, IL-22, and the IL-1 family members IL-1β and IL-18. However, whether their contribution to inflammation-associated cancers is universal, or specific to individual types of cancers, remains to be elucidated. This review will explore our current understanding of the known roles of these cytokines in gastritis and discuss how their therapeutic inhibition may be useful for GC.

1. Introduction

The "Hallmarks of Cancer" describe a number of important characteristics that are required for the progression of normal cells to malignancy, including tumor-promoting inflammation [1]. Infiltrating inflammatory cells in the tumor microenvironment produce various growth factors and cytokines that sustain the proliferation of cancer cells, allowing them to resist cell death, and promote invasion and metastasis. Among these immune cell populations are T helper (Th) 17 cells, which produce interleukin (IL)-17A and IL-22. Other immune and non-immune cell types can produce IL-1β and IL-18. While the role of these cytokines has been extensively explored in inflammatory diseases, our understanding of their function in other gastrointestinal (GI) cancers, including gastric cancer (GC), remains to be fully defined. Here we review our understanding of the contribution of these cytokines to GC, and discuss the potential therapeutic utility of their inhibition.

1.1. Gastric cancer epidemiology

Cancer represents a significant cause of morbidity and mortality, accounting for approximately 8.8 million deaths each year worldwide [2]. GC is the fifth most common cause of cancer in the world, accounting for approximately one million new cases each year, and is the third most common cause of cancer related mortality [3]. GC is particularly prevalent in developing regions, including Asia (Eastern, and South-Central), South America, and Eastern Europe; with over half of new cases diagnosed in Eastern Asia and China [3].

1.2. Architecture of the stomach

Macroscopically, the stomach can be divided into three main regions: the fundus, body, and antrum (also known as antral-pyloric region). Histologically, the stomach is organized into glandular structures containing gastric glands with additional specialized cells depending on the location; for example, the fundus and body of the stomach are comprised of oxyntic glands containing parietal cells, which produce gastric acid (HCl), along with chief cells, which produce pepsin to break down proteins. The antral-pyloric region contains G cells, which produce gastrin to stimulate HCl production, and mucous neck cells that produce a layer of mucus to prevent invasion by microbes and damage to the gastric epithelium by gastric acid [4]. Tumors can arise in the body or antral-pyloric region of the stomach.

1.3. Histological classification of gastric cancer

Traditionally, GCs were classified as adenocarcinomas, lymphomas associated with the mucosa-associated lymphoid tissue (MALToma), gastrointestinal stromal tumors (GIST), or carcinoid tumors [5].

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Squamous cell carcinomas and adenosquamous carcinomas can also occur, although they are less common [5]. However, approximately 90% of GCs arise as adenocarcinomas, which are tumors arising from the glandular epithelium of the stomach and are classified as either intestinal-type GC (IGC) or diffuse-type GC (DGC), accounting for approximately 54% and 32% of GC cases, respectively [6].

DGCs are characterized as undifferentiated and lack well-defined glandular structures. Instead, they infiltrate the gastric mucosa as single cells or loosely associated cell clusters that may contain mucus [5,7]. It has been suggested that hereditary DGC, which accounts for 1–3% of GC cases, is associated with a mutation to *CDH1*, which encodes for the protein E-cadherin [8,9]. In contrast, IGC tumors are usually well differentiated, maintaining the glandular appearance of the stomach, although at the invasive front poorly differentiated cells may be present [5]. The progression of IGC involves the development of chronic gastritis accompanied by atrophy known as atrophic gastritis, intestinal metaplasia, dysplasia, and carcinoma [10]. While atrophic gastritis and intestinal metaplasia have classically been considered the precursor lesions for IGC development, the recent identification of metaplastic changes in patients involving the expression of spasmolytic polypeptide, also known as trefoil factor 2, and the presence of deep antral gland cells in spasmolytic polypeptide expressing metaplasia (SPEM) suggest that this may be a pre-neoplastic event [11]. Persistence of these pre-neoplastic lesions can lead to gastric dysplasia, characterized by changes in the size, shape, and orientation of epithelial cells, which results in abnormalities to the glandular arrangement, as well as nuclear atypia [12].

1.4. Gastric cancer risk factors

Differences in the incidence rates of GC are related to environment, bacterial and viral infections, and genetic alterations. Environmental factors that have been attributed to GC development include smoking [13] and diets that are high in salt, or foods that have been picked or smoked, which may explain the variance in geographical GC incidence, as consumption of these types of foods is highest in Eastern Asia and South America [3,14,15].

GC risk is most strongly linked to infection with the Gram-negative bacterium *Helicobacter pylori* (*H. pylori*) [16]. *H. pylori* is present in approximately half of the population, although the majority of infected people remain asymptomatic; however, approximately 1–3% of infected individuals will develop GC, with 60% of all GC cases associated with *H. pylori* colonization [7,16,17]. Chronic infection with *H. pylori* results in extensive wounding of the gastric epithelium and associated infiltration of inflammatory cells [18]. Accompanying these changes is atrophic gastritis, whereby atrophy of specialized glandular cells occurs, for example, to the gastric acid secreting parietal cells, which contributes to an altered gastric pH and changes in the composition of microflora that are able to colonize the stomach [19]. While atrophic gastritis is commonly observed in IGC patients, DGC patients also commonly have features of gastritis, but often lack gastric atrophy [7]. Intestinal metaplasia following atrophic gastritis leads to the replacement of gastric glands with tubular crypts comprising cells with a phenotypic appearance of the absorptive intestinal cells and mucus-producing goblet cells of the intestinal mucosa [5,7]. Molecular changes associated with IGC include a reduction in gastric-associated mucins such as MUC1 and MUC6, and an increase of intestinal mucins including MUC2 [5]. These changes can be facilitated, in part, by *H. pylori* through the expression of cytotoxin-associated gene A (CagA), which can influence cellular differentiation through upregulation of the β-catenin dependent gene *Cdx1*, which promotes the transdifferentiation of gastric cells to intestinal cells and expression of MUC2 [20,21].

