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Review article

The important role played by chemokines influence the clinical outcome of *Helicobacter pylori* infection

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ABSTRACT

The extended infection with *Helicobacter pylori* (*H. pylori*), one of the most frequent infectious agents in humans, may cause gastritis, peptic ulcers, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer. During *H. pylori* infection, different kinds of inflammatory cells such as dendritic cells, macrophages, neutrophils, mast cells, eosinophils, T cells and B cells are accumulated into the stomach. The interactions between chemokines and their respective receptors recruit particular types of the leukocytes that ultimately determine the nature of immune response and therefore, have a main influence on the consequence of infection. The suitable production of chemokines especially in the early stages of *H. pylori* infection shapes appropriate immune responses that contribute to the *H. pylori* elimination. The unbalanced expression of the chemokines can contribute in the induction of inappropriate responses that result in the tissue damage or malignancy. Thus, chemokines and their receptors may be promising potential targets for designing the therapeutic strategies against various types *H. pylori*-related gastrointestinal disorders. In this review, a comprehensive explanation regarding the roles played by chemokines in *H. pylori*-mediated peptic ulcer, gastritis and gastric malignancies was provided while presenting the potential utilization of these chemoattractants as therapeutic elements.

1. Introduction

The extended infection with *Helicobacter pylori* (*H. pylori*), one of the most frequent pathogen in humans, lead to several gastrointestinal diseases such as peptic ulcers (PU), mucosa-associated lymphoid tissue (MALT) lymphomas and gastric cancer in the 10.0–15.0%, 1.0–3.0% and < 1.0% of the infected individuals, respectively [1,2]. Some extra-gastrointestinal exhibitions such as metabolic, hematologic, neurologic, cardiovascular, and dermatologic have been also correlated with *H. pylori* infection [3–5]. A complex network of communications between several parameters, in particular virulence factors of *H. pylori*, host genetic predisposition, host innate and specific immunity, and environmental elements determine the expression of the different types of the *H. pylori*-linked clinical outcomes [6,7]. The cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) proteins are the most potent virulence factors that have been related to the severity of gastric lesions and immune responses [6,8]. The infection with $CagA^+$ or $VacA^+$ strains induces more inflammation, ulceration and tumorigenesis [7,9,10]. The prevalence of CagA among *H. pylori* isolates obtained from patients with gastrointestinal diseases was reported to be 70.0% in Iran, 78.0% in Turkey, 66.0% in United States, 46.0% in the Netherlands, 87.2% in Germany, 87.0% in Estonia, 45.0% in Sri Lanka, 81.7% in Brazil, 97.0% in Korea, 95.0% in Japan, 94.0% in Malaysia and 90.0% in China [11].

In *H. pylori* infection, various kinds of inflammatory cells, including dendritic cells (DCs), macrophages, neutrophils, eosinophils, mast cells, and T- and B cells are gathered into the stomach and the intensity of mucosal injury is related with the levels of leukocyte infiltration, in particular neutrophils [12,13]. The increased quantities of pro-inflammatory cytokines and chemokines such as IL-1β, TNF-α and CXCL8 were indicated in the gastric mucosa from patients with *H. pylori*-mediated gastritis [7,14]. The intestinal Peyer's patches and the mesenteric lymph nodes are the earlier sites of the induction of *H. pylori*-related immune responses [15,16]. The *H. pylori*-specific T cells are activated in Peyer's patches and move to mesenteric lymph nodes, and subsequently are aggregated in the gastric mucosa [15]. The $CD4^+$ T

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cells perform a more prominent role in the regulating of the *H. pylori*-specific immune responses that may lead to bacterial elimination, local inflammation, and cause immunopathologic consequences [17].

In contrast to the most of bacteria, which cause illness and then are eradicated by the pathogen-specific immune response, *H. pylori* establishes an extended infection for decades or for lifetime despite the induction of powerful innate and specific immune responses [18]. Therefore, *H. pylori* has been achieved several adaptation mechanisms that permit the bacterium to evade the host immunity [17]. However, the infection outcome toward pathogen elimination, pathogen evasion and persistence, or immunopathologic sequels mainly is determined by the nature of immunity initiated by *H. pylori* [1].

As mentioned, the leukocyte recruitment is one of the earliest processes happens during *H. pylori* infection [12,13]. The local expression of pro-inflammatory chemokines play a pivotal role in the recruitment of different subsets of leukocytes to the stomach during *H. pylori* infection. Chemokines are small polypeptides (8–14 kDa), which attract different types of leukocytes to the sites of infection and inflammation [19]. Chemokines are categorized into CXC, CC, CX3C or C chemokines, based on the location of conservative cysteines (C) residues in their structure [19,20]. Chemokines exert their functions by binding to transmembrane G protein-coupled receptors, and trigger cells to move along a concentration gradient [19]. Chemokine receptors were identified as CXCR, CCR, CR, and CX3CR [19,20]. A set of proinflammatory chemokines especially CXCL8, CXCL10, CXCL12, CXCL13, CXCL16, CCL5, CCL17, CCL20, CCL22, CCL25 and CCL28 are involved in *H. pylori*-related immune or immunopathologic responses. The CXC chemokines play more prominent role in the *H. pylori*-mediated gastric inflammation than CC chemokines [21]. Determination of how chemokines and their receptors contribute in the immunity to *H. pylori* and in the pathogenesis of the bacterium-related gastrointestinal diseases is essential for designing the novel therapeutic strategies. In this review a comprehensive explanation regarding the roles played by chemokines in *H. pylori*-mediated peptic ulcer, gastritis and gastric cancer was provided while presenting the potential utilization of these chemoattractants as therapeutic elements.

2. CXC chemokines

2.1. CXCL8

CXCL8 (also known as IL-8) is one the most powerful pro-inflammatory chemokines that is secreted by different cell subsets including monocytes, macrophages, fibroblasts, endothelial cells, and epithelial cells [22]. CXCL8 expression is stimulated by different inducers such as IL-1, IL-6, IL-17A, IL-22, TNF-α, CXCL12, hypoxia, reactive oxygen species (ROS), and mediated by transcription factors NF-κB and activator protein-1 (AP-1) [1,22]. Some *H. pylori*-related factors also induce the CXCL8 expression which will be explained in the following. CXCL8-related signals are mediated *via* binding to two receptors namely CXCR1 and CXCR2 [23].

The CXCL8 generation by gastric epithelial cells (GECs) is a main characteristic of *H. pylori* infection [7]. The raised CXCL8 expression was measured in antral biopsy specimens from *H. pylori*-infected patients with PU or gastritis in comparison with uninfected cases, and the CXCL8 expression has been detected in GECs and macrophages [7,24]. Further, the elevated CXCL8 expression in human GECs, and gastric biopsy specimens from patients with duodenal ulcer is linked to infection by $CagA^+$ *H. pylori* strains [7,25]. The CXCL8 is also produced by macrophages and neutrophils placed in the lamina propria of stomach in *H. pylori*-infected subjects with chronic active gastritis [26]. Some *H. pylori*-derived components such as urease, JHP940 protein, and VacA also stimulate the human peripheral blood mononuclear cells (PBMCs) or human monocytes to secrete CXCL8 *in vitro* [7].

The *H. pylori*-induced CXCL8 production happens in the type IV secretion system (T4SS)-dependent or independent manners. The T4SS is one of the most powerful CXCL8 inducers of *H. pylori* [27,28]. The CXCL8 induction by *H. pylori* in epithelial cells is potently dependent to the T4SS [27]. In T4SS-dependent process, a number of bacterial components, such as peptidoglycan, DNA or CagA are transported into the GECs and trigger the CXCL8 expression [27,28]. The *H. pylori*-stimulated CXCL8 expression in GECs needs the phosphorylation of the CagA in the initial steps of the infection [7]. The $CagA^+$ *H. pylori* strains induce more CXCL8 than CagA-deficient strains and the prevention of CagA phosphorylation decreases the CXCL8 expression [7]. Upon transportation of the CagA into the GECs, it induces the CXCL8 expression *via* the induction of the tyrosine phosphatase SHP2, mitogen-activated protein (MAP) kinase pathway and NF-κB [27,29]. The injected peptidoglycan into the GECs is also sensed by an intracellular receptor NOD1 and leads to the CXCL8 production *via* signal inducer and activator of transcription-1 (STAT-1), IRF-1 and NF-κB activation [30,31].

There are controversies regarding the contribution of the OipA (an outer membrane protein of the *H. pylori*) in the CXCL8 expression. It has been reported that the CagA-induced CXCL8 in human GECs is dependent on the OipA expression and OipA is necessary for transportation of the CagA into the epithelial cells [32]. According to the results from another *in vitro* study, it has been concluded that CagA and OipA regulate CXCL8 expression in human GECs *via* different pathways [33].

The *H. pylori*-induced CXCL8 production may also occur in a T4SS-independent manner because a *cagE* mutant maintains its inducing activity [34]. The VacA directly increases the CXCL8 expression in a human monocytic cell line by induction of the p38 MAPK that activates a transcription factor, namely the c-AMP response element-binding protein-1 (CREB1) that binds to the AP-1 site in the CXCL8 gene promoter [35].

Following the *H. pylori* establishment in the human gastric antrum, HP-NAP also first attracts and then stimulates neutrophils to secrete IL-12 and IL-23 accompanied with the production of CXCL8, CCL3 and CCL4 [12]. Because neutrophils are quickly aggregated in great numbers at infection location, they may also act as chemokine producers that recruit more neutrophils *via* CXCL8 production and attract additional monocytes, DCs, and lymphocytes *via* secretion of CCL3 and CCL4 [36].

HP-NAP also elicits macrophages to secrete IL-12 and IL-23 that potentiate the Th1- and Th17 cell-connected responses against *H. pylori* [36]. The Th17 cell-derived cytokines such as IL-17A and IL-22 work synergistically to induce the expression CXCL8 and antimicrobial peptides in GECs [37].

The CagL also triggers the CXCL8 secretion from *H. pylori*-infected cultured human GECs by activating Src tyrosine kinase, MAP kinase cascade, NF-κB, and through direct interaction with a host cell receptor integrin $\alpha_5\beta_1$ *via* an arginine-glycine-aspartate motif [38]. Moreover, integrin $\alpha_5\beta_1$ perform a key role in the CXCL8 induction by *H. pylori*-infected human GECs during *in vitro* experiments [38].

The OipA and bacterial urease also lead to the CXCL8 secretion from human GECs through activation of STAT-1 and NF-κB, respectively [30,33].

The investigations using human and murine models indicate that GECs and macrophages produce CXCL8 in response to different *H. pylori* factors such as VacA, urease, and JHP940, whereas the T4SS-dependent injection of CagA or peptidoglycan are involved in the epithelial cell activation [7,38,39].

Based on the *in vitro* investigations, using human GECs, it was indicated that the MAPK p38, NF-κB or the extracellular signal-regulated kinases 1/2 (ERK1/2, MAPK1/3)-related signals perform a role in the CXCL8 expression during *H. pylori* infection [7]. The *H. pylori*-induced CXCL8 production in a human monocytic cell line is also blocked by ERK1/2, p38, and NF-κB inhibitors, representing the contribution of the MAPK/NF-κB pathway in this process [7]. Other pathways such as AP-1 also lead to CXCL8 expression and are essential for maximal CXCL8 expression [7].

In addition, the *in vitro* experiments using human GECs revealed that epidermal growth factor receptor (EGFR) pathway may perform a considerable role in the *H. pylori*-induced CXCL8 expression [40]. It has been demonstrated that induction of the EGFR *via* an endogenous ligand, namely heparin-binding epidermal growth factor (HB-EGF) contributes in the *H. pylori*-induced CXCL8 expression from human GECs [41]. Thus, different signaling pathways contribute in the CXCL8 production after *H. pylori* infection.

The *H. pylori* infection causes the CXCL1, CXCL5 and CXCL8 expression in cultured primary human GECs and the inhibitors of EGFR, MAPK and JAK reduce the chemokine production [30]. Using a neutralizing antibody against TLR2 also reduces the chemokine secretion by *H. pylori*-infected primary human gastric cells *in vitro*. Therefore, some *H. pylori*-derived molecules are recognized by TLR2 and cause CXCL1, CXCL5 and CXCL8 expression in a T4SS-independent manner *via* EGFR, MAPK and the JAK/STAT signaling pathways [30].

H. pylori is also found in the proximity of endothelial cells in the underneath of gastric mucosa in infected humans and monkeys [27,42].The results from an *in vitro* study showed that the *H. pylori*-infected human endothelial cells secrete IL-6 and CXCL8 [27]. This inflammatory response is induced by a T4SS-linked adhesin CagL, but in a CagA translocation-independent manner. *H. pylori*-related T4SS activates the NF-κB that contributes to the CXCL8 induction in *H. pylori*-infected endothelial cells [27]. The EGFR is also need for *H. pylori*-induced CXCL8 response in endothelial cells [27]. Therefore, the T4SS-associated adhesin CagL and EGFR may consider as potential therapeutic targets for modulating the *H. pylori*-mediated inflammation.

The CXCL8-CXCR1/2 axis recruits granulocytes, primarily neutrophils into the sites of inflammation and infection that increase bacterial elimination [22,23]. It was reported that the incubation of *H. pylori* with human neutrophils reduces the expression of the CXCR1 and CXCR2 after 30 min, which may limit their migration [43]. However, neutrophils are recruited into the stomach during *H. pylori* infection, but there are *in vitro* evidence indicating that they are not capable to eliminate the bacteria [44]. A chronic gastric neutrophil-dominant inflammation occurs during *H. pylori* infection, and neutrophils density is related to disease intensity and tissue damage [45]. A strong association was also indicated between expression of CXCL8 in GECs with the inflammation with the risk of gastric pathological changes during *H. pylori* infection [7,45] (Table 1).

The CXCL8 may also contribute to the development of the *H. pylori*-related malignancies. The serum CXCL8 concentration in *H. pylori*-positive patients with gastric cancer is higher than those without carcinoma [46]. Interestingly, elevated expression of NOD1, CXCL8, and IRF1 were reported in human gastric tumor tissues compared with paired non-malignant specimens [31]. Tumor cells also secrete CXCL8 which acts as a key element in the development, severity, and metastasis of gastric carcinoma [7,46]. Further, the CXCL8 secretion from cancerous cells and tumor-associated macrophages (TAM) induces tumor cell proliferation, and chemoresistance [47]. CXCL8 promotes tumor development by stimulating vascular endothelial growth factor (VEGF) expression, enhances cell proliferation and survival, potentiates epithelial-mesenchymal transition (EMT), and activates inflammatory and stromal cells within the tumor microenvironment [46] (Table 1). A positive association was indicated between the CXCL8 expression and the number of blood vessels in the human gastric carcinomas [46]. Moreover, CXCL8 directly induces the angiogenesis through expansion of the $CXCR1^+$ and $CXCR2^+$ human endothelial cell and capillary formation *in vitro*, and these effects are blocked using anti-CXCL8 antibodies [22,46,48]. In an *in vitro* study, it was also indicated that *H. pylori*-derived HSP60 expands the human endothelial cells through triggering CXCL8 from GECs which contributes to the angiogenesis [49]. Further, CXCL8 induces the expression of the MMP-2 and MMP-9 in cultured human endothelial cells, which promote their migration [48].