1.5. Current treatment options for GC

While the 5-year survival rate for GC is 70% when disease is detected in its early stages, the overall 5-year survival rate considering all stages is only 27% for both Australia and in the United States [22,23]. The poor survival rate of GC patients is often due to delayed diagnosis as the disease is commonly asymptomatic. While early screening programs to detect GC are used in some high-risk countries such as Japan, countries including Australia and the USA have no routine screening methods. In Japan, screening methods include photofluorography, endoscopy, evaluation of serum pepsinogen levels, and *H. pylori* antibody analysis [24]. When early-stage disease is detected, gastrectomy with curative intent can involve resection of at least two-thirds of the stomach and surrounding lymph nodes [25]. Palliative surgery is also performed in urgent cases involving bleeding or gastric obstruction to relieve symptoms of the disease [25].

In Japan, first-line chemotherapy includes S1, an oral form of fluorouracil (5-FU), and cisplatin, while in some cases either S1 or fluorouracil alone may be used [25]. In Australia, on the other hand, gastrectomy is coupled with epirubicin, cisplatin, and 5-FU, or chemoradiotherapy using 5-FU, leucovorin, and radiotherapy [26,27]. In the United States, a two-drug cytotoxic regimen is employed due to lower toxicity and involves a combination of 5-FU/capecitabine with either cisplatin or oxaliplatin, with the addition of trastuzumab in the case of HER2-neu overexpressing metastatic adenocarcinomas [28]. However, as current treatment options for GC are not curative, and recurrence of disease is common, there is an urgent need to better understand GC development to design more effective therapies [27]. A number of genetic polymorphisms are associated with increased risk of GC development include genes involved in cytokine signaling such as *IL1B*, *IL1RN*, *IL17A*, and *STAT3* [29–31]. Here, we discuss the potential of these cytokines as therapeutic targets.

2. IL-17 and IL-23 are Th17 cell-associated cytokines

The IL-17 family consists of six members, designated IL-17A to IL-17F [32]. IL-17A, along with IL-17F, is found on chromosome 6p12 in humans (1A4 in mice), and encodes for a 155-amino acid protein, which is secreted as a homodimer or a heterodimer with IL-17F [33]. Although members of this family share little sequence identity, the highest homology occurs between IL-17A and IL-17F (48%), while all have been shown to adopt a similar structure, including conserved cysteine residues forming disulfide bonds [34,35]. The receptors for this family include five receptor chains, IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE [36]. All members are single transmembrane domain proteins, with several conserved structural motifs: an extracellular fibronectin III-like domain, and a cytoplasmic “similar expression to fibroblast growth factor” (SEFIR), IL-17R, and TIR family domain [36].

In contrast, IL-23 belongs to the IL-12 family of cytokines, which consists of the three additional members IL-12, IL-27, and IL-35 [37]. IL-23 is secreted as a heterodimeric protein consisting of an α-chain IL23p19, and a β-chain IL-12p40, which is also shared by IL-12 [38]. The p19 α-subunit for IL-23 was found to encode a 189-amino acid protein, 196 amino acids in length in mice, corresponding to mature proteins with molecular weights of 18.7 kDa and 19.7 kDa, respectively [38]. The α-chain for these cytokines consists of a four-helix bundle structure, while the β-chain subunits share homology with class I receptor chains for cytokines, such as IL-6Rα [37]. The receptors utilized by the IL-12 cytokine family include GP130, IL-12Rβ1, IL-12Rβ2, IL-23R, and WSX-1 [37]. While both IL-12 and IL-23 utilize IL-12Rβ1, the secondary receptor for these cytokines is IL-12Rβ2 and IL-23R, respectively. IL-27 and IL-35 similarly share use of GP130, while their secondary receptors consist of WSX-1 and IL-12Rβ2, respectively.