CXCL8 also recruits neutrophils into tumor microenvironment that can be polarized into either anti-tumor N1 or pro-tumor N2 subsets [50,51]. The aggregated neutrophils promote cancerous cell migration, invasion, and metastasis through several ways, such as releasing growth factors and MMPs [50,51]. CXCL8 promotes the accumulation of the myeloid-derived suppressor cells (MDSCs) into the tumor site, which inhibit the anti-tumor immune responses [47]. The CXCL8-over-producing transgenic mice display more infiltration of MDSCs into colonic mucosa that promote the colon carcinogenesis [47]. Further, CXCL8 attracts *in vitro* the $CXCR1^+$ and $CXCR2^+$ MDSCs separated from PBMCs of malignant patients [52]. CXCL8 also promotes cancer development through induction EMT, a process in which epithelial cells miss their properties and acquire mesenchymal characteristics [47]. The results from *in vitro* experiments indicate that treatment of human malignant cells with CXC8 promote EMT [47]. There are also reports indicating that CXCL8 *in vitro* expands the human cancer stem cells (CSC) through CXCR1 and CXCR2 and the targeting of the mentioned receptors limit that CSC formation [23,47].

The inhibitors of the factors that contribute to the CXCL8 expression such as inhibitors of MAPK, AP-1, NF-κB, EGFR and ROS may limit cancer development [46]. A number of microRNAs was also modulate the CXCL8 expression [46]. The interventions in CXCL8-CXCR1/2 axis may have therapeutic potentials. For example, small inhibitor molecules targeting the CXCL8 receptors are interesting therapeutic agents to suppress the CXCR1/2-related signaling pathway. Reparixin, an inhibitor of CXCR1 and CXCR2, prevents the CXCL8 interaction with its receptors, reduce the expansion of CSC and decrease the tumor metastasis [23]. The anti-CXCL8 neutralizing antibodies also reduce invasion and angiogenesis in melanoma tumor-bearing mice by inhibiting the MMP-2 expression and increasing the tumor cell apoptosis [47].

Taken together, the aforementioned studies indicate that the various kinds of *H. pylori*-linked elements trigger the CXCL8 expression in GECs, endothelial cells and infiltrated leukocytes. CXCL8 recruits neutrophils into the sites of inflammation, but they are unable to eliminate the *H. pylori*. During *H. pylori* infection, the extended excessive CXCL8 expression induces a chronic neutrophil-dominant that contributes in the tissue damages such as gastritis. The improper expression of CXCL8 may play a main role in the development of the *H. pylori*-related gastric cancer (Fig. 1).

2.2. CXCL10

During the inflammatory process, CXCL10 [known as interferon gamma-induced protein 10 (IP-10)] is released from neutrophils, eosinophils, monocytes, keratinocytes, epithelial- and endothelial cells in response to IFN-γ [53]. CXCL10 specifically binds to CXCR3, which is expressed on the natural killer (NK) cells, DCs, macrophage and activated T- and B lymphocytes [19].

The expression of CXCR3 and its ligands CXCL9, CXCL10 and CXCL11 are increased in human or murine gastric mucosa during *H. pylori* infection [26,54,55]. The proinflammatory cytokines TNF-α and IFN-γ synergistically trigger the CXCL9 and CXCL10 expression from cultured human GECs [56]. The *H. pylori*-stimulated NOD1 pathway leads to the activation of STAT1 and IRF1 in cultured human GECs that promotes the CXCL8 and CXCL10 expression [31]. The expression of NOD1, CXCL8, and CXCL10 in gastric biopsy specimens from *H. pylori*-infected patients with severe gastritis is greater than those without gastritis [31]. A positive association has been also observed between infection with $CagA^+$ *H. pylori* strains and serum CXCL10 levels in PU patients [57].

Among T cell subgroups, CXCR3 is mainly expressed on Th1 cells, hence, CXCL9, CXCL10, and CXCL11 preferentially contribute to the selective recruitment of Th1 cells into the inflammation sites [19,58,59]. Elevated expression of Th1 cell-related chemokines (including CXCL9, CXCL10, and CXCL11) were detected in the *H. pylori*-infected human stomach mucosa [26,55]. However, the gastric $CD4^+$ T cells isolated from *H. pylori*-infected healthy individuals display lower

Table 1
The role of CXC chemokines during *Helicobacter* infection.

Chemokines	Cell producers	Played roles	Mechanisms of action	Ref.
CXCL8	- GECs	- Gastric inflammation	- Recruitment of neutrophils.	[45]
	- Vascular endothelial cells	- Development of gastric cancer	- Promotion of tumor cell proliferation and survival.	[7,46] [47].
			- Expression of VEGF and angiogenesis.	[22,46].
	- Infiltrated macrophages		- Induction of EMT	[46].
	- Infiltrated neutrophils		-Expression of MMPs	[48].
	- Tumor-associated		- Expansion of cancer stem cells	[23].
	- Macrophages		- Recruitment of MDSCs into the tumor	[47].
	- Gastric tumor cells		- Recruitment of neutrophils into the tumor	[50,51]
CXCL10	GECs	- Bacterium elimination (In coordination with CXCL9 and CXCL11)	- Recruitment of Th1 cells	[61,62].
			- Contributes to the induction suitable Th1 cell-mediated immune response against *H. pylori*	[1,194].
		- Development of PU and gastritis (In coordination with CXCL9 and CXCL11)	- Contributes to the induction uncontrolled Th1-mediated immune response against *H. pylori*	[1,26,55,60].
		- Progression of gastric cancer	- Promotes cancerous cell invasion	[70,71].
			- Induction of MMP production	[70,71].
			- Promotes cancerous cell migration	
		- Regression of gastric cancer	- Attraction and activation of $CD8^+$ CTLs	[67].
			- Attracting NK- and Th1 cells	[66].
CXCL12	- GECs	- Promotion of the inflammation	- Recruitment of Macrophages.	[77]
	- Endothelial cells		- Recruitment of DCs.	[77]
	- Gastric cancer cells		- Recruitment of T cells.	[76].
	- MALT lymphoma cells	- Wound healing	- Recruitment of epidermal stem cells	[78,79]
			- Recruitment of bone marrow-derived stromal stem cells	[78,79]
			- Induction of angiogenesis.	[80].
		- Progression of gastric cancer	- Induction of angiogenesis.	[86,91,92].
			- Recruitment of bone marrow-derived mesenchymal stem cells	[75].
			- Recruitment of $CXCR4^+$ CAF	[86].
			- Expansion of gastric epithelial progenitor cells	[86].
			- Trigger the EMT	[87].
			- Promotes proliferation of myofibroblasts	[86].
		- Progression of MALT lymphoma	- Exert proliferative and pro-survival effects in the lymphoma cells.	[77].
CXCL13	GECs	- Induction of anti-*H. pylori* immune responses	- Induction of Th17 cell response	
		-Induction of anti-*H. pylori* IgG and IgA	- Recruitment of B cells	[98].
				[98].
		- Development of MALT lymphoma	- Formation of tertiary lymphoid tissues in the mucosa of stomach	[94,98] [94,100] [96,101,102].
CXCL16	GECs	- Induction of anti-*H. pylori* immune responses	- Recruitment of DCs	[106].
		- Development of gastritis	- Recruitment of $CD8^+$ T cells	[104].
		- Progression of gastric cancer	- Promotion of cell proliferation, migration and invasion	[107].
			- Induction of EMT	[107].

CXCR3 expression in comparison with *H. pylori*-negative healthy individuals [60]. High CXCL9 and CXCL10 expression in the stomach mucosa of patients with *H. pylori*-related chronic gastritis represents that both chemokines involve in the development of the Th1 cell responses [61]. The Th1 cell-secreted cytokines such as IFN-γ, TNF-α and IL-2 cause macrophage recruitment into the infection sites. The activation of macrophages by Th1 cell cytokines (especially IFN-γ) performs a central role in the *H. pylori* elimination [62]. An adequate and appropriate Th1-dependent cell mediated immune response against *H. pylori* is essential for bacterium clearance [63–65]. The results from human and mouse studies indicate a reverse correlation between Th1 cell-dependent immune response and *H. pylori* colonization, representing that the insufficient Th1 cell response is related to elevated bacterium colonization [1,62]. However, if the *H. pylori* evades the Th1-cell mediated immune responses, the continuation of an excessive and inappropriate immune of Th1 cells-related responses may involve in the development of PU and gastritis [1].

It has also been indicated that the serum CXCL10 quantities in *H. pylori*-infected PU patients were lower than those without the disease [57]. Further, the *H. pylori*-derived fractions inhibit the *in vitro* CXCL10 expression in GECs [56]. Therefore, low CXCL10 production may represent a poor Th1 cell-related response in the gastric mucosa of *H. pylori*-infected patients. Diminished CXCL10 levels may reduce the influx of the $CD4^+$ Th1 cells into the of *H. pylori*-infected gastric mucosa. It seems to be logical that *H. pylori* may have evolved strategies (such as inhibition of the CXCL10 production) to minimize the aggregation of Th1 cells to the gastric mucosal and evade the host's immune system.

Some anti-tumor and pro-tumor effects were attributed to CXCL10. CXCL10 may trigger anti-tumor responses through attracting NK cells, Th1 and $CD8^+$ CTLs [66]. However, there are also reports from *in vitro* and *in vivo* experiments indicating the higher expression of CXCR3 ligands by antigen-presenting cells and endothelial cells within gastric cancer leads to the attraction and activation of $CD8^+$ CTLs which may cause tumor regression [67]. In addition to chemotaxis, CXCL10 also influence the apoptosis, cell proliferation and angiostasis [19,59]. Elevated plasma levels of CCL2, CCL4, CCL5, CXCL8, CXCL9, and CXCL10 were indicated in patients with gastric cancer [68]. A significant role has been implicated for CXCL10 in the progression of gastric cancer and antibiotic treatment inhibits the *H. pylori*-induced gastric cancer development in a murine model which is related to lower expression CXCL10 in gastric mucosa [69]. The overexpression of the CXCR3 was also indicated in human gastric cancer cells, and *in vitro* investigations revealed that the CXCL10/CXCR3 axis leads to the MMP2 and MMP9 production through PI3K/AKT pathway that promotes cancer cell invasion and migration [70]. In an *in vitro* analysis, it has also been observed that CXCL10 promotes the human gastric cancer cell migration and invasion *via* CXCR3A, but not through CXCR3B [71]. Using a mouse model, it was found that the downregulation of CXCR3A in a gastric

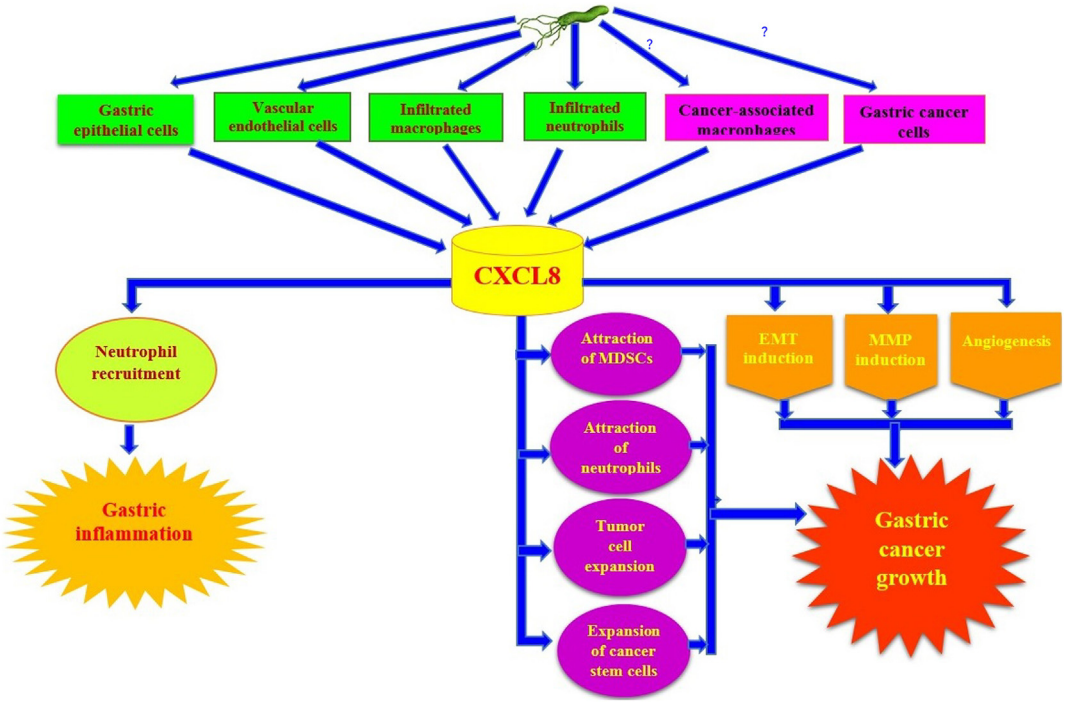

Fig. 1. The role played by CXCL8 during *H. pylori* infection. Various types of *H. pylori*-linked elements trigger the CXCL8 expression in GECs, endothelial cells and infiltrated leukocytes. CXCL8 recruits neutrophils into the sites of inflammation, but they are not capable to eliminate the *H. pylori*. The extended excessive CXCL8 expression induces a chronic neutrophil-dominant that causes tissue damages such as gastritis. The improper CXCL8 expression play a main role in the development of the *H. pylori*-related gastric cancer. EMT: Epithelial-mesenchymal transition, MMP: Matrix metalloproteinase.

cancer cell using siRNA reduces the MMP13 expression, reduces ERK1/2 activation and reduces the migration and invasion of this malignant cell *in vitro*, and *in vivo* [71]. Therefore, it seems that CXCR3A is involved in the progression of gastric cancer. Hence, CXCR3 (especially CXCR3A variant) may consider as a potential therapeutic target for the gastric cancer treatment.

Collectively, the aforementioned studies indicate the adequate and proper expression of CXCL10 may contribute to the *H. pylori* eradication due to the attracting of the balanced number of the specific Th1 cells in the gastric mucosa, which in turn trigger a balanced cell-mediated immunity against bacterium. However, inadequate or overexpression of the CXCL10 may lead to the low or large influx of Th1 cells into the gastric mucosa which finally cause tissue damage (such as PU) due to occurring of the direct *H. pylori*-linked pathologic effects or immunopathologic reactions, respectively. The CXCL10 involvement in gastric cancer is also complex and may display anti- or pro-tumoral activities, perhaps in a time-dependent manner. Therefore, during initial phases of tumor establishment, it may have anti-tumoral effects, but in later stages it may have more pro-tumoral influences, as the chemokine directly exerts promoting effects on the some cancer development process (Fig. 2).

2.3. CXCL12

CXCL12 [also called stromal cell-derived factor-1 (SDF-1)] is produced by various cells, such as fibroblasts and epithelial cells, and exerts its activities through binding to CXCR4 and CXCR7 [72]. CXCL12/CXCR4 axis contributes in a number of physiological processes such as haematopoiesis, vascular development, cardiogenesis, and neurogenesis [72,73]. It also involves in autoimmune and infectious diseases, and tumor metastasis [72,73].