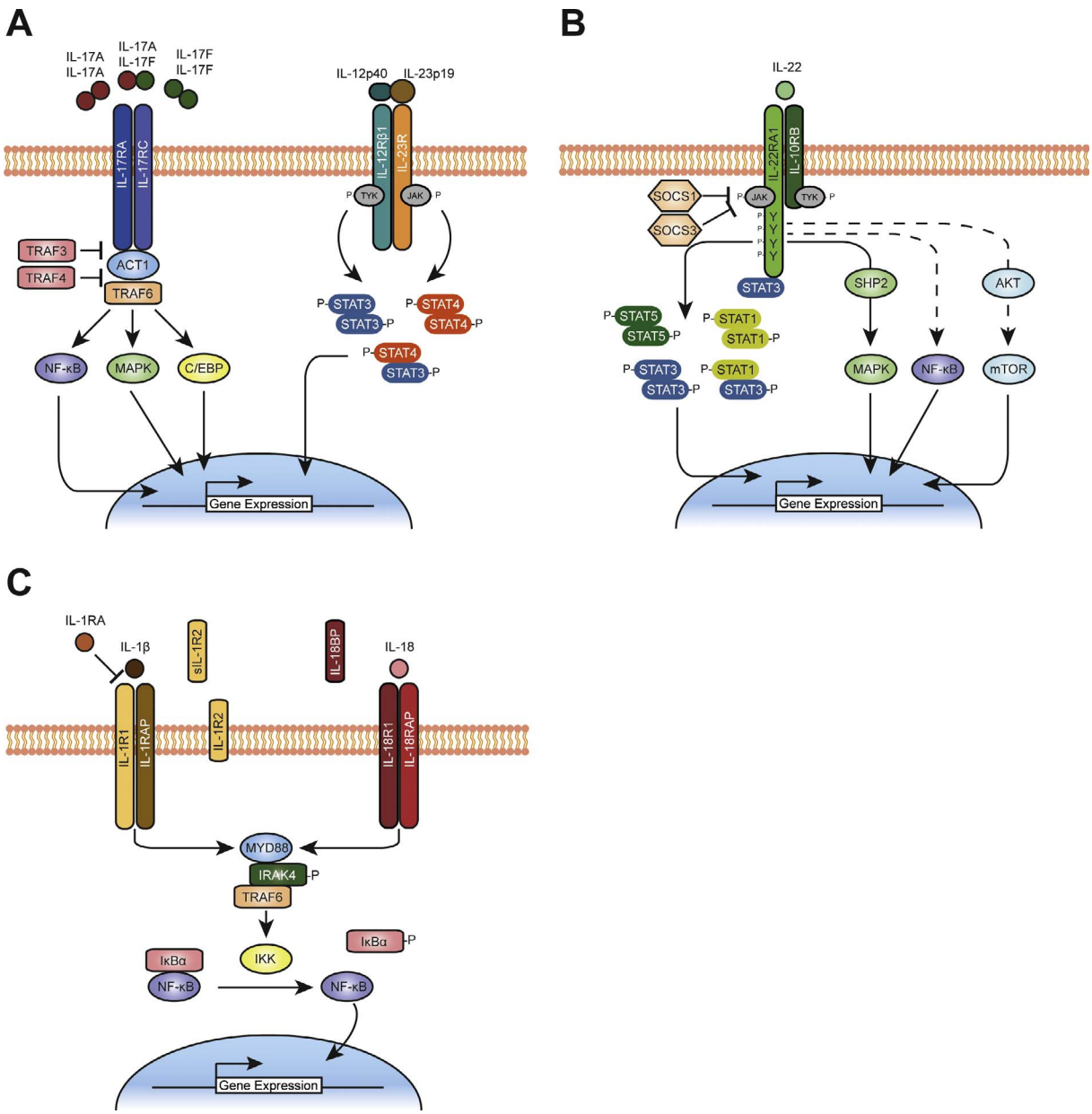

Fig. 1. Signaling pathways of Th17-cell associated cytokines, and IL-1 and IL-18. (A) IL-17A signals through a heterodimeric complex consisting of a homodimer or heterodimer of IL-17A/IL-17F to mediate NF-κB, MAPK, and C/EBP signaling. IL-23 consisting of a dimer of IL-12p40 and IL-23p19 activates the JAK/STAT pathway and the transcription factors STAT3 and STAT4. (B) IL-22 signaling through the receptors IL-22RA1 and IL-10RB predominantly activates the JAK/STAT pathway, with activation of STAT3, and to a lesser extent STAT1 and STAT5. Signaling by IL-22 has also been reported to activate the MAPK, NF-κB, and PI3K/AKT/mTORC1 pathways. (C) IL-1β and IL-18 mediated signaling is initiated by the binding of IL-1β and IL-18 to their respective α-receptors IL-1R1 and IL-18R1, followed by association with IL-1RAP and IL-18RAP. Recruitment of MYD88, IRAK4, and TRAF6 leads to activation of NF-κB. IL-1RA negatively regulates IL-1 signaling by competing for binding to IL-1R1, while IL-1R2 and IL-18BP act as decoy receptors for their respective cytokines.

Additionally, IL-35 has been demonstrated to signal through two separate homodimeric complexes consisting of GP130-GP130 and IL-12Rβ1-IL-12Rβ1.

2.1. Cellular sources of IL-17A and IL-23

IL-17A is predominantly expressed by adaptive immune cell populations including Th-17 cells, cytotoxic T cells, and γδ T cells [39]. Recently, the discovery of innate lymphoid cells (ILCs) has shown that IL-17A can also be produced by innate immune cells, namely lymphoid tissue inducer (LTi)-like cells and natural cytotoxicity receptor (NCR) negative cells of the ILC3 subset [39,40]. Additionally, non-immune cells such as Paneth cells are able to secrete IL-17A [41]. Production of IL-23 by innate immune cells such as dendritic cells (DCs) and macrophages predominantly occurs in response to infection to elicit an inflammatory immune response [37,42,43]. In cases of autoimmune diseases, such as multiple sclerosis, psoriasis, or inflammatory bowel disease, the production of IL-23 by these cells can promote disease through the activation of Th17 cells.

2.2. Signaling by IL-17A activates the NF-κB, AP1, and C/EBP pathways

Signal transduction by IL-17A homodimers and heterodimers occurs through a heterodimeric receptor complex consisting of one IL-17RA and one IL-17RC chain (Fig. 1A) [33,44,45]. IL-17RA is ubiquitously expressed, with the highest expression in hematopoietic tissues

including the spleen and thymus, while IL-17RC expression has been observed in the colon, small intestine, lung, liver, and kidney [36,46]. Following formation of the IL-17A receptor complex, TNF receptor-associated factor (TRAF)-3 interacting protein 2 (TRAF3IP2) is recruited through the interaction between its SEFIR domain with the reciprocal SEFIR domain in IL-17RA and IL-17RC [47,48]. Serving as an adaptor protein, TRAF3IP2 (also known as ACT1) is then able to mediate the recruitment of TRAF6 and transforming growth factor β-activated kinase 1 (TAK1), leading to the activation of the NF-κB, MAPK-activator protein-1 (AP1), and CCAAT/enhancer-binding protein (C/EBP) pathways [48,49]. Additionally, TRAF3 is also able to be recruited following receptor complex formation, and serves as a negative regulator of IL-17R signaling, suppressing NF-κB and MAPK activation by competing with ACT1 for binding to the SEFIR domain of IL-17RA [50]. Similarly, TRAF4 acts as a negative regulator by competing with TRAF6 for binding with ACT1 [51]. While IL-17A signaling does not directly activate the JAK/STAT pathway, it is able to activate STAT3 indirectly through AKT signaling, which leads to the production of IL-6 and activation of the JAK/STAT pathway [52] (see Fig. 1).

2.3. Signaling by IL-23 activates the JAK/STAT pathway

IL-23-mediated signal transduction occurs following the formation of a heterodimeric receptor complex consisting of IL-23R and IL-12Rβ1 (Fig. 1A) [53]. Analysis of IL-23R-GFP reporter mice revealed that γδ T cells primarily expressed IL-23R, with lower expression in $CD4^+$ T cells (likely Th17 cells), macrophages, and dendritic cells [54]. Additionally, ILC3s express IL-23R [55]. IL-12Rβ1, on the other hand, is highly expressed by natural killer (NK) cells, and moderately expressed in T cells (CD4+, CD8+, γδ) and B cells [56]. Signaling of the IL-23 receptor complex leads to activation of the JAK/STAT pathway through the tyrosine kinases JAK2, which is constitutively associated with IL-23R, and TYK2, which is associated with IL-12Rβ1, resulting in phosphorylation of tyrosine residues present in IL-23R and IL-12Rβ1, which act as STAT binding sites (YxxQ), leading to the activation of STAT3 and STAT4 [37,53]. Interestingly, IL-23 mediated signaling is able to induce expression of IL-23R through STAT3 with RORγT to further enhance its own signaling cascade [37].

3. IL-22 is a member of the IL-10 family of cytokines

The IL-10 family of cytokines consists of nine members: IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28A, IL-28B, and IL-29 [57]. In addition, the three most recently discovered cytokines in this family IL-28A, IL-28B, and IL-29 belong to the type III interferon group (IFNλ), which interact with type I IFNs in disease [57]. The mature secreted protein is 146 amino acids in length, and has a molecular weight of approximately 17 kDa [58,59]. Although these cytokines share a common six α-helical fold structure [57], considerable differences are present in their amino acid sequences, with IL-22 for example, sharing only 22% homology with IL-10 [58]. The majority of these cytokines are secreted as monomers, with the exception of IL-10, which is secreted as a dimer, and IL-26, which has both monomeric and dimeric forms [60,61]. The receptors for IL-22 were identified as a heterodimeric complex consisting of IL-10RB and IL-22RA1, previously known as CRF2-4 and CRF2-9, respectively [59,62]. Additionally, IL-22 has a soluble receptor known as IL-22 binding protein (IL-22BP, encoded by *IL22RA2*), which shares 34% sequence homology to the extracellular region of IL-22RA1 [63,64].

3.1. Cellular sources of IL-22

The IL-10 family of cytokines are mainly produced by leukocytes and myeloid cells, while IL-19, IL-20, IL-24, IL-28, and IL-29 can also be produced by epithelial cells [57]. The receptors for these cytokines are mainly found on epithelial cells [57]. IL-22 is only produced by immune cells, specifically lymphocytes including those of the adaptive immune system such as $CD4^+$ T cells (Th1, Th17, Th22) and γδ T cells, and the innate immune system including ILCs and NK cells [65–71]. Although initially described as a Th1-associated cytokine, the discovery of Th17 cells has shown that this cell type along with Th22 cells, are likely the major source of IL-22 in humans and mice. At mucosal sites such as the GI tract, ILCs are a major source of IL-22, while γδ T cells have been suggested to contribute to IL-22 production at epithelial sites including the skin, lung, and intestinal tract [72]. Production of IL-22 by Th17 cells is dependent on IL-23 expression, as well as the transcription factor aryl hydrocarbon receptor (AHR). This is in contrast to IL-17A, where optimal production is dependent in part on TGFβ expression, which inhibits IL-22 expression [73]. Similarly, IL-21 has been shown to induce robust IL-22 expression in $CD4^+$ T cells, which is dependent on the transcription factors STAT3, AHR, and RORγT, while in Th22 cells, IL-22 expression was promoted by IL-6 and TNFα [74]. γδ T cells have also been shown to secrete IL-22 when stimulated with IL-23 in combination with IL-1β or IL-18, which was further enhanced with the addition of the vitamin A metabolite retinoic acid [75]. Group 3 ILCs, which have been identified as the main IL-22 producing ILC subset, are dependent on the transcription factors RORγT and AHR for their development and function, with IL-23 and IL-1β promoting its expression [72,76]. Similar to the other lymphocytes described, NK cells are capable of secreting IL-22 in response to IL-23 stimulation, as well as the combination of IL-12 and IL-18, which also serve to activate these cells [72].

Several cytokines and transcription factors have been associated with the regulation of IL-22 production and signaling. For instance, TGFβ, inducible T-cell co-stimulator (ICOS), and IL-27 dependent induction of the transcription factor c-MAF has been shown to inhibit production of IL-22 in Th17 cells by directly binding to the *Il22* promoter region to repress its expression [73,77,78]. IL-27 may also induce expression of SOCS1 to inhibit the expression of IL-22 in naïve and memory $CD4^+$ T cells from peripheral blood mononuclear cells (PMBCs) [79]. IL-22-mediated signaling has been shown to be potently inhibited by the soluble receptor IL-22BP, with IL-22 displaying considerably higher binding affinity for IL-22BP than IL-22RA1 (K_d: 1 pM compared to 20 nM) [80].