It has been reported that *H. pylori* infection is not able to induce CXCL12 expression in cultured mouse intestinal cells [74]. However, co-culturing of *H. pylori* with human GECs enhances the CXCL12 secretion by these cells that recruits $CXCR4^+$ cells [75]. This controversy may be attributed to the species differences of epithelial cells, as epithelial cell from humans is naturally targeted by *H. pylori*. A *H. pylori*-derived protein, namely HP1454 separated from *H. pylori*-infected patients with gastric adenocarcinoma or chronic gastritis stimulates the differentiation of naïve $CD4^+$ T cells toward effector Th1/Th17 phenotype and induces the CXCR4 expression on the T cells, hence causes T cell migration *in vitro*, in a CXCL12-dependent manner [76].

In *H. pylori*-related human gastritis, a greater CXCL12 expression occurs in the GECs that lead to the accumulation of the inflammatory cells such as macrophages, and DCs [77]. It was reported that the CXCL12 levels in serum and gastric lesions of patients with active ulcer were higher than those with healing ulcer and control individuals [21]. The enhanced CXCL12 levels may represent a host inflammatory response during active ulcer stages [21]. However, the CXCL12 expression is markedly reduced, while the CXCR4 expression is increased during healing ulcer stage, representing that CXCL12/CXCR4 may play a prominent role in gastric wound healing [21]. The results from *in vitro* and *in vivo* experiments displayed that the CXCL12/CXCR4-related pathways may contribute to the ulcer healing in mice by recruitment of epidermal stem cells and bone marrow-derived stromal stem cells to ulcer sites [78,79]. Further, CXCL12 increases the VEGF-A expression and lead to the aggregation of pro-angiogenic $VEGFR2^+$ $CXCR4^+$ cells, which play a main role in the neovascularization in mice [80]. The results from mouse and human studies revealed that the $CXCR4^+$ monocytes are attracted by CXCL12, which induce angiogenesis by producing pro-angiogenic elements such as VEGF-A and angiopoietin [81,82].

The CXCL12-related signals may have a key role in the growth and progression of malignancies (Table 1). It has been indicated that the CXCL12 expression in gastric biopsies of patients with gastric cancer who were positive for *H. pylori* was higher than patients without *H. pylori* infection [75]. CXCL12 expression has been introduced as an independent prognostic marker for aggressive properties of human gastric carcinoma such as tumor size, staging, invasion and metastasis, and surgical outcome [83]. *H. pylori* also promote the *in vitro* expression

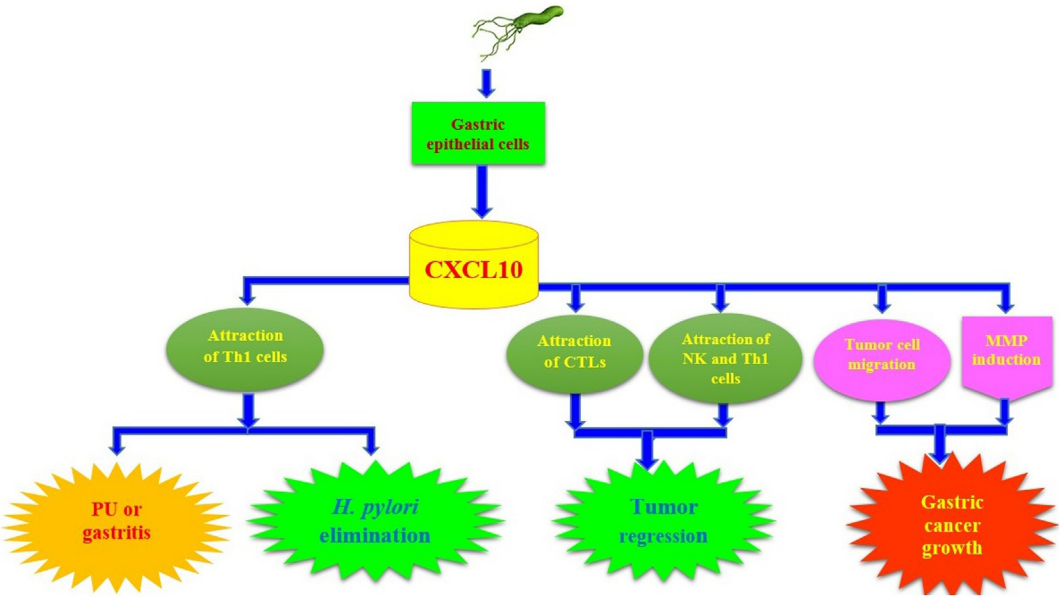

Fig. 2. The role played by CXCL10 during *H. pylori* infection. The proper CXCL10 expression may cause *H. pylori* eradication due to the attracting of the balanced number of the specific Th1 cells, which in turn trigger a balanced cell-mediated immunity against bacterium. However, the CXCL10 overexpression may lead to a large influx of Th1 cells into the gastric mucosa which cause tissue damage (such as PU) due to occurring immunopathologic reactions. During initial phases of tumor establishment, CXCL10 may have anti-tumoral effects, but in later stages it may have more pro-tumoral influences, as the chemokine directly exerts promoting effects on the some cancer development process. MMP: Matrix metalloproteinase.

of CXCR4 in bone marrow-derived mesenchymal stem cells (BM-MSCs) from healthy subjects and enhance their migration through the CXCL12/CXCR4 axis [75]. During chronic *H. pylori* infection, BD-MSCs move to the gastric tissue and may initiate the development of the gastric adenocarcinoma [75].

The CXCR4 expression on cancer cells represents that the CXCL12/CXCR4 axis may play an essential role in metastasis of $CXCR4^+$ malignant cells to target organs that produce high CXCL12 levels [84]. Elevated CXCR4 expression was detected in gastric biopsies obtained from patients with gastric cancer plus *H. pylori* infection compared to specimens collected from gastric cancer patients without *H. pylori* infection [85]. In combination with *Helicobacter* infection in mice, CXCL12 may contribute in the development of gastric cancer through expansion of gastric epithelial progenitor cells, proliferation of myofibroblasts, recruitment of CXCR4-positive cancer-associated fibroblasts (CAFs) and promoting angiogenesis [86]. The results from an *in vitro* experiment displayed that the CXCL12/CXCR4 axis also triggers the EMT and increases the migration of the human gastric cancer cells, which is associated with activation of the proto-oncogene MET [87]. Moreover, CXCL12/CXCR4 axis expands a subset of the CXCR4-expressing stem cells that may transform into gastric cancer cells [88]. In addition, the synergistic activity of CXCL12/CXCR4 axis with other proinflammatory mediators such as IL-1β may promote the development of malignancies [86]. The CXCL12/CXCR4-related signaling pathways may be promising potential targets for cancer treatment. For example, the useful effects of a small molecule compound AMD3100 that acts as a CXCR4 antagonist have been reported in some human malignant diseases [83].

The CXCR7 (another functional receptor for CXCL12 with 10 times higher affinity) expression was also indicated in human gastric cancer tissues and an *in vivo* evaluation in mice indicate that the CXCL12/CCR7 axis contributes to the metastasis of cancerous cells in the liver and lymph node through induction of MAPK pathways [89,90]. The *H. pylori*-derived LPS induces the CXCR7 expression in the several human originated gastric cancer cell lines *via* a TLR4-MD2 pathway [91]. CXCL12/CXCR7 axis performs a main role in the angiogenesis, invasion, and progression of gastric cancer cells, suggesting that this axis may be a prominent potential target for development of therapeutic agents against gastric cancer [91,92]. The targeting of CXCR7 pathway reduces the tumor growth in different types of human and mouse cancer cell lines originated from colon-, lung-, liver-, pancreas-, and head and neck cancer [83]. CCX754 as a CXCR7 antagonist reduces the growth of lung cancer in mouse models [83].

The experiments using human tissue biopsies indicate that the conversion from *H. pylori*-associated gastritis to MALT lymphoma, is associated with upregulation of the CXCR3, CXCR7, and CCR7 and downregulation of CXCR4 [77]. The up-regulation of the CXCR3, CXCR6, CXCR7, CCR1, CCR5, CCR7, CCR8, CCR9, and XCR1 is associated with the transformation from gastric MALT lymphomas to extranodal diffuse lymphoma. The CXCR4 is expressed by nodal B-cell lymphomas, but not by MALT- or gastric extranodal lymphomas indicating that CXCR4 may consider as a valuable prognostic marker [77]. In malignant tissues, CXCL12 is expressed by inflammatory cells, epithelial cells, endothelial cells, and lymphoma cells, suggesting that CXCL12 may act in part *via* an autocrine manner [77].

Together, the aforesaid studies indicate the appropriate expression of CXCL12 contributes in the induction immune responses against *H. pylori* through the attraction of leukocytes such as macrophages and DCs. The CXCL12/CXCR4 axis also involves in the inflammatory responses during active ulcer stages and later in gastric wound healing. As cancerous cells express CXCR4 and CXCR7, both CXCL12/CXCR4 and CXCL12/CXCR7 pathways may involve in the development and progression of *H. pylori*-related malignancies (Fig. 3).

2.4. CXCL13

CXCL13 [also named B-cell-attracting chemokine-1 (BAC-1) or B-lymphocyte chemoattractant (BLC)] is primarily produced by follicular dendritic cells (FDCs) in lymphoid organs and perform a significant role in the germinal center formation [93]. CXCL13 performs fundamental roles in the selective aggregation of B cells and some T cell subsets to the follicular regions in the spleen and lymph nodes, and plays a significant role in the formation of gastric lymphoid follicles through binding to its receptor CXCR5 [93,94]. CXCL13/CXCR5 axis plays a main role in the development of different types of inflammatory and autoimmune disorders such as multiple sclerosis and rheumatoid

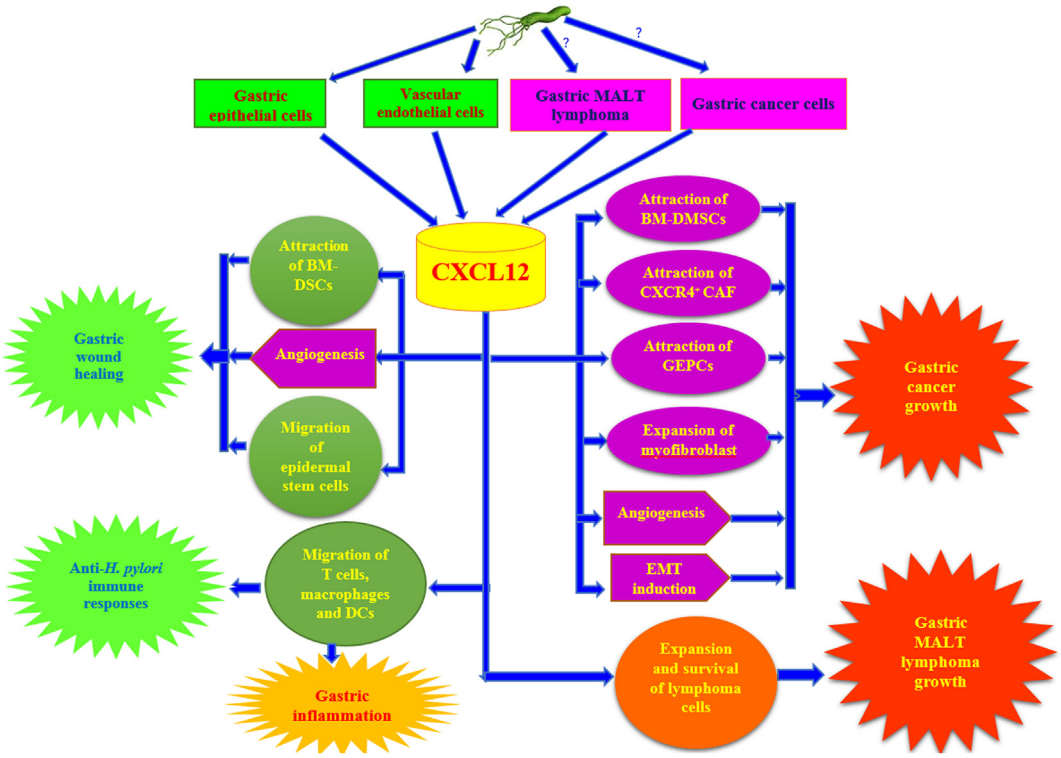

Fig. 3. The role played by CXCL12 during *H. pylori* infection. The appropriate expression of CXCL12 contributes in the induction immune responses against *H. pylori* through the attraction of leukocytes such as macrophages and DCs. The CXCL12/CXCR4 axis also involves in the inflammatory responses during active ulcer stages and later in gastric wound healing. CXCL12 may involve in the development and progression of *H. pylori*-related malignancies. BM-DSC: Bone marrow-derived stromal stem cells, BM-DMSC: Bone marrow-derived mesenchymal stem cells, CAF: Cancer-associated fibroblast, GEPC: Gastric epithelial progenitor cells.

arthritis [93].

Infection of mice with *H. suis* strain lead to the considerable upregulation of CXCL13 in gastric tissue [95]. Moreover, elevated CXCL13 expression has been detected in the antrum of *H. suis*-infected-gerbils [95]. The CXCL13 expression in human gastric cancer cell lines is increased after *H. pylori* infection [96]. The higher CXCL13 expression is also indicated in gastric biopsy specimens from *H. pylori*-positive patients-compared with *H. pylori*-negative patients that may be influenced by the presence of bacterial virulence factors such as CagA and BabA [97]. However, there are also reports that the GECs are not the main source of CXCL13 production in *H. pylori*-associated gastritis [96].

CXCL13 also contributes to the pathogenesis of the *H. pylori*-associated disorders [95,98] (Table 1). In a human study, a positive association was also found between the gastric CXCL13 expression with *H. pylori* load and the severity of chronic inflammation (especially mononuclear cell infiltration) in *H. pylori*-associated gastritis [96]. The mucosal CXCL13 expression was decreased after eradication therapy [96].

CXCL13 principally guides the homing of B cells into the lymphoid tissues, but it is also introduced as an inflammatory chemokine in the *H. pylori*-infected mucosa and may contribute to in the pathology of chronic *H. pylori* infection [93,99]. According to the results from an *in vivo* experiment using a mouse model, it was observed that the CXCR5 deficiency reduces the Th17 cell response, but has no influence on the Th1 cell-mediated immunity against *H. pylori* infection [98]. Further, lower serum amounts of the anti-*H. pylori* IgG and IgA, and reduced gastric immune responses were detected in the CXCR5-defective mice [98].

CXCR5/CXCL13 axis may be a key player in the formation of tertiary lymphoid organ during *H. pylori*-induced gastritis. CXCR5-deficient mice unable to develop gastric lymphoid follicles, although they have similar *H. pylori* load as infected wild-type mice [94,98]. The formation of gastric lymphoid follicles in *H. suis*-infected monkeys is efficiently inhibited by the administration of anti-CXCL13 antibodies [94].

The *H. pylori*-related chronic inflammation may lead to the organization of the tertiary lymphoid tissues in the mucosa of the stomach that is also named mucosa-associated lymphoid tissue (MALT) [94,100]. The development of gastric MALT lymphoma is a multistage process that beginning with *H. pylori* infection and lead to the accumulation of B and T cells and other leukocytes into the gastric mucosa [100]. The recruited B cells are induced by the *H. pylori*-stimulated T cells and then undergo some genetic disorders that lead to their transformation to a malignant phenotype [100]. MALT represents a premalignant situation that may eventually result in the gastric MALT lymphomagenesis in a low number of chronically infected subjects. CXCL13 and CXCR5 are highly expressed in malignant areas of MALT that develop in *H. pylori*-induced stomach mucosa of humans and mice [96,101,102]. Hence, CXCL13 may be one of the key chemokines involves in the establishment of gastric MALT lymphoma associated with *Helicobacter* infection [95]. CXCL13/CXCR5 seems to contribute to the pathogenesis *H. pylori*-related diseases and may consider as an attractive therapeutic target using inhibitors such as neutralizing monoclonal antibodies and siRNA. In a mouse model of *H. suis* infection, it has been indicated that the *in vivo* CXCL13 neutralization using monoclonal antibody inhibits the formation of the gastric lymphoid follicles accompanied with higher concentrations of secretory IgA, greater expression of TGF-β (an inducer of IgA synthesis), and lower number of *Helicobacter* in stomach mucosa [94]. Although, lower number of B cells was infiltrated in the stomach after CXCL13 neutralization, the most of the IgA in gastric mucosa may be originated from the IgA^+ B lymphocytes in salivary glands [94].

Collectively, the aforementioned studies indicate that CXCL13 participates in the movement of B cells into the *H. pylori*-infected gastric tissues, induction of antibody response against *H. pylori*, formation of the gastric-related tertiary, and development of gastric MALT

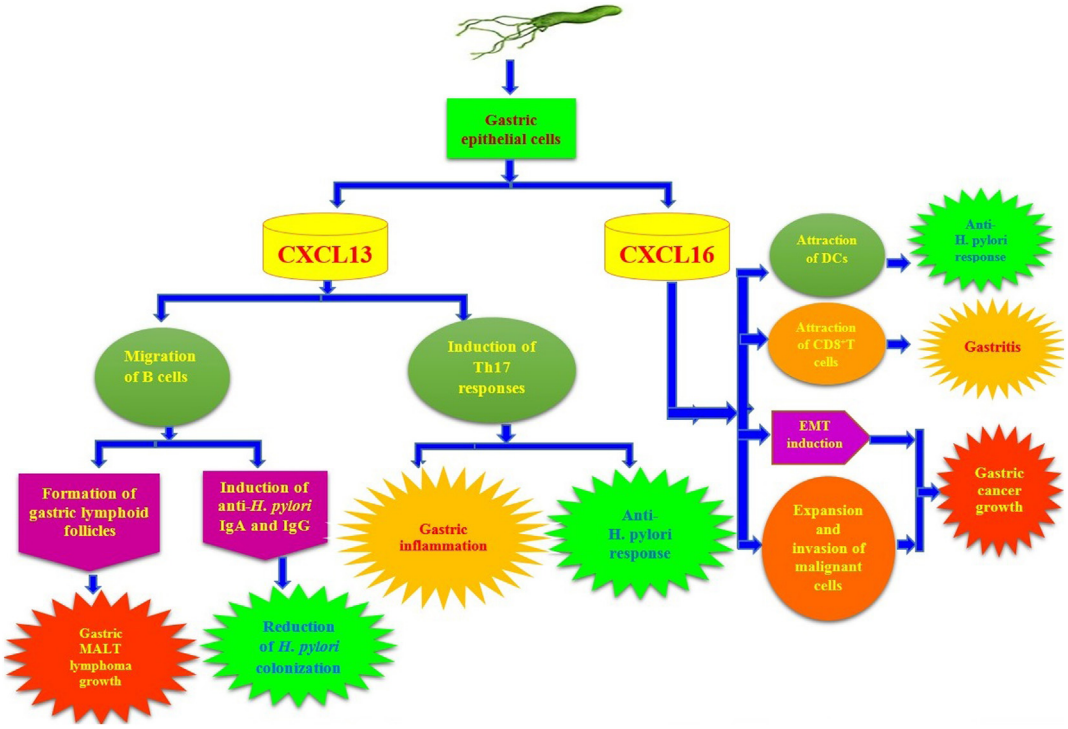

Fig. 4. The role played by CXCL13 and CXCL16 during *H. pylori* infection. CXCL13 participates in the movement of B cells into the *H. pylori*-infected gastric tissues, induction of antibody response against *H. pylori*, formation of the gastric-related tertiary, and development of gastric MALT lymphoma. CXCL13 may also contribute to the development of gastritis through attracting some mononuclear cells and induction of Th17 cell-linked responses. CXCL16 recruits $CD8^+$ T cells into infected gastric tissues, which may in turn contributes in the pathogenesis of *H. pylori*-induced gastritis. CXCL16 may also participate in the development of gastric cancer. EMT: Epithelial-mesenchymal transition.

lymphoma. Further, CXCL13 may contribute to the development of *H. pylori*-associated gastritis through attracting some mononuclear cells and induction of Th17 cell-linked responses (Fig. 4).

2.5. CXCL16

CXCL16 is produced by monocytes, macrophages, B cells, DCs, keratinocytes, and endothelial cells. The receptor of CXCL16 is named CXCR6, and this chemokine promotes the migration of $CXCR6^+$ cells, such as $CD4^+$ T cells, and NK cells [103]. CXCL16/CXCR6 axis also participates in the invasion and metastasis of tumor cells [103]. Recently, it has been indicated that *H. pylori* infection lead to the CXCL16 production in the cultured human GECs [104]. An *in vivo* analysis using a mouse model also revealed that CXCL16 leads to the accumulation of $CD8^+$ T cells into the stomach mucous, so that the blocking of CXCL16 reduces the recruitment of the $CD8^+$ T cells in the gastric mucosa [104]. Although, there are evidence indicating the contribution of the $CD8^+$ T cells in *H. pylori*-induced gastritis, the elucidation of the precise role of $CD8^+$ T cells during *H. pylori* infection needs more consideration [105]. In a co-culture model manufactured by spheroids of human GECs and DCs, it was indicated that the spheroid epithelial cells produce large quantities of CXCL1, CXCL16, CXCL17, and CCL20 that mediate DC migration and, the presence of *H. pylori* has no significant influence on the production of the CXCL16 and CXCL17 [106].

Although, there are controversies regarding the contribution of the CXCL16 in cancer developments, elevated CXCR6 expression was detected in tumor tissues from patients with gastric cancer [107]. There are evidence indicating that CXCL16/CXCR6 axis may participate in the tumor progression *via* promotion of cell proliferation, migration and invasion, and induction of EMT [107].The CXCR16/CXCR6 axis as a novel potential target for treatment *H. pylori*-mediated gastrointestinal diseases need to be evaluated in future researches. It was shown that the treatment with a neutralizing antibody against CXCL16 or down-regulation of CXCR6 reduces the invasiveness and viability of cultured human lung cancer cell lines [108]. An *in vitro* experiment also indicates that human metastatic brain CAFs recruit breast cancer cells through CXCL16, and treatment with a neutralizing anti-CXCL16 antibody reduces the migration of malignant cells toward CAFs [109].

Together, CXCL16 is involved in the movement of $CD8^+$ T cells into infected gastric tissues, which may in turn contributes in the pathogenesis of *H. pylori*-induced gastritis. Although, elucidation of the precise role of CXCL16 needs more consideration, some evidence indicates that CXCL16/CXCR6 axis may also participate in the development and progression of *H. pylori*-induced gastric cancer (Fig. 4).

3. CC chemokines

3.1. CCL5

CCL5 [also named regulated on activation normal T cell expressed and secreted (RANTES)] is produced by epithelial cells, fibroblasts, $CD8^+$ T cells, and platelets that mediates the movement and homing of T cells and monocytes through binding to its receptors CCR3 and CCR5 [110].

It has been reported that the *H. pylori*-induced CCL5 expression in cultured human GECs mainly depends on the presence of the Cag-PAI and OipA as infection with *Cag-PAI-OipA* double negative mutant cause a profound reduction in the CCL5 expression compared with single negative either *OipA* or *Cag-PAI* mutants [111]. According to *in vitro* analyses on the human GECs, it was proposed that OipA-dependent pathway leads to the induction of the p38 MAPK that triggers IRF-1, ATF-2, C/EBP that bind to certain regions in the CCL5 gene promoter and induce its expression. Cag-PAI-dependent pathway causes CCL5 expression through induction of the JNK that triggers NF-κB and c-JUN [111]. Further, the results from an *in vitro* study demonstrate that the ROS produced by NADPH oxidase activates inflammatory signaling

pathways, including JAK1/STAT-3 which induces the expression of CCL5 in *H. pylori*-infected human GECs [112]. The blood group antigen–binding adhesin (BabA) of *H. pylori* also induces the CCL5 gene promoter *via* MAPK p38 pathway in human GECs [113]. Moreover, the *in vitro* CCL2 production by human GECs is increased, whereas the CCL5 production is decreased by VacA-deficient strains compared with wild-type *H. pylori* [114].

There are reports indicating similar expression of CCL5 in the gastrointestinal mucosa of *H. pylori*-positive and *H. pylori*-negative healthy individuals [60], however, the increased CCL5 expression has been introduced as a characteristic of the *H. pylori* infection in patients with gastritis [111]. Indeed *H. pylori* induces the CCL5 expression in GECs, which may lead to the infiltration of the inflammatory cells such as lymphocytes into the infected tissues [111,115,116]. It has been indicated that *H. pylori* promotes the *in vitro* expression of the CCL2, CCL5, and GM-CSF by human GECs which cause eosinophil recruitment. A positive correlation was indicated between the CCL5 quantities in gastric mucosa and the local infiltration of eosinophils, and memory T lymphocytes in *H. pylori*-infected subjects with chronic gastritis [116] that represent the overexpression of CCL5 in the inflammatory conditions. The infiltration of the eosinophils into the human gastric mucosa is a characteristic of *H. pylori*-mediated chronic gastritis and the excessive degranulation of eosinophils promote the gastric tissue damage [117]. The persistent CCL5 expression is also related to the local aggregation of memory T cells in the gastric mucosa for a long time after *H. pylori* elimination [116].

In addition to Chemoattractant activity, CCL5 is also one of the most powerful angiogenic elements that performs a crucial role in growth, invasion, and metastasis of tumors [110] (Table 2). Higher plasma CCL5 levels were indicated in gastric adenocarcinoma patients than in healthy controls, especially in more advanced stages [118]. The greater serum CCL5 quantities were also related to lesser histological differentiation and more tumor invasion, and the overall survival rate of patients with CCL5 concentrations > 70.671 Pg/ml is lesser than patients with chemokine concentrations lower than this value [118].

It has been indicated that the *in vitro* CCL5 production by PBMCs treated with conditioned supernatants from highly metastatic gastric cancer cells is greater than in PBMCs induced by conditioned medium from gastric cancer cells with low metastatic potential [110]. According to the human and animal studies on gastric cancer, it has been concluded that CCL5 is produced by malignant cells, TAM, CAFs and $CD4^+$ tumor-infiltrating lymphocytes (TILs) that increase tumor cell growth, invasion and metastasis partly through down-regulation of gelsolin (an actin-binding protein) expression, and recruitment of the MDSCs and Treg cells [110,119] (Table 2). The invasion properties of gastric cancer cells are reduced in mice using neutralizing anti-CCL5 antibodies [110]. Further, many blockers of the CCL5/CCR5 axis are used in clinical trials and preclinical studies for treatment of various types of human cancers [110].

The data presented here indicate a potential role for CCL5 in the *H. pylori*-linked gastritis mainly through recruitment of eosinophils memory T cells. A number of cells within the microenvironment of the gastric cancer produce CCL5, which promotes tumor growth, invasion and metastasis. Thus, downregulation of the CCL5 may be considered as a therapeutic strategy to ameliorate the *H. pylori*-associated diseases (Fig. 5).

3.2. CCL17

CCL17 [also known as thymus and activation-regulated chemokine (TARC)] is constitutively expressed in thymus, and by other cells, such as keratinocytes, endothelial cells, DCs, fibroblasts and bronchial epithelial cells [120]. CCL17 signals through CCR4 and plays a pivotal role in the attracting of the $CCR4^+$ Treg and Th2 cells [120,121].

Higher expression of CCL17 was detected in the antrum biopsies from *H. pylori*-infected asymptomatic individuals compared with uninfected subjects [122]. $CCR4^+$ Treg cells are also accumulated into the non-malignant microenvironments through locally produced CCL17 or CCL22 [121]. The amounts of the CCL17 and CCL22 expression within the microenvironment of the human gastric cancer are positively associated with the number of Treg cells in the TILs [123]. In human, the gastric cancer cell-derived CCL17 and CCL22 act as attractants for Treg cells [123]. In a mouse model of *H. felis*–mediated MALT lymphoma, the most frequent of the tumor-infiltrating T cells are Treg cells that are recruited through B cell-derived chemokines CCL17 and CCL22 [124]. Interestingly, in *H. felis*-infected mice with MALT lymphoma, the Treg cell migration partly is blocked by neutralization of CCL17 and/or CCL22. Treg cell migration is completely abrogated by neutralization of

Table 2
The role of CC chemokines during *Helicobacter* infection.

Chemokines	Cell produces	Played roles	Mechanisms of action	Ref.
CCL5	- GECs	- Promotion of gastric inflammation	- Recruitment of eosinophils.	[116,200].
	- Malignant cells		- Recruitment of memory T cells.	[112,116].
	- TAMs	- Progression of gastric cancer	- Induction of angiogenesis.	[110].
	- CAFs		- Down-regulation of gelsolin	[110,119]
	- $CD4^+$ TILs		- Recruitment of Treg cells	[110,119]
			- Recruitment of MDSCs	[110,119]
CCL17	- GECs	- Development of MALT lymphoma	- Recruitment of Treg cells	(2).
	- B cells	- Progression of gastric cancer	- Recruitment of Treg cells	[123].
CCL20	- GECs	- Induction of anti-*H. pylori* immune responses	- Recruitment of DCs, ILC3, and Th17	
	- Gastric epithelial progenitor cells	- Promotion of gastric inflammation	- Recruitment of $CCR6^+$ $CD3^+$ T cells	[135].
	- Infiltrated macrophages		- Recruitment of Th17 cells	[1,131,132,135].
	- Gastric cancer cells	- Reduction of inflammatory responses	- Recruitment of $CCR6^+$ Treg cells	[139].
		- Development of gastric cancer	- Maintenance of a chronic inflammation	[140–142].
			- Induction of EMT	[144].
CCL22	- GECs	- Induction of anti-*H. pylori* antibodies	- Recruitment of Th2 cells	[152–154].
	- Infiltrated macrophages	- Reduction of *H. pylori* colonization	- Recruitment of Th2 cells	[152–154] [1].
	- Tumor cells	- Progression of gastric cancer	- Recruitment of Treg cells	[1,123,157,158,201].
		- Development of MALT lymphoma	- Recruitment of Th2 cells	[155,157,158,201].
		- Reduction of tissue injury	- Recruitment of Treg cells	[159,160]
		- Persistence of *H. pylori*	- Recruitment of the Treg cells	[159,160]
CCL25	- Mucosal epithelial cells	- Anti-H. pylori immune responses	- Recruitment macrophages and DCs	[137,138].
			- Recruitment of $CD4^+$ T cells	[175].
		- Progression of MALT lymphoma	- Proliferative effects on malignant B cells	[77].
CCL28	- Mucosal epithelial cells	- Induction of anti-*H. pylori* antibodies	- Recruitment of IgA-producing cells	[177].
			- Recruitment of $CD19^+$ B cells	[178].