3.2. Signaling by IL-22 activates the JAK/STAT pathway

While IL-10RB is widely expressed in most tissues and cell types, the expression of IL-22RA1 is restricted to non-hematopoietic cells including epithelial cells and fibroblasts in a number of tissues, with highest expression observed in the GI tract, liver, lung, pancreas, and skin [81]. Similarly, IL-22BP expression has been demonstrated in the GI tract, lung, skin, spleen, mammary gland, mesenteric lymph node, and thymus [64,82,83]. In these tissues, DCs were shown to be responsible for IL-22BP expression, which could be induced by RA, but downregulated upon DC maturation [83,84]. Collectively, these results demonstrate the immune cell specificity of IL-22 production, and non-immune cell specificity of IL-22 signaling predominantly to epithelial cells.

IL-22-mediated signal transduction occurs through the formation of a heterodimeric receptor complex consisting of IL-22RA1 and IL-10RB [59]. Surface plasmon resonance (SPR) analysis of binding kinetics

demonstrated that IL-22 displayed higher binding affinity for IL-22RA1 (K_d: 20 nM) than IL-10RB (K_d: 120 μM), suggesting that IL-22 signaling is initiated by binding of ligand to IL-22RA1, followed by a rotational and/or conformational change, allowing for formation of the heterodimeric receptor complex with IL-10RB [80]. Following formation of the IL-22 receptor complex, the tyrosine-associated kinases JAK1 and TYK2 then phosphorylate eight tyrosine residues present in the cytoplasmic region of IL-22RA1, of which four can serve as potential STAT binding sites (YxxQ) when phosphorylated [85]. Interestingly, while mutation of the tyrosine residues in IL-22RA1 abolishes the phosphorylation of STAT1 and STAT5, STAT3 phosphorylation can occur independently of the interaction of its SRC homology (SH)-2 domain with the cytoplasmic domain of the receptor through interaction of its coiled-coil domain with the C-terminal region of IL-22RA1 [85]. While IL-22 has been predominantly studied in the context of JAK/STAT signaling, and in particular STAT3 activation, in specific cell types such as epidermal keratinocytes, IL-22 may also activate the MAPK pathway through MAPK1, c-Jun N-terminal kinase (JNK), and p38, the PI3K/AKT/mTORC1 pathway, and NF-κB pathway (Fig. 1B) [86–88].

4. IL-1β and IL-18 are members of the IL-1 family of cytokines

The IL-1 family consists of 11 members: seven cytokines with pro-inflammatory activity (IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β, and IL-36γ), one anti-inflammatory cytokine (IL-37), and three receptor antagonists (IL-1RA, IL-36Rα, and IL-38) [89]. IL-1 comprises two distinct proteins, IL-1α and IL-1β which share approximately 24% amino acid sequence homology [90,91]. IL-1α is 269 amino acids in length, while IL-1β is 271 amino acids in length, with the molecular weights of the secreted peptides being 18 kDa and 17.4 kDa, respectively [92]. IL-18 was initially described as "IFN-γ-inducing factor", due to its ability to induce expression of this cytokine in mice following injection with bacterial lipopolysaccharide (LPS) [93]. The gene for IL-18 encodes a 193-amino acid protein, while the mature secreted protein has a molecular weight of approximately 17.2 kDa [94]. Additionally, IL-1RA serves as a naturally occurring receptor antagonist, binding to IL-1R1 to prevent IL-1-mediated signaling [95]. It is encoded by the *IL1RN* gene, and shares 19% and 26% amino acid homology with IL-1α and IL-1β, respectively [95].

Both IL-1β and IL-18 proteins are produced as inactive precursors that require enzymatic cleavage before becoming biologically active and secreted from the cell [96,97]. Caspase-1, which is biologically activated following inflammasome signaling is responsible for cleavage of the pro-form of IL-1β and IL-18 [96,97]. However, other reports have also shown that these two cytokines may be activated by other proteases under certain conditions, such as by proteinase-3 when processed extracellularly, or by caspase-8 following the formation of the "ripoptosome" consisting of receptor-interacting serine/threonine-protein kinase 1 (RIPK1), RIPK3, and Fas-associated protein with death domain (FADD) [98–100].

The receptors associated with IL-1β are IL-1R1 and IL-1RAP, while the IL-18 receptor complex is composed of IL-18R1 and IL-18RAP [101–106]. An important characteristic of these receptors is their expression of an intracellular TIR domain, which mediates signaling through the adaptor protein MYD88 [89]. Both IL-1β and IL-18 also have decoy receptors, IL-1R2 and IL-18BP, which act to inhibit cytokine signaling. IL-1R2 has a similar structure to the extracellular region of IL-1R1, containing a short cytoplasmic region that is only 29 amino acids long [107]. Additionally, IL-1R2 can be produced as a soluble protein through proteolytic processing by secretases or a disintegrin and metalloproteinase (ADAM)-17 [108,109]. IL-18BP shows high affinity for IL-18 (K_d: 399 pM), and contains a single immunoglobulin (Ig) domain that is homologous to the third Ig domain of IL-1R2 [110,111].

4.1. Cellular sources of IL-1β and IL-18

IL-1β and IL-18 are expressed mainly by hematopoietic cells including monocytes, macrophages, dendritic cells, and neutrophils, as well as non-immune cells such as epithelial cells [112–115]. IL-1R1 is widely expressed on a number of different cell types including monocytes, DCs, T cells, and epithelial cells [89,116]. While IL-18R1 is widely expressed, IL-18RAP expression has been observed in immune cells including T cells, NK cells, macrophages, and dendritic cells, as well as non-immune cells such as endothelial and smooth muscle cells [94,103,117].

4.2. Signaling by IL-1β and IL-18 activates the NF-κB pathway

Formation of the IL-1β and IL-18 receptor complexes first involves the binding of ligand to the alpha chain IL-1R1 and IL-18R1, respectively. As this binding is a low-affinity interaction, the expression of the co-receptor, IL-1RAP or IL-18AP, is important for the formation of the signaling complex (Fig. 1C) [101,104]. The formation of these heterodimeric receptor complexes results in recruitment of the adaptor protein MYD88, as well as IL-1 receptor-activated protein kinase (IRAK)-4 [118]. IRAK4 is then able to be autophosphorylated, allowing for subsequent recruitment of IRAK1, IRAK2, and TRAF6 [119]. Recruitment of TRAF6 leads to the subsequent activation of the NF-κB pathway through formation of the inhibitor of NF-κB kinase (IKK) complex and the phosphorylation and degradation of IκBα, allowing for NF-κB to translocate to the nucleus to mediate gene transcription [120,121].

5. Contribution of Th17 cell-associated cytokines and IL-1 family cytokines to gastritis

The role of Th17 cells, and specifically IL-17 and IL-23, have been investigated in a number of chronic inflammatory GI pathologies, including gastritis. In human gastritis patients that were *H. pylori* positive, IL-17 expression was increased in the mononuclear cells in the stomach compared to uninfected patients, which upon *H. pylori* eradication, was reduced in the gastric mucosa [122]. In mouse models of gastritis and *H. pylori* infection, *Il17a*$^{-/-}$ mice displayed lower levels of *H. pylori* colonization compared to WT mice up to 6-months post-infection [123]. This was associated with a reduction in the number of infiltrating neutrophils to the stomach, suggesting that IL-17A may play a pathogenic role during *H. pylori* induced gastritis [123]. Concordant with these findings, *H. pylori* infection induced expression of IL-17A and IFNγ in mouse gastric tissue, while IL-23 and IL-12 expression was induced in macrophages in the presence of the bacteria [124]. Conversely, treatment of mice with recombinant IL-17A prior to *H. pylori* infection resulted in increased bacterial colonization in the stomach compared to control mice, while inhibition of IL-17A signaling by using a neutralizing IL-17A antibody reduced *H. pylori* colonization and inflammation one-month post-infection [124].

Activation of IL-22 signaling induces expression of genes involved in tissue defense and regeneration, and therefore, has been extensively studied in the context of inflammatory disease and infection; the tissue in which IL-22 signaling occurs, as well as the immune cells present, largely determine whether a protective or pathogenic response takes place. For instance, IL-22 has been suggested to have a pro-inflammatory role in *H. pylori*-associated gastritis. It was found that IL-22-producing Th22 cell numbers were higher in *H. pylori* positive patients compared to uninfected patients, and correlated with disease severity [125]. Additionally, IL-22 was shown to induce the expression of CXCL2 and recruit myeloid-derived suppressor cells (MSDCs) to suppress Th1 cell responses, which usually act to protect against *H pylori* infection [125,126]. Recently, IL-22 receptor expression has been

reported on leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5)-positive intestinal stem cells, prompting investigation into the potential effects of IL-22 signaling on these cells [127]. It was found that following bone-marrow transplantation, *Il22*$^{-/-}$ recipient mice had increased graft-versus-host disease (GVHD) mortality than WT controls [127]. This was shown to be dependent on IL-22, which was produced by ILCs and targeted intestinal stem cells to protect them from damage, through expression of genes such as *Reg3b*, and *Reg3g* [127]. Additionally, IL-22 has been shown to be important for the regeneration of LGR5^{+} intestinal stem cells that have been cultured as organoids, through STAT3 signaling [128]. It is of note, that LGR5+ stem cells are also present in the antrum of the stomach [129].

Polymorphisms in *IL1B* are associated with an increased risk of developing hypochlorhydria, which is low HCl secretion in the stomach, predisposing them to *H. pylori* infection [30]. On the other hand, it has been shown that the expression of IL-18 is elevated in *H. pylori* infected patients [130]. In mouse models, IL-1β overexpression in transgenic mice has been shown to induce spontaneous gastritis, which was exacerbated with infection of *H. felis* [131]. Associated with these changes was the ability for IL-1β to recruit MSDCs the stomach to promote inflammation through NF-κB mediated signaling [131]. Consistent with these findings, *Il1r1*$^{-/-}$ mice were protected from *Helicobacter*-associated gastritis, while interestingly, *Il18*$^{-/-}$ mice showed exacerbated disease, characterized by a Th17 response, highlighting the divergent roles of these cytokines [132].

6. Association of Th17 cell-associated cytokines and IL-1 family cytokines with GC

Th17 cells have been detected at elevated levels in the peripheral blood of GC patients compared to healthy controls, with late stage patients having elevated CD4^{+}IL17^{+} cells compared to early stage patients suggesting a correlation with disease stage [133]. However, in a Japanese GC patient cohort, elevated Th17 cells were not detected in the peripheral blood, but shown to be elevated in GC tissue compared to normal gastric tissue [134]. While not mutually supportive, these studies do highlight that Th17 cells are detected in GC patients; however, the role of Th17 cells in the gastric mucosa has not been addressed. Previous studies suggest that Th17 cells may have a beneficial role in pathogen clearance in the colon, while other studies suggest that they may have a pathogenic role leading to tissue destruction [135,136].