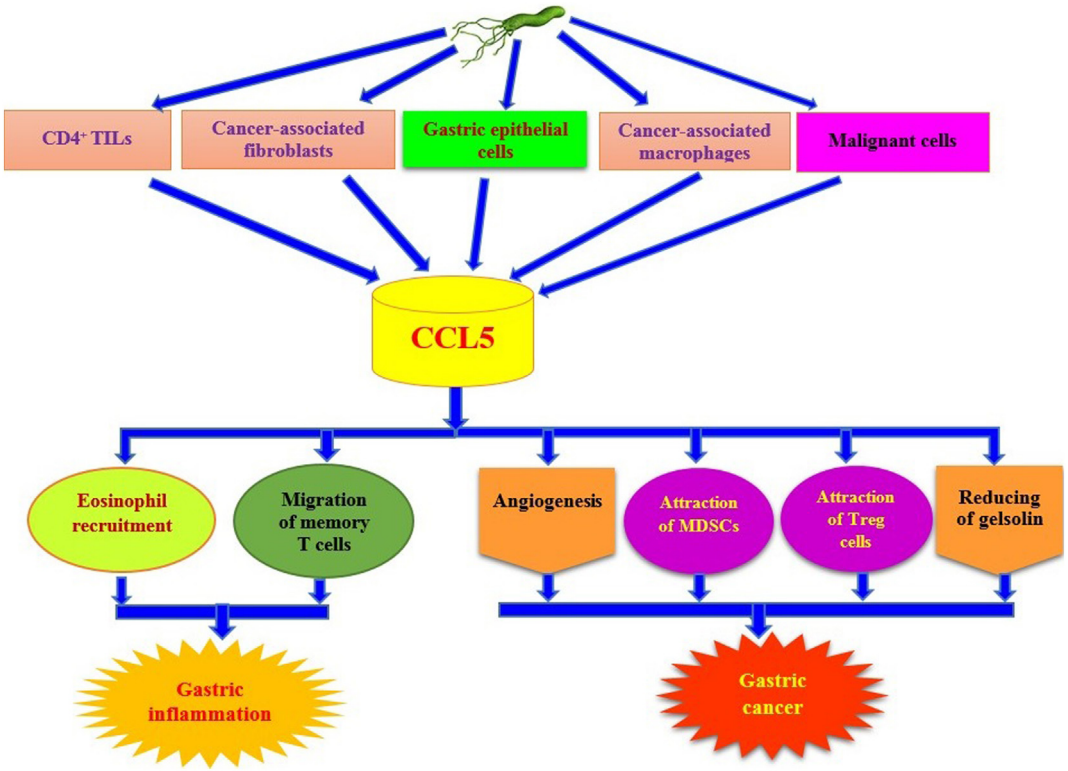

Fig. 5. The role played by CCL5 during *H. pylori* infection.
CCL5 may participate in the *H. pylori*-linked gastritis mainly through recruitment of eosinophils and memory T cells. A number of cells within the microenvironment of the gastric cancer produce CCL5, which promotes tumor growth, invasion and metastasis. TILs: Tumor-infiltrating lymphocytes.

both chemokines, together [124]. Therefore, CCL17/CCR4 axis may play a crucial role in the development of the gastric cancer and MALT lymphoma through recruiting of the Treg cells. Accordingly, the targeting of the CCL17/CCR4 axis presumably using receptor antagonists, monoclonal antibodies or siRNA may be considered as therapeutic strategies to interfere with the development of the *H. pylori*-related malignancies including MALT lymphoma and gastric cancer. For example, Mogamulizumab, a monoclonal antibody against CCR4, decreases the numbers of $CCR4^+$ Treg cells and $CCR4^+$ malignant T cells in patients with cutaneous T-cell lymphoma [125].

Together, an appropriate CCL17 expression recruits a balanced number of Treg- and Th2 cells into the *H. pylori*-infected gastric mucosa that limits serious immunopathologic reactions and tissue injury. However, the extreme CCL17 expression causes a high influx of Treg- and Th2 cells into the *H. pylori*-infected gastric mucosa that contribute in the development of the gastric cancer and MALT lymphoma (Fig. 6).

3.3. CCL20

CCL20 [also known as macrophage inflammatory protein (MIP)-3α, exodus 1, and liver and activation-regulated chemokine (LARC)] is expressed in lung, intestines, liver, thymus, skin, prostate and testis [126,127]. The organ expression of CCL20 indicates its participation in the supporting of immunological homeostasis [126]. The leukocytes include Th17 cells, $CD8^+$ T cells, neutrophils, macrophages, DCs, mast cells and endothelial cells also produce CCL20 in response to TNF-α, IL-1β, and microbial components such as LPS [126,128]. CCL20 expression is also up-regulated by other inflammation-inducing cytokines, namely, IFN-γ, IL-17, IL-21 [127]. CCL20 has only one receptor known as CCR6 that is expressed on Th17 cells, memory $CD4^+$ T- and $CD8^+$ T cells [126,129]. Further, CCR6 may be expressed by DCs, Langerhan's cells, neutrophils, NKT cells and various B cell subtypes [126,127]. As an inflammatory chemokine, CCL20 plays a main role in innate immunity and cause a marked influx of immune cells [126].

The *H. pylori*-induced mouse macrophages secrete CCL20 *in vitro* [130]. The *H. pylori* infection also triggers the CCL20 generation *in vitro* from human GECs [131]. The *in vitro* CCL20 generation by human GECs upon interaction with *H. pylori* is upregulated by proinflammatory cytokines IL-1β and TNF-α that are largely released from *H. pylori*-activated macrophages [132,133]. Significantly higher *in vitro* expression of CXCL1, CXCL5, CXCL8, and CCL20 was also indicated in human stomach-originated epithelial progenitor cells that were stimulated by wild types of *H. pylori* as compared to cells induced with T4SS-deficient strains of *H. pylori* [134].

Low number of T cells is recruited into the gastric mucosa in the absence of *H. pylori* infection. The *H. pylori*-induced CCL20 production lead to the aggregation of T cells into stomach mucosa that promotes inflammation and causes apoptosis in human GECs [135]. A considerable number of $CCR6^+$ $CD3^+$ T cells are infiltrated into the human gastric mucosa during *H. pylori* infection, and CCL20 is exclusively expressed in inflamed gastric tissues [135]. The CCL20-CCR6 interaction plays a role in lymphocyte aggregation during gastric *Helicobacter*-linked inflammation [132]. The infiltrated T cells into the human stomach mucosa are largely from $CD45RO^+CD69^+CD4^+$ T cell subset, displaying that the infiltration of activated memory $CD4^+$ T cells occur during *H. pylori* infection [133]. *H. pylori* recruits the activated $CCR6^+$ $CD4^+$ T cells into the inflamed human gastric mucosa through CCL20, and then recruited $CD4^+$ T cells induce apoptosis in the GECs *via* providing the TRAIL that interact with death receptors on epithelial cells [133,135]. During *H. pylori* infection, the degree of apoptosis induced in the human GECs is influenced by the inflammatory response [135].

CCL20 also acts as a potent chemokine for recruitment of the Th17 cells [131]. The major cytokine of Th17 cells (IL-17A) may induce gastritis through the induction of the neutrophil-attracting chemokine CXCL8 from DCs and macrophages [17]. IL-17 induces epithelial cells

Fig. 6. The role played by CCL17 and CCL22 during *H. pylori* infection.
An appropriate CCL17 and CCL22 expression recruits a balanced number of Treg- and Th2 cells into the *H. pylori*-infected gastric mucosa that limits serious immunopathologic reactions and tissue injury. An appropriate Th2 cell-related antibody response, especially sIgA reduce the bacterium colonization. However, the extreme CCL17 and CCL22 expression causes a high influx of Treg- and Th2 cells into the *H. pylori*-infected gastric mucosa that contribute in the development of the gastric cancer (GC) and MALT lymphoma.

and fibroblasts to release more proinflammatory cytokines and chemokines, which recruit more inflammatory cells into the gastric tissue and promote the gastritis [1,136]. The results from an *in vivo* investigation in *H. pylori*-infected mice indicate that the IL-17-activated GECs secrete MMP9 and chemokines CCL25 and their production is decreased when IL-17 is eliminated or neutralized [15]. MMP9 enhances the tissue damage during *H. pylori*-linked gastritis and may promote tumor invasion *via* interrupting the epithelium organization [15]. CCL25 attracts activated monocytes, macrophages, DCs, and T cells [137,138].

It has been indicated that the frequency of $CCR6^+$ Treg cells is markedly increased in gastric biopsy samples from patients with *H. pylori*-mediated gastritis, which is positively associated with the number of $CD4^+$ IFN-γ^+ T cells, while inversely is related with the number of IFN-γ^+ $CD8^+$ T cells [139]. The infiltrated $CCR6^+$ Treg cells may have a main role in the limitation of inflammation.

According to the results from an *in vitro* analysis, the *H. pylori*-induced CCL20 expression is also regulated by IL-22 [131]. *H. pylori*-induced CCL20 production in human GECs requires the activation of NF-κB, and IL-22 inhibits the CCL20 expression by reducing the NF-κB binding to the CCL20 gene promoter and by inducing the STAT3 phosphorylation in *H. pylori*-infected GECs [131]. The human GECs express IL-22R and an inverse correlation was indicated between the IL-22 expression and CCL20 production in gastric tissues from *H. pylori*-infected patients with gastritis [131]. Hence, the IL-22/IL-22R axis may act as a negative regulator for *H. pylori*-induced CCL20, inhibits the overproduction of the CCL20 in GECs, limits the vigorous inflammation and performs a main role in homeostasis.

During the initial stages of *H. pylori* infection the human GECs-derived CCL20 recruits the CCR6-bearing DCs, ILC3, and Th17 cells to limit the infection [131]. However, during the last phases of infection the presence of a protector (in this case IL-22) needs to prevent the CCL20 overexpression and limit the tissue damages caused by the inflammatory responses [131].

Experimentally, in a mouse model, it was observed that the differentiation of the Th17 cells is related to the production of IL-6, IL-23 and CCL20 by *H. pylori*-induced macrophages and is regulated through STAT3 and NF-κB pathways [130]. As regards an association between *H. pylori*-induced chronic gastritis and the expression of gastric cancer is well specified. The infiltration of Th17 cells in the *H. pylori*-infected tissues causes chronic inflammation that promotes carcinogenesis [140–142]. High plasma CCL20 levels were detected in patients with gastric cancer compared with control non-malignant group [143]. The CCL20/CCR6 axis-mediated EMT has been postulated as an initiator for gastric carcinogenesis and as a potential target for treatment of this malignancy [144]. It has been also indicated that the CCL20 production by gastric cancer cells, and the CCR6 expression by some immune cell subsets such as B cells may contribute in the organization of lymphoid compartments in a lymphocyte-rich gastric cancer [145]. In a mouse model of colorectal cancer, it was indicated that the TAM recruit $CCR6^+$ Treg cells and promote the tumor progression through CCL20 production. The targeting of CCL20 (or reducing the TAM activity) or its receptor CCR6 have been also presented as promising strategies for the treatment of colorectal cancer [146].

Collectively, the aforementioned studies indicate the proper expression of CCL20 may involve in the *H. pylori* limitation through attracting of a balanced number of the CCR6-expressing DCs, ILC3, and Th17 cells into the gastric mucosa, which in turn trigger balanced

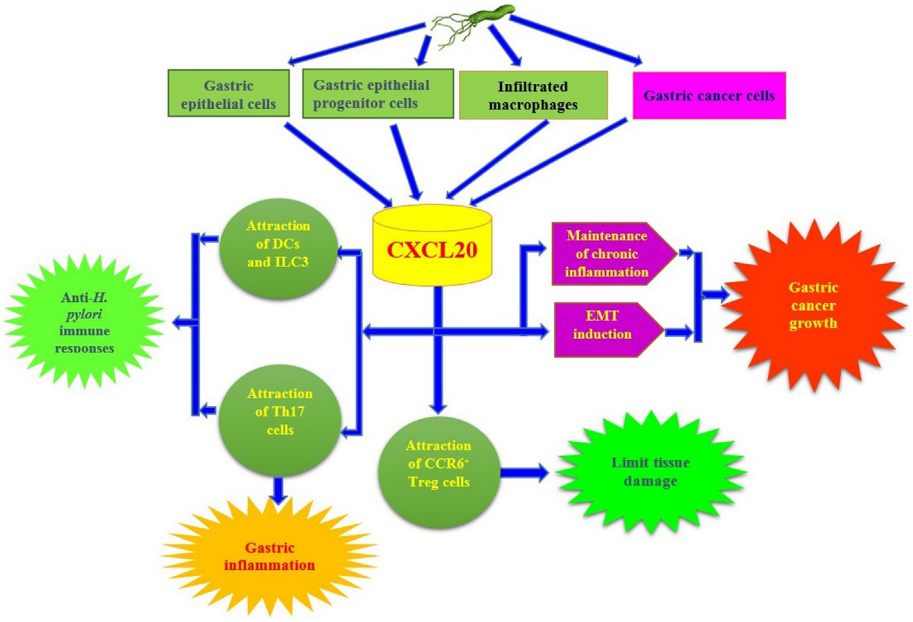

Fig. 7. The role played by CCL20 during *H. pylori* infection. The proper expression of CCL20 may involve in the *H. pylori* limitation through attracting of a balanced number of the CCR6-expressing DCs, ILC3, and Th17 cells into the gastric mucosa, which in turn trigger balanced immune responses against bacterium. The overexpression of the CXCL20 may lead to the large influx of $CCR6^+$ $CD3^+$ T cells, (such as Th17 cells) into the gastric mucosa, which finally cause gastritis and tissue damage. The CCL20/CCR6 axis may also promote gastric carcinogenesis process. ILC3: Innate lymphoid cells-3,

immune responses against bacterium. However, overexpression of the CXCL20 may lead to the large influx of $CCR6^+$ $CD3^+$ T cells, (such as Th17 cells) into the gastric mucosa, which finally cause gastritis and tissue damage by induction of neutrophil-attracting chemokines and MMPs, and by induction of apoptosis in the GECs. The CCL20/CCR6 axis may also promote gastric carcinogenesis process (Fig. 7).

3.4. CCL22

CCL22 (also named as macrophage-derived chemokine) is produced by macrophages and DCs upon the stimulation by microbial products (such as LPS), or CD40 ligand, and is upregulated by Th2 cell-type cytokines (such as IL-4 and IL-5), but is downregulated by Th1 cell-type cytokines (such as IFN-γ) [121,147]. The CCL22 receptor is named CCR4 that is mostly expressed on Treg- and Th2 cells and accordingly CCL22 causes the movement of $CCR4^+$ T cells, including Treg- and Th2 cells into the inflammatory sites [121,128].

In humans, the increased CCL22 expression has been detected in the *H. pylori*-infected mucosa in comparison with uninfected mucosa [60]. The freshly separated epithelial cells from *H. pylori*-infected patients with PU also secrete CCL22 [148,149]. The elevated number of $CD4^+$ T cells was observed in stomach biopsy samples from *H. pylori*-positive healthy individuals that express high amounts of homing receptor L-selectin, and CCR4 as a CCL22 receptor [60]. Further, the gastric $CD4^+$ T cells isolated from *H. pylori*-infected healthy individuals display the low amounts of CXCR3 expression [60]. The CXCR3 was related with the production of Th1 cell-related cytokines, while CCR4 was associated with the Th2 cell polarization [150].

The Th2 cell-related humoral responses confer immunity against extracellular pathogens, however, in a mouse model it has been reported that the Th2 cell-linked protective responses against *H. pylori* are poorly triggered [1,151]. The local and systemic specific IgA, IgM and IgG against *H. pylori* were detected in infected individuals [152]. The results from studies on humans and mice indicate that the anti-*H. pylori* antibodies, in particular secretory IgA, can diminish the *H. pylori* attachment to the GECs, reduce bacterium colonization and efficiently limit infection [153,154]. The adoptive transfer of Th2 cell from the *H. felis*-immunized mice into unimmunized naïve mice reduces the bacterial burden after challenging the latter group with live bacterium. The increased *H. pylori* load was also indicated in IL-4-defective mice [153], that support the preventive role for Th2 cells against the bacterium colonization (Table 2).

A dominant Th2 cell activity was indicated in patients with *H. pylori*-related intestinal and gastric malignancies [155]. The gastric MALT lymphomas in mice are also infiltrated by great numbers of Th2 cells expressing related cytokines [124,156]. The overproduction of GATA-3 (a chief transcription factor of Th2 cells) was also indicated in T cells separated from patients with *H. pylori*-associated gastric carcinoma, which is associated with a poor prognosis [157,158]. Further, GATA-3 down-regulates Connexin 43 (a tumor suppressor protein) in patients with *H. pylori*-related gastric malignancies [158].

CCR4 may also contribute in the mucosal recruitment of the Treg cells into the stomach mucosa during *H. pylori* infection [1]. Treg cells powerfully inhibit the effector T cells and limit the inflammatory responses to *H. pylori* in humans by producing modulatory cytokines such as IL-10, TGF-β and IL-35 [159,160]. Although, this process may limit tissue injury, but lead to the bacterium persistence and is related to chronic gastritis and development of the gastric adenocarcinoma [159,161,162].

Despite the induction of the inflammation and immune responses, the elimination of the *H. pylori* is often incomplete, which is attributed to the Treg cell activation [163]. The *H. pylori*-infected PU patients exhibit lower gastric Treg cell, but higher Th1- and Th2 cell activity than infected individuals without ulcers, indicates a deviation in the balances between Treg- and Th1/Th2 cells which may predispose the development of *H. pylori*-related disorders [164].

According to the *in vivo* studies in mice and humans, it has been revealed that the Treg cells promote *H. pylori* colonization, reduce gastritis, and diminish immunopathologic responses in *H. pylori* infection through the suppression of the IFN-γ producing $CD4^+$ T cells [165,166]. Further, T cells isolated from Treg cell-deficient mice exhibit an enhanced expression of the Th2 cytokines after *in vitro* stimulation with *H. pylori*-derived crude extract, represent a role for Treg cells not only in downregulating of the Th1 cell response, but also in modulating of the Th2 cell response [167].

Within the tumor microenvironment, the tumor cells and local macrophages can secrete CCL22 [168,169] and the CCR4-CCL22 interaction is essential for the recruitment of Treg cell to *H. pylori*-induced gastric adenocarcinoma in humans that impair anti-tumor immunity [123,170]. It has been observed that the overexpression of CCR4 in the human gastric cancer specimens contributes to the tumor-mediated immunosuppression, and inhibition of CCR4 restore the antitumor

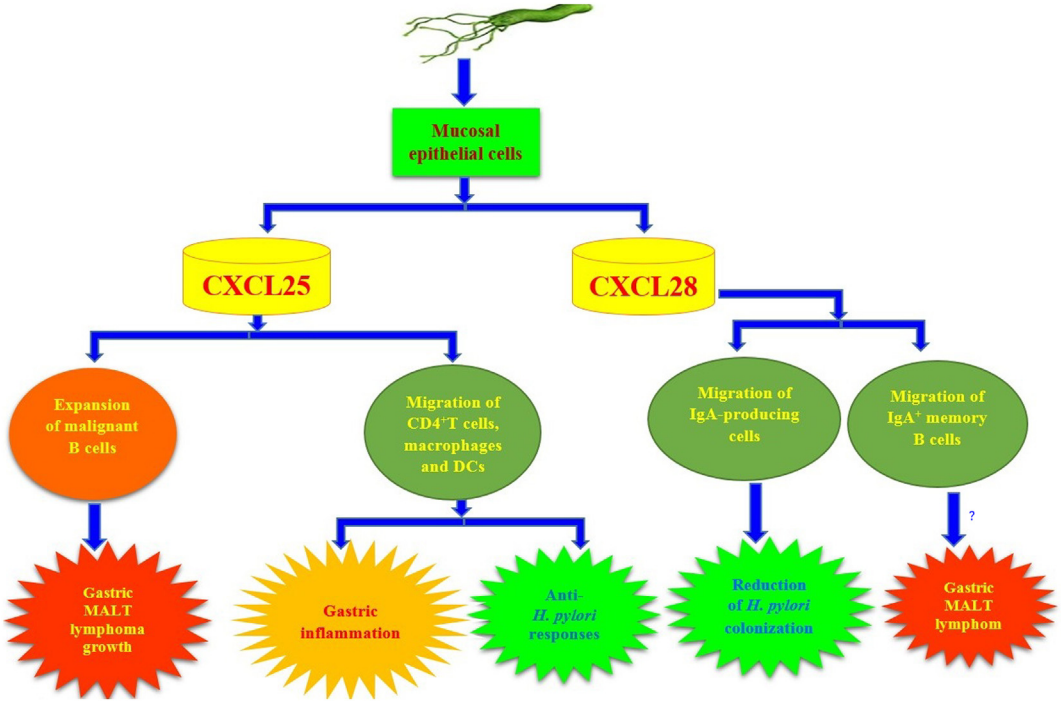

Fig. 8. The role played by CCL25 and CCL28 during *H. pylori* infection. CCL25 may participates in the induction of anti-*H. pylori* immune responses *via* attracting macrophages, DCs and $CD4^+$ T cells. CCL25 also expands malignant cells. CCL28 expression may contribute mainly to the induction of the mucosal antibody responses against *H. pylori* through recruitment of the antibody secreting cells, which limit bacterium colonization.

immunity [171]. Experimentally, in a mouse model of ovarian cancer, it has been indicated that *in vivo* administration of the blocking anti-CCR4 antibodies promotes the antitumor immunity by reducing the tumor-infiltrating Treg cells [172]. Using a mouse model, it was indicated that a great number of tumor-infiltrating $CD4^+$ T cells in MALT lymphoma are Treg cells with highly suppressive activity, that are attracted *via* tumor cell-derived chemokines CCL17 and CCL22, which bind to a unique receptor CCR4 [124]. MALT lymphoma B cells may actively recruit Treg cells to the tumor microenvironment in a CCL17- and CCL22-dependent manner [124]. These observations represent that Treg cell accumulation in the tumor microenvironment may be blocked by CCL17 and CCL22 neutralization. In a mouse model of hepatocarcinoma, it has been indicated that the treatment of the tumor-bearing mice with monoclonal antibody against CCL17 and/or CCL22 decreases the numbers of the tumor infiltrated Treg cells [173].

Collectively, a suitable CCL22 expression recruits a balanced number of Th2- and Treg cells into the *H. pylori*-infected gastric mucosa. An appropriate Th2 cell-related antibody response, especially sIgA can confer resistance against *H. pylori* infection through reducing the attachment of bacterium to the GECs, and preventing its colonization. Further, a suitable Treg cell-mediated response limits severe immunopathologic reactions and tissue damage, and may lead to an asymptomatic infection. However, the excessive expression of the CCL22 causes a high influx of Th2- and Treg cell cells into the *H. pylori*-infected gastric mucosa that contribute in the MALT lymphoma and gastric cancer development.

3.5. CCL25

CCL25 [also known as thymus-expressed chemokine (TECK)] is a ligand for CCR9 which is expressed on the some precursors of T cells [174]. Therefore, the CCL25/CCR9 axis plays a major role in the recruitment of the T cell precursors from the bone marrow to the thymus [174]. Further, CCL25 is expressed by mucosal epithelial cells in the small intestine, hence, CCL25/CCR9 axis also performs an essential role in the homing of $CCR9^+$ T- and B cells to the small intestine [174].

As mentioned, IL-17 stimulates mice GECs to produce CCL25 that acts as a chemoattractant for activated monocytes, macrophages, DCs and T cells [15,137,138]. Further, it has been demonstrated CCL25-CCR9 interaction contributes in the migration of *H. felis*-specific $CD4^+$ T lymphocytes into the infected gastric mucosa [175]. It has been indicated that the serum levels CCL25 in *H. pylori*-infected children with gastroduodenitis were greater than those were negative for bacteria [176]. However, similar amounts of CCL25 expression were reported in gastric mucosa from healthy subjects with- and without *H. pylori* infection [177]. It was also reported that *H. pylori* infection has no significant influence on the CCL25 expression in the stomach mucosa of mice [178].

CCL25/CCR9 axis also plays a main role in the tumorigenesis and contributes to the tumor chemoresistance and metastasis in humans [179]. Besides the homing properties, anti-apoptotic and proliferating effects have been attributed to CCL25/CCR9 axis in various cancer cell lines [179]. As CCR9 is expressed in human MALT lymphoma and extranodal diffuse large B-cell lymphoma likewise, it has been postulated that CCR9 may contribute to the localization of the gastric extranodal lymphoma and involve in the conversion of the low proliferating MALT lymphoma to the high proliferating extranodal diffuse large B-cell lymphoma [77]. Therefore, CCL25/CCR9 axis may be a potential targeted molecule for cancer therapy because it is highly expressed in various cancers [179]. For instance, it was revealed that the CCR9-CCL25 axis exerts anti-apoptotic effects on the human prostate cancer cell lines *in vitro* through suppression of caspase-3 activity, which is blocked using anti-CCR9 antibody [180]. Further, treatment of the prostate cancer-bearing mice with neutralizing antibody against CCL25 decreases the tumor sizes in combination with a chemotherapeutic agent [180].

According to the aforesaid studies, there are evidence regarding the influences of *H. pylori* infection on the CCL25 expression. CCL25 may participate in the induction of anti-*H. pylori* immune responses *via* attracting macrophages, DCs and $CD4^+$ T cells. CCL25 also expands malignant cells. However, the elucidation of the precise role of CCL25 in the immune response to bacterium and in the pathogenesis of *H.*

pylori-mediated complication should be considered in future investigations (Fig. 8).

3.6. CCL28

CCL28 [also known mucosa-associated epithelial chemokine (MEC)] is a common mucosal chemokine, which is constitutively expressed by epithelial cells in most mucosal sites [181]. The CCL28 expression is promoted by pro-inflammatory cytokines and some bacterial components [181]. CCL28 induces the mucosal homing of $CCR10^+$ T- and $CCR10^+$ B cells, and the migration of $CCR3^+$ eosinophils [177,181]. CCL28/CCR10 axis also plays an essential role in the Treg cell accumulation into the tumor microenvironment [182]. Both CCL28 and CCL25 play a key role in the lymphocyte migration to gastrointestinal tissues. CCL28 attracts IgA-producing cells, but not IgG- or IgM-secreting cells, from both intestinal and extraintestinal mucosal tissue, while CCL25 preferentially attracts IgA-producing cells from the small intestine and its draining lymphoid tissues, as well as $\alpha4\beta7^+$ T cells [177,181,183].

The sublingual immunization of mice with *H. pylori* lysate causes immunity against challenge with live *H. pylori*, which is associated with high levels *H. pylori*-specific IgG and IgA in the gastrointestinal system, and with strong IFN-γ and IL-17 expression in the stomach [178]. Enhanced infiltration of $CD4^+$ T cells and $CD19^+$ B cells into the *H. pylori*-infected mouse stomach mucosa is accompanied with high expression of the MAdCAM-1 and CXCL10 and CCL28 [178].

Following the human mucosal immunization with an inactivated vaccine, *H. pylori* infection leads to the induction of B cell response and great infiltration of IgA-producing cells in the gastric mucosa [184]. The gastric tissue from *H. pylori*-infected individuals express elevated CCL28 levels than uninfected individuals. The high expression of CCL28 lead to a great influx of IgA-producing cells in the human gastric mucosa during *H. pylori* infection [177]. The IgA-producing cells and IgA^+ memory B cells from *H. pylori*-infected human tissues are migrated *in vitro* toward CCL28 but not CCL25 [177].

Collectively, the proper CCL28 expression may contribute mainly to the induction of the mucosal antibody responses against *H. pylori* through recruitment of the antibody secreting cells, which may limit the attachment of bacterium to the GECs, and prevent its colonization. The exact contribution of the CCL28 in the pathogenesis of *H. pylori*-related disorders is not clear. If the involvement of the CCL28 in the *H. pylori*-related diseases is proven, then the targeting of CCL28 and/or its receptors may be considered as a therapeutic goal (Fig. 8). For example, the results from an *in vitro* analysis are indicated that the expression of VEGF by Treg cells, and the Treg cell movement toward liver cancer cell-derived supernatant are efficiently reduced using an anti-CCL28 antibody [185].

4. Other chemokines

CXCL-1 to 6 are powerful neutrophil attractants that play a pivotal role in the reinforcement of inflammation. In an *in vitro* experiment, it was found that *H. pylori* stimulates human GECs to express CXCL1, CXCL2, CXCL3 CXCL5, CXCL8 and CCL20 [186]. Further, CagA abolishes the TGF-β-mediated inhibition of the CXCL1, CXCL3 and CXCL8 from cultured human GECs [187].

Both *H. pylori* and *H. felis* induce mice GECs to produce CXCL1 and CXCL2 *in vitro* [188]. The expression of the CXCL1 and CXCL2 is also increased in gastric tissues from *Helicobacter*-infected mice [188]. It has been indicated that estradiol prevents the *H. pylori*-mediated gastric cancer in mice, partly through downregulation of in the CXCL1 expression [189].