Polymorphisms in the promoter region of the *IL17A* gene (rs2275913) have been associated with increased risk of GC development in Japanese and Chinese patients [137,138]. Additionally, IL-17A expression is elevated in the sera of GC patients compared to healthy controls, although this may not occur in all patients, as reduced expression has also been reported [133,134,139]. Similarly, polymorphisms in two regions of the receptor for IL-23A, IL-23R, have been linked to decreased risk of GC. One in exon 2 encoding the signal peptide, and the other one in the 3′-untranslated region (UTR), suggested to result in decreased receptor expression and reduced induction of the IL-23/IL-17 mediated inflammation [140,141]. While no polymorphisms have been reported for *IL23A* in relation to GC risk, a polymorphism in *IL12B*, which serves as a subunit of IL-23, has been described to increase the risk of GC development [142]. Similar to IL-17A, the expression of IL-23 is also elevated in the sera and PBMCs of GC patients compared to healthy controls, as well as correlating with tumor stage [133,143]. The rs1179251 polymorphism in the intron of the *IL22* gene was found to significantly increase the risk of GC development [144,145]. However, interestingly this polymorphism was also found to confer protection against precancerous changes such as atrophic gastritis and intestinal metaplasia suggesting differing roles for this cytokine during the progression of lesions to adenocarcinomas [145]. Elevated expression of IL-22 in Th22 cells is also observed in GC patients, with higher expression observed in tumor compared to peri-tumor or adjacent non-tumor tissue, which also correlated with disease stage [146]. Similarly, IL-22 expression was also detected in the gastric tumor tissue in stromal cells at the invasive front of the tumor, but not in normal gastric mucosa [147]. Taken together, these results suggest that IL-17A, IL-23, and IL-22 may be associated with the pathogenesis of GC (Fig. 2). Studies investigating Th17 cell-associated cytokines *in vivo* have been limited so far; however, the few studies investigating IL-17 suggest a protumorigenic role for this cytokine. Upregulation of IL-17 in GC stem cells transplanted into mice demonstrated increased tumor burden and metastasis, which was mediated through STAT3 activation [148].

H. pylori-infected patients with polymorphisms in the *IL1B* gene have increased production of IL-1β protein, which was associated with increased gastritis and gastric atrophy, suggesting an important role for IL-1β in IGC [149]. Similarly, *H. pylori* has been shown to induce IL-18 protein production from epithelial cells and monocytes in gastritis patients, and elevated levels of this cytokine correlating with gastric inflammation [150]. Polymorphisms in the promoter region of the *IL18* gene have also been reported, and were linked to a predisposition for the development of GC [151]. In line with these observations, increased levels of IL-1β and IL-18 protein have also been observed in the serum and tumor tissue from GC patients when compared to healthy controls or non-tumor tissue [151–153]. Collectively, these findings implicate IL-1β and IL-18 in the pathogenesis of GC.

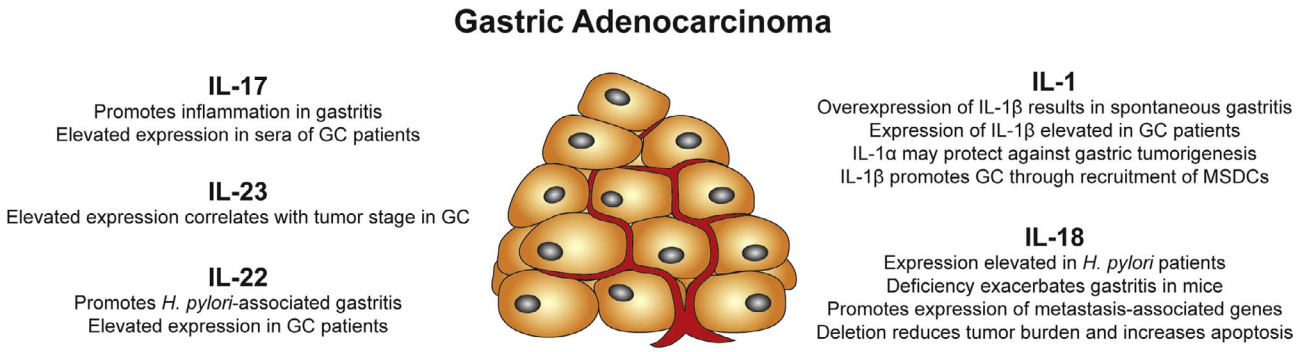

Fig. 2. Role of Th17 cell-associated cytokines, and IL-1 and IL-18 in GC. Summary of contribution of IL-17, IL-23, IL-22, IL-1, and IL-18 to GC progression. While elevated expression of IL-17, IL-23, and IL-22 have been detected in GC patients, their role in the pathogenesis of GC remains poorly understood. IL-1 and IL-18 are elevated in GC patients, with animal models suggesting a protumorigenic role for these two cytokines; IL-1β through the recruitment of MSDCs, while IL-18 may modulate tumor cell survival and metastasis.

Table 1
Potential therapeutics that could be repurposed for the treatment of GC.

Agent	Target	Mechanism of action	Current trials/ approvals	References[a]
Secukinumab	IL-17A	Anti-IL-17A mAb	Psoriasis	[159]
Ixekizumab	IL-17A	Anti-IL-17A mAb	Plaque psoriasis	[160]
Ustekinumab	IL-23	Anti-IL-12B mAb	Psoriasis	[161]
Anakinra	IL-1	Recombinant IL-1RA	Rheumatoid arthritis	[162]
			Pancreatic cancer	NCT02021422
			CRC	NCT02090101
Rilonacept	IL-1	Modified Soluble IL-1R	Cryopyrin-associated periodic syndrome	[163]
Canakinumab	IL-1β	Anti-IL-1β mAb	Cryopyrin-associated periodic syndrome	[164]
			CRC/NSCLC/Breast Cancer	NCT02900664

mAb: Monoclonal antibody.
CRC: colorectal cancer, NSCLC: non-small cell lung cancer.
[a] ClinicalTrials.gov identifier.