Elevated quantities of the CXCL5 and CXCL6 were also detected in the serum from teenagers with gastroduodenitis [176]. It has been proposed that IL-17 induces human GECs and local macrophages to produce CXCL5 and CXCL6, which promote the neutrophil accumulation in the gastric tissue during *H. pylori* infection [176].

The expression of the CXCL1, CXCL2, CXCL5, CCL3, and CCL4, which may have tumor-promoting properties, is also promoted in *H. pylori*-mediated gastritis and gastric cancer *via* COX2/PGE2-dependent pathways in mice and humans [190].

CCL7 also known as monocyte chemotactic protein-3 (MCP-3) recruits monocytes to the inflammatory sites through binding to several receptors, including CCR1, CCR2, CCR3, and CCR5 [191]. It was reported that CCL7 expression in the serum and adipose tissues from *H felis*-infected obese mice was higher than lean mice, which represent that diet may influence the chemokine production [192]. Moreover, a *H. pylori*-derived protein, namely TNF-α inducing protein (Tipalpha) induces the expression of the several chemokines such as CXCL1, CXCL2, CXCL5, CXCL10, CCL2, CCL7 and CCL20 by mouse gastric cancer cells *in vitro* [193].

The immunization of the C57BL/6 mice with *H. pylori* lysate also causes higher expression of T cell- (CXCL10, CXCL11, CCL19 and CCL20), DC- (CCL19 and CCL20), neutrophil- (CXCL2 and CXCL5) and eosinophil- (CCL8) attracting chemokines, and their receptors in the stomach after challenging with live bacteria compared with unimmunized mice [194]. A reduction in the *H. pylori* load was also associated with an increasing in the expression of the aforementioned chemokines [194]. These data indicate that vaccination with *H. pylori* antigens induces chemokines that guide the aggregation of the leukocytes into the stomach of *H. pylori*-infected mice.

5. Conclusion

H. pylori induces GECs and infiltrated leukocytes to produce different kinds of chemokines. Chemokine profiles determine the outcome of *H. pylori* infection through orchestrating of the immune responses. The protection against *H. pylori* is dependent on the induction of appropriate specific Th1- or Th17 cell responses. However, excessive uncontrolled Th1/Th17 cell responses are associated with the development of the more severe *H. pylori*-related pathologies (including PU and gastritis) due to the induction of immunopathologic reactions [1]. Therefore, the suitable and balanced expression of the Th1-cell-attracting chemokines (such as CXCL9, CXCL10 and CXCL11) and Th17 cell-attracting chemokines (such as CCL20) orchestrate the adequate recruitment of Th1- and Th17 cells into the *H. pylori*-infected mucosa that cause *H. pylori* containment. However, the excessive and unbalanced expression of the Th1- and Th17 cell-attracting chemokines lead to the very high recruitment of Th1- and Th17 cells into the *H. pylori*-infected mucosa that may cause PU and gastritis. On the other hand, the Th2/Treg cell-mediated responses modulate inflammatory responses and tissue damage, but results in the bacteria persistence and contribute to the *H. pylori*-related malignancies [1]. Accordingly, the suitable expression of the Th2- and Treg cell-attracting chemokines orchestrate a balanced recruitment of the Th2- and Treg cells into the *H. pylori*-infected mucous that prevent tissue damage in the presence of *H. pylori* and lead to an asymptomatic infection. However, the excessive expression of the Th2- and Treg cell-attracting chemokines (such as CCL17 and CCL22) lead to very high recruitment of Th2- and Treg cell cells into the *H. pylori*-infected mucosa that contribute to the MALT lymphoma and gastric cancer. Overall, the overexpression of the lymphocyte-attracting chemokines, especially B cell-attracting chemokines (such as CXCL13) may involve in the MALT lymphoma. Therefore, chemokines may perform a protective or pathologic roles during *H. pylori*-infection.

The proper and balanced expression of chemokine and chemokine receptor is a fundamental stage in the normal immune responses. The expression of chemokines and their receptors is impaired in different types of immunopathologic situations such as infectious, autoimmune and malignant disorders [195]. At early phase of *H. pylori* infection, it mainly induces GECs to express chemokines, which attract various types of leukocytes, which in turn shape the nature of the innate and

adaptive immunity against bacteria. As mentioned, *H. pylori* infection persists for many years or for lifetime despite the induction of potent immune responses [18]. The inability in the *H. pylori* eradication may lead to the extended epithelial cell hyper-activation and overproduction of chemokines that cause excessive and uncontrolled chronic inflammation. The absence of the modulatory mechanisms such as anti-inflammatory elements also promotes the development of the immunopathologic consequences or malignancies. Chemokines as the key elements of inflammation, act as double-edged swords. During the early phase of infection, the proper expression of chemokines exerts beneficial effects due to attracting of leukocytes, which in turn induce immune responses against infectious agent. However, during chronic inflammation a gradual deviation may take places on the expression of the chemokines, which eventually may lead to tissue damage or malignancy. The inflammatory elements may help tumor growth *via* promoting cell proliferation, stimulating the angiogenesis, inducing the DNA damage, remodeling of the cytoskeleton, and triggering the extracellular matrix degradation [196,197].

Therefore, during the early phase of *H. pylori* infection, the directing of the chemokine expression in a correct direction may lead to the bacteria elimination and prevents its progression to the chronic inflammation. After the occurrence of *H. pylori*-related clinical complications, the targeting of the chemokines and/or their receptors may have therapeutic application. Due to the differential involvement of the some chemokines in the different *H. pylori*-related clinical complications, the targeting of certain chemokines may be more efficient in the treatment of a particular *H. pylori*-related disease.

Chemokines also regulate the infiltration of the leukocytes into the tumor microenvironment. There are clear evidence displaying that chemokines exert bi-functional effects, including tumor promoting- and tumor preventing capabilities [198]. Some chemokines, such as Th1 cell-, CTL- and NK cell-attracting chemokines promote anti-tumor activities, whereas Th2 cell- and Treg cell-attracting chemokines promote pro-tumor activities [195]. Some infiltrated leukocytes (such as macrophages and neutrophils) into the tumor microenvironment, exhibit plasticity and acquire anti-tumor or pro-tumor properties depending on the tumor microenvironment factors [195,199]. Further, chemokines are directly involved in the some tumor-linked processes, such as tumor cell expansion, angiogenesis, and metastasis [198]. Accordingly, it seems that before tumor establishment, the proper expression of chemokines has beneficial effects, whereas after tumor establishment the deleterious effects may overcome the beneficial influences. The aforementioned descriptions clearly highlight that a certain chemokine may exerts fruitful or deleterious effects depending on the situations and times of action. Therefore, determination of the time ranges in which chemokines perform beneficial or harmful during the infectious, autoimmune and malignant diseases need more consideration for designing more efficient interventions.

It should be also noted that several factors such as host genetic, bacterial strain, or nutritional status may influence the gastric expression of chemokines. Understanding the factors influencing the expression of chemokines and their receptors is essential for designing the effective therapeutic strategies against *H. pylori*-mediated disorders. The chemokine-related pathways may be inhibited using the antibodies (that bind chemokines or their receptors), small molecule inhibitors of chemokines and chemokine receptors, and siRNA that prevent the translation of chemokines and their related receptors. The targeting of the chemokines/chemokine receptors, alone or in combination with other therapeutic agents needs to be evaluated as promising strategies for treatment of the *H. pylori*-related complications.

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Declaration of Competing Interest

The authors have no any conflict of interest.

References

[1] A. Jafarzadeh, T. Larussa, M. Nemati, S. Jalapour, T cell subsets play an important role in the determination of the clinical outcome of Helicobacter pylori infection, Microb. Pathog. 116 (2018) 227–236.
[2] A. Jafarzadeh, M.T. Rezayati, M. Nemati, Specific serum immunoglobulin G to H pylori and CagA in healthy children and adults (south-east of Iran), World J. Gastroenterol. 13 (22) (2007) 3117–3121.
[3] A. Jafarzadeh, M.T. Rezayati, M. Nemati, Helicobacter pylori seropositivity in patients with type 2 diabetes mellitus in south-east of Iran, Acta medica Iranica 51 (12) (2013) 892–896.
[4] A. Jafarzadeh, V. Akbarpoor, M. Nabizadeh, M. Nemati, M.T. Rezayati, Total leukocyte counts and neutrophil-lymphocyte count ratios among Helicobacter pylori-infected patients with peptic ulcers: independent of bacterial CagA status, The Southeast Asian journal of tropical medicine and public health 44 (1) (2013) 82–88.
[5] A. Jafarzadeh, A. Esmaeeli-Nadimi, M. Nemati, M. Tahmasbi, P. Ahmadi, Serum concentrations of Helicobacter pylori IgG and the virulence factor CagA in patients with ischaemic heart disease, Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit 16 (10) (2010) 1039–1044.
[6] S. Nejati, A. Karkhah, H. Darvish, M. Validi, S. Ebrahimpour, H.R. Nouri, Influence of Helicobacter pylori virulence factors CagA and VacA on pathogenesis of gastrointestinal disorders, Microb. Pathog. 117 (2018) 43–48.
[7] A.P. Gobert, K.T. Wilson, Human and Helicobacter pylori interactions determine the outcome of gastric diseases, Curr. Top. Microbiol. Immunol. 400 (2017) 27–52.
[8] A. Jafarzadeh, M. Salari, Seroprevalence of anti-Helicobacter pylori and anti-CagA antibodies in peptic ulcer and healthy subjects in the city of Rafsanjan, Journal of Research in Medical Sciences 11 (5) (2006) 285–291.
[9] A. Jafarzadeh, M. Nemati, M.T. Rezayati, M. Ebrahimi, H. Abdollahi, Higher circulating levels of anti-phosphatidylserine antibody in peptic ulcer patients infected with CagA-positive strains of Helicobacter pylori, Clin. Lab. 59 (9–10) (2013) 977–984.
[10] A. Jafarzadeh, G.H. Hassanshahi, M. Nemati, Serum levels of high-sensitivity C-reactive protein (hs-CRP)in helicobacter pylori-infected peptic ulcer patients and its association with bacterial CagA virulence factor, Dig. Dis. Sci. 54 (12) (2009) 2612–2616.
[11] F. Sayehmiri, F. Kiani, K. Sayehmiri, S. Soroush, K. Asadollahi, M.Y. Alikhani, A. Delpisheh, M. Emaneini, L. Bogdanovic, A.M. Varzi, R. Zarrilli, M. Taherikalani, Prevalence of cagA and vacA among Helicobacter pylori-infected patients in Iran: a systematic review and meta-analysis, Journal of infection in developing countries 9 (7) (2015) 686–696.
[12] A. Polenghi, F. Bossi, F. Fischetti, P. Durigutto, A. Cabrelle, N. Tamassia, M.A. Cassatella, C. Montecucco, F. Tedesco, M. de Bernard, The neutrophil-activating protein of Helicobacter pylori crosses endothelia to promote neutrophil adhesion in vivo, Journal of immunology (Baltimore, Md.: 1950) 178 (3) (2007) 1312–1320.
[13] K. Robinson, R.H. Argent, J.C. Atherton, The inflammatory and immune response to Helicobacter pylori infection, Best Pract. Res. Clin. Gastroenterol. 21 (2) (2007) 237–259.
[14] H. Abdollahi, S. Shams, M.J. Zahedi, S. Darvish Moghadam, M.M. Hayatbakhsh, A. Jafarzadeh, IL-10, TNF-alpha and IFN-gamma levels in serum and stomach mucosa of Helicobacter pylori-infected patients, Iranian journal of allergy, asthma, and immunology 10 (4) (2011) 267–271.
[15] Y. Shi, X.F. Liu, Y. Zhuang, J.Y. Zhang, T. Liu, Z. Yin, C. Wu, X.H. Mao, K.R. Jia, F.J. Wang, H. Guo, R.A. Flavell, Z. Zhao, K.Y. Liu, B. Xiao, Y. Guo, W.J. Zhang, W.Y. Zhou, G. Guo, Q.M. Zou, Helicobacter pylori-induced Th17 responses modulate Th1 cell responses, benefit bacterial growth, and contribute to pathology in mice, Journal of immunology (Baltimore, Md.: 1950) 184 (9) (2010) 5121–5129.
[16] S. Nagai, H. Mimuro, T. Yamada, Y. Baba, K. Moro, T. Nochi, H. Kiyono, T. Suzuki, C. Sasakawa, S. Koyasu, Role of Peyer's patches in the induction of Helicobacter pylori-induced gastritis, Proc. Natl. Acad. Sci. 104 (21) (2007) 8971–8976.
[17] T. Larussa, I. Leone, E. Suraci, M. Imeneo, F. Luzza, Helicobacter pylori and T helper cells: mechanisms of immune escape and tolerance, J Immunol Res 2015 (2015) 981328.
[18] A. Walduck, L.P. Andersen, S. Raghavan, Inflammation, immunity, and vaccines for Helicobacter pylori infection, Helicobacter 20 (Suppl. 1) (2015) 17–25.
[19] O.M. Koper, J. Kaminska, K. Sawicki, H. Kemona, CXCL9, CXCL10, CXCL11, and their receptor (CXCR3) in neuroinflammation and neurodegeneration, Advances in clinical and experimental medicine: official organ Wroclaw Medical University 27 (6) (2018) 849–856.
[20] A.E. Vilgelm, A. Richmond, Chemokines modulate immune surveillance in tumorigenesis, metastasis, and response to immunotherapy, Front. Immunol. 10 (2019) 333.
[21] V. Bagheri, G. Hassanshahi, V. Mirzaee, H. Khorramdelazad, CXC chemokine CXCL12 tissue expression and circulating levels in peptic ulcer patients with Helicobacter pylori infection, Cytokine 85 (2016) 1–4.
[22] H. Ha, B. Debnath, N. Neamati, Role of the CXCL8-CXCR1/2 axis in cancer and inflammatory diseases, Theranostics 7 (6) (2017) 1543–1588.
[23] P.A. Ruffini, The CXCL8-CXCR1/2 axis as a therapeutic target in breast cancer