Animal models have increased our understanding of the role of IL-1β in GC development, with IL-1β transgenic mice spontaneously developing gastritis, with progression to gastric atrophy, metaplasia, and carcinoma formation [131]. Furthermore, when these mice were infected with *H. felis*, as an animal model of *H. pylori* infection, disease severity was increased [131]. In contrast, IL-1α signaling has been suggested to prevent tumor formation, as loss of IL-1R1, which mediates both IL-1α and IL-1β signaling, in the $Gp130^{F/F}$ mouse model of GC was shown to increase tumor incidence and size [154], although in other studies, loss of IL-1R1 through therapeutic treatment of $Gp130^{F/F}$ mice with Anakinra, an IL-1R antagonist, had no impact on tumor burden [155]. These conflicting results suggest that our understanding of the contribution of IL-1 signaling to GC tumorigenesis is still in its infancy, and may be related to differences in microflora.

The role of IL-18 in promoting GC development is less well understood, with most studies focused on human GC cell lines grown as xenografts in immune compromised mice. In human GC cells, it has been shown that IL-18 may promote tumorigenesis by increasing the metastatic potential of xenograft tumors [153]. Human GC cell lines have also been used to demonstrate that following neutralization of endogenous IL-18 with IL-18BP, CD70 expression, which has been suggested to be involved with the NK-cell mediated anti-tumor immune response, was elevated and resulted in tumor rejection and tumor immune susceptibility [153]. Additionally, neutralization of IL-18 signaling decreased expression of CD44, which is involved in metastasis of tumors to the peritoneum, prostaglandin-endoperoxidase synthase 2 (PTGS2, also known as COX2), and VEGF involved in neovascularization of the tumor [153]. Furthermore, following the establishment of human GC cell line xenografts in mice, inhibition of IL-18 signaling using IL-18 small interfering RNA (siRNA), was shown to significantly reduce tumor burden compared to control mice [153]. These findings are consistent with a previous study that found following the establishment of human GC cell line xenografts in immune compromised mice, injection of recombinant human IL-18 resulted in a reduction in overall survival, and was associated with tumor dissemination into the peritoneal cavity of these mice [156]. In the $Gp130^{F/F}$ mouse model of GC, genetic ablation of IL-18 signaling reduced tumor burden and was associated increased apoptosis in the gastric adenomas [155]. Collectively these studies suggest that IL-18 may contribute to the progression of GC, potentially through mechanisms involving modulating tumor cell survival and metastasis (Fig. 2).

7. Conclusions and therapeutic perspectives

The tumor microenvironment has an important role in dictating the development and growth of tumors, with the production of cytokines by immune and non-immune cells that are found in the microenvironment having an important role in disease progression. Studies examining the role of cytokines produced by Th17 cells, and that of the IL-1 family in the GI tract have found both protective and pathogenic roles depending on disease location, as well as disease type. Given that GC represents the third highest cause of cancer related mortality worldwide, research into the development of effective therapies to treat the disease are required. One such avenue may be to target the pro-inflammatory cytokines that are produced in the tumor microenvironment, with research characterizing the importance of these cytokines in different stages of disease development and progression essential to translation of preclinical findings into clinical practice.

The studies outlined in this review suggest that the therapeutic inhibition of Th17 associated cytokines may be of benefit in GC, and could involve specifically targeting IL-17A, IL-23, or IL-22 (Table 1). For IL-17, Secukinumab and Ixekizumab represent two FDA-approved IL-17A inhibitors that could be repurposed for GC, while Ustekinumab is an approved inhibitor of the IL-12B subunit of IL-23; however, no trials have been conducted so far for these agents in a cancer setting. Numerous genetic studies in mice suggest that inhibition of these cytokines may reduce inflammation in the stomach and may prevent their pro-tumorigenic activities such as inducing cell proliferation and anti-apoptotic genes. Inhibition of these cytokines may also resensitize cells to cytotoxic treatments, as it has been shown that IL-17A can promote chemoresistance in colon cancer, and treatment with neutralizing antibodies is able to restore responsiveness to chemotherapy [157].

The studies outlined in this review also suggest that the therapeutic inhibition of IL-1 and IL-18 may alleviate GC (Table 1). For IL-1, Anakinra, Rilonacept, and Canakinumab are three FDA-approved inhibitors that could be repurposed for GC, while none have been approved for IL-18. Anakinra has previously been shown to improve progression-free survival in myeloma [158], and is currently in clinical trials for metastatic colon cancer (Clinical trial ID: NCT02090101), breast cancer (Clinical trial ID: NCT01802970), and other advanced cancers (Clinical trial ID: NCT01624766). For IL-1, inhibition of this cytokine in the IL-1β transgenic model of GC was associated with a reduction in infiltration of MSDCs, which are associated with the suppression of host immune responses, thereby facilitating tumor immune evasion [131]. Although in the $Gp130^{F/F}$ GC model inhibition of IL-1R signaling demonstrated no therapeutic benefit, inhibition of IL-18 reduced tumor burden and may be a tractable therapeutic target [155]. Inhibition of IL-18 may also reduce tumor progression by preventing the metastatic ability of cells by downregulating the expression of CD44 and VEGF for example [153].

Which of these cytokines plays a dominant role in GC, and thus represents the best therapeutic target, remains to be elucidated. Antibody mediated inhibition of the formation of receptor complexes on cell surfaces is easily achieved, and permits a level of tissue specificity that is not possible when targeting downstream kinases or transcription factors that are utilized by multiple cytokine families, many of which are not detrimental in cancers. Targeting cytokine signaling complexes also has the potential to limit unwanted side-affects, with cytokines chosen based on their stage-specific role in disease, with their roles in pathogen clearance and epithelial barrier integrity a consideration when contemplating systemic treatment strategies for patients, minimizing off-target complications.

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