stem-like cells, Front. Oncol. 9 (40) (2019) 40.
[24] T. Ando, K. Kusugami, M. Ohsuga, M. Shinoda, M. Sakakibara, H. Saito, A. Fukatsu, S. Ichiyama, M. Ohta, Interleukin-8 activity correlates with histological severity in Helicobacter pylori-associated antral gastritis, Am. J. Gastroenterol. 91 (6) (1996) 1150–1156.
[25] Z. Fazeli, M. Alebouyeh, M. Rezaei Tavirani, M. Azimirad, A. Yadegar, Helicobacter pylori CagA induced interleukin-8 secretion in gastric epithelial cells, Gastroenterology and hepatology from bed to bench 9 (Suppl1) (2016) S42–s46.
[26] M. Eck, B. Schmausser, K. Scheller, A. Toksoy, M. Kraus, T. Menzel, H.K. Muller-Hermelink, R. Gillitzer, CXC chemokines Gro(alpha)/IL-8 and IP-10/MIG in Helicobacter pylori gastritis, Clin. Exp. Immunol. 122 (2) (2000) 192–199.
[27] M. Tafreshi, J. Guan, R.J. Gorrell, N. Chew, Y. Xin, V. Deswaerte, M. Rohde, R.J. Daly, R.M. Peek Jr., B.J. Jenkins, E.M. Davies, T. Kwok, Helicobacter pylori type IV secretion system and its adhesin subunit, CagL, mediate potent inflammatory responses in primary human endothelial cells, Front. Cell. Infect. Microbiol. 8 (2018) 22.
[28] W. Fischer, Assembly and molecular mode of action of the Helicobacter pylori Cag type IV secretion apparatus, FEBS J. 278 (8) (2011) 1203–1212.
[29] S. Brandt, T. Kwok, R. Hartig, W. Konig, S. Backert, NF-kappaB activation and potentiation of proinflammatory responses by the Helicobacter pylori CagA protein, Proc. Natl. Acad. Sci. U. S. A. 102 (26) (2005) 9300–9305.
[30] C.T. Tran, M. Garcia, M. Garnier, C. Burucoa, C. Bodet, Inflammatory signaling pathways induced by Helicobacter pylori in primary human gastric epithelial cells, Innate immunity 23 (2) (2017) 165–174.
[31] C.C. Allison, J. Ferrand, L. McLeod, M. Hassan, M. Kaparakis-Liaskos, A. Grubman, P.S. Bhathal, A. Dev, W. Sievert, B.J. Jenkins, R.L. Ferrero, Nucleotide oligomerization domain 1 enhances IFN-gamma signaling in gastric epithelial cells during Helicobacter pylori infection and exacerbates disease severity, Journal of immunology (Baltimore, Md.: 1950) 190 (7) (2013) 3706–3715.
[32] D.N. Horridge, A.A. Begley, J. Kim, N. Aravindan, K. Fan, M.H. Forsyth, Outer inflammatory protein a (OipA) of Helicobacter pylori is regulated by host cell contact and mediates CagA translocation and interleukin-8 response only in the presence of a functional cag pathogenicity island type IV secretion system, Pathogens and disease 75 (8) (2017).
[33] Y. Yamaoka, T. Kudo, H. Lu, A. Casola, A.R. Brasier, D.Y. Graham, Role of interferon-stimulated responsive element-like element in interleukin-8 promoter in Helicobacter pylori infection, Gastroenterology 126 (4) (2004) 1030–1043.
[34] S. Maeda, M. Akanuma, Y. Mitsuno, Y. Hirata, K. Ogura, H. Yoshida, Y. Shiratori, M. Omata, Distinct mechanism of Helicobacter pylori-mediated NF-kappa B activation between gastric cancer cells and monocytic cells, J. Biol. Chem. 276 (48) (2001) 44856–44864.
[35] J. Hisatsune, M. Nakayama, H. Isomoto, H. Kurazono, N. Mukaida, A.K. Mukhopadhyay, T. Azuma, Y. Yamaoka, J. Sap, E. Yamasaki, K. Yahiro, J. Moss, T. Hirayama, Molecular characterization of helicobacter pylori VacA induction of IL-8 in U937 cells reveals a prominent role for p38MAPK in activating transcription factor-2, cAMP response element binding protein, and NF-kappaB activation, Journal of immunology (Baltimore, Md.: 1950) 180 (7) (2008) 5017–5027.
[36] M.M. D'Elios, A. Amedei, A. Cappon, G. Del Prete, M. de Bernard, The neutrophil-activating protein of Helicobacter pylori (HP-NAP) as an immune modulating agent, FEMS Immunol. Med. Microbiol. 50 (2) (2007) 157–164.
[37] B.R. Dixon, J.N. Radin, M.B. Piazuelo, D.C. Contreras, H.M. Algood, IL-17a and IL-22 induce expression of antimicrobials in gastrointestinal epithelial cells and may contribute to epithelial cell defense against helicobacter pylori, PLoS One 11 (2) (2016) e0148514.
[38] R.J. Gorrell, J. Guan, Y. Xin, M.A. Tafreshi, M.L. Hutton, M.A. McGuckin, R.L. Ferrero, T. Kwok, A novel NOD1- and CagA-independent pathway of interleukin-8 induction mediated by the Helicobacter pylori type IV secretion system, Cell. Microbiol. 15 (4) (2013) 554–570.
[39] J. Viala, C. Chaput, I.G. Boneca, A. Cardona, S.E. Girardin, A.P. Moran, R. Athman, S. Memet, M.R. Huerre, A.J. Coyle, P.S. DiStefano, P.J. Sansonetti, A. Labigne, J. Bertin, D.J. Philpott, R.L. Ferrero, Nod1 responds to peptidoglycan delivered by the Helicobacter pylori cag pathogenicity island, Nat. Immunol. 5 (11) (2004) 1166–1174.
[40] E.J. Beswick, V.E. Reyes, Macrophage migration inhibitory factor and interleukin-8 produced by gastric epithelial cells during Helicobacter pylori exposure induce expression and activation of the epidermal growth factor receptor, Infect. Immun. 76 (7) (2008) 3233–3240.
[41] S. Keates, S. Sougioultzis, A.C. Keates, D. Zhao, R.M. Peek Jr., L.M. Shaw, C.P. Kelly, cag+ Helicobacter pylori induce transactivation of the epidermal growth factor receptor in AGS gastric epithelial cells, J. Biol. Chem. 276 (51) (2001) 48127–48134.
[42] M. Aspholm, F.O. Olfat, J. Norden, B. Sonden, C. Lundberg, R. Sjostrom, S. Altraja, S. Odenbreit, R. Haas, T. Wadstrom, L. Engstrand, C. Semino-Mora, H. Liu, A. Dubois, S. Teneberg, A. Arnqvist, T. Boren, SabA is the H. pylori hemagglutinin and is polymorphic in binding to sialylated glycans, PLoS Pathog. 2 (10) (2006) e110.
[43] B. Schmausser, C. Josenhans, S. Endrich, S. Suerbaum, C. Sitaru, M. Andrulis, S. Brandlein, P. Rieckmann, H.K. Muller-Hermelink, M. Eck, Downregulation of CXCR1 and CXCR2 expression on human neutrophils by Helicobacter pylori: a new pathomechanism in H. pylori infection? Infect. Immun. 72 (12) (2004) 6773–6779.
[44] H.M. Algood, T.L. Cover, Helicobacter pylori persistence: an overview of interactions between H. pylori and host immune defenses, Clin. Microbiol. Rev. 19 (4) (2006) 597–613.
[45] L.A. Allen, Phagocytosis and persistence of Helicobacter pylori, Cell. Microbiol. 9 (4) (2007) 817–828.
[46] K.E. Lee, P.N. Khoi, Y. Xia, J.S. Park, Y.E. Joo, K.K. Kim, S.Y. Choi, Y.D. Jung, Helicobacter pylori and interleukin-8 in gastric cancer, World J. Gastroenterol. 19 (45) (2013) 8192–8202.
[47] J.M. David, C. Dominguez, D.H. Hamilton, C. Palena, The IL-8/IL-8R axis: a double agent in tumor immune resistance, Vaccines 4 (3) (2016).
[48] A. Li, S. Dubey, M.L. Varney, B.J. Dave, R.K. Singh, IL-8 directly enhanced endothelial cell survival, proliferation, and matrix metalloproteinases production and regulated angiogenesis, Journal of immunology (Baltimore, Md.: 1950) 170(6) (2003) 3369–76.
[49] C.S. Lin, P.J. He, W.T. Hsu, M.S. Wu, C.J. Wu, H.W. Shen, C.H. Hwang, Y.K. Lai, N.M. Tsai, K.W. Liao, Helicobacter pylori-derived heat shock protein 60 enhances angiogenesis via a CXCR2-mediated signaling pathway, Biochem. Biophys. Res. Commun. 397 (2) (2010) 283–289.
[50] M. Giese, L. Hind, A. Huttenlocher, Neutrophil plasticity in the tumor microenvironment, Blood 133 (20) (2019) 2159–2167.
[51] D.R. Powell, A. Huttenlocher, Neutrophils in the tumor microenvironment, Trends Immunol. 37 (1) (2016) 41–52.
[52] C. Alfaro, A. Teijeira, C. Onate, G. Perez, M.F. Sanmamed, M.P. Andueza, D. Alignani, S. Labiano, A. Azpilikueta, A. Rodriguez-Paulete, S. Garasa, J.P. Fusco, A. Aznar, S. Inoges, M. De Pizzol, M. Allegretti, J. Medina-Echeverz, P. Berraondo, J.L. Perez-Gracia, I. Melero, Tumor-produced interleukin-8 attracts human myeloid-derived suppressor cells and elicits extrusion of neutrophil extracellular traps (NETs), Clin. Cancer Res. 22 (15) (2016) 3924–3936.
[53] M. Liu, S. Guo, J.M. Hibbert, V. Jain, N. Singh, N.O. Wilson, J.K. Stiles, CXCL10/IP-10 in infectious diseases pathogenesis and potential therapeutic implications, Cytokine Growth Factor Rev. 22 (3) (2011) 121–130.
[54] K.B. Hahm, D.H. Kim, K.M. Lee, J.S. Lee, Y.J. Surh, Y.B. Kim, B.M. Yoo, J.H. Kim, H.J. Joo, Y.K. Cho, K.T. Nam, S.W. Cho, Effect of long-term administration of rebamipide on Helicobacter pylori infection in mice, Aliment. Pharmacol. Ther. 18 (Suppl. 1) (2003) 24–38.
[55] T. Ikuse, Y. Ohtsuka, T. Kudo, K. Hosoi, N. Obayashi, K. Jimbo, Y. Aoyagi, T. Fujii, S. Nagata, T. Shimizu, Microarray analysis of gastric mucosa among children with Helicobacter pylori infection, Pediatrics international: official journal of the Japan Pediatric Society 54 (3) (2012) 319–324.
[56] M. Kraft, S. Riedel, C. Maaser, T. Kucharzik, A. Steinbuechel, W. Domschke, N. Luegering, IFN-gamma synergizes with TNF-alpha but not with viable H. pylori in up-regulating CXC chemokine secretion in gastric epithelial cells, Clin. Exp. Immunol. 126 (3) (2001) 474–481.
[57] A. Jafarzadeh, M. Nemati, M.T. Rezayati, H. Khoramdel, M. Nabizadeh, G. Hassanshahi, H. Abdollahi, Lower circulating levels of chemokine CXCL10 in Helicobacter pylori-infected patients with peptic ulcer: influence of the bacterial virulence factor CagA, Iranian journal of microbiology 5 (1) (2013) 28–35.
[58] J.R. Groom, A.D. Luster, CXCR3 in T cell function, Exp. Cell Res. 317 (5) (2011) 620–631.
[59] A. Jafarzadeh, H. Fooladseresht, M. Nemati, Z. Assadollahi, A. Sheikhi, A. Ghaderi, Higher circulating levels of chemokine CXCL10 in patients with breast cancer: evaluation of the influences of tumor stage and chemokine gene polymorphism, Cancer biomarkers: section A of Disease markers 16 (4) (2016) 545–554.
[60] A. Lundgren, C. Trollmo, A. Edebo, A.M. Svennerholm, B.S. Lundin, Helicobacter pylori-specific CD4+ T cells home to and accumulate in the human Helicobacter pylori-infected gastric mucosa, Infect. Immun. 73 (9) (2005) 5612–5619.
[61] K. Minaga, T. Watanabe, K. Kamata, N. Asano, M. Kudo, Nucleotide-binding oligomerization domain 1 and Helicobacter pylori infection: a review, World J. Gastroenterol. 24 (16) (2018) 1725–1733.
[62] T. Korn, E. Bettelli, M. Oukka, V.K. Kuchroo, IL-17 and Th17 cells, Annu. Rev. Immunol. 27 (2009) 485–517.
[63] J.M. Taylor, M.E. Ziman, J.L. Huff, N.M. Moroski, M. Vajdy, J.V. Solnick, Helicobacter pylori lipopolysaccharide promotes a Th1 type immune response in immunized mice, Vaccine 24 (23) (2006) 4987–4994.
[64] J.M. Taylor, M.E. Ziman, D.R. Canfield, M. Vajdy, J.V. Solnick, Effects of a Th1- versus a Th2-biased immune response in protection against Helicobacter pylori challenge in mice, Microb. Pathog. 44 (1) (2008) 20–27.
[65] B. Kayhan, M. Arasli, H. Eren, S. Aydemir, E. Aktas, I. Tekin, Analysis of peripheral blood lymphocyte phenotypes and Th1/Th2 cytokines profile in the systemic immune responses of Helicobacter pylori infected individuals, Microbiol. Immunol. 52 (11) (2008) 531–538.
[66] V. Mollica Poeta, M. Massara, A. Capucetti, R. Bonecchi, Chemokines and chemokine receptors: new targets for cancer immunotherapy, Front. Immunol. 10 (2019) 379.
[67] H. Verbeke, K. Geboes, J. Van Damme, S. Struyf, The role of CXC chemokines in the transition of chronic inflammation to esophageal and gastric cancer, Biochim. Biophys. Acta 1825 (1) (2012) 117–129.
[68] M. Baj-Krzyworzeka, K. Weglarczyk, J. Baran, A. Szczepanik, M. Szura, M. Siedlar, Elevated level of some chemokines in plasma of gastric cancer patients, Central-European journal of immunology 41 (4) (2016) 358–362.
[69] S. Zhang, D.S. Lee, R. Morrissey, J.R. Aponte-Pieras, A.B. Rogers, S.F. Moss, Early or late antibiotic intervention prevents Helicobacter pylori-induced gastric cancer in a mouse model, Cancer Lett. 359 (2) (2015) 345–351.
[70] H. Zhou, J. Wu, T. Wang, X. Zhang, D. Liu, CXCL10/CXCR3 axis promotes the invasion of gastric cancer via PI3K/AKT pathway-dependent MMPs production, Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie 82 (2016) 479–488.
[71] C. Yang, W. Zheng, W. Du, CXCR3A contributes to the invasion and metastasis of gastric cancer cells, Oncol. Rep. 36 (3) (2016) 1686–1692.
[72] N. Kawaguchi, T.T. Zhang, T. Nakanishi, Involvement of CXCR4 in normal and

abnormal development, Cells 8 (2) (2019).
[73] J. Teixido, M. Martinez-Moreno, M. Diaz-Martinez, S. Sevilla-Movilla, The good and bad faces of the CXCR4 chemokine receptor, Int. J. Biochem. Cell Biol. 95 (2018) 121–131.
[74] J. Ferrand, P. Lehours, A. Schmid-Alliana, F. Megraud, C. Varon, Helicobacter pylori infection of gastrointestinal epithelial cells in vitro induces mesenchymal stem cell migration through an NF-kappaB-dependent pathway, PLoS One 6 (12) (2011) e29007.
[75] S. Fakhari, E. Kalantar, M. Nikzaban, M.S. Hakhamneshi, F. Fathi, B. Nikkhoo, M.R. Rahmani, M. Beiraghdar, A. Jalili, Effect of Helicobacter pylori infection on stromal-derived factor-1/CXCR4 axis in bone marrow-derived mesenchymal stem cells, Advanced biomedical research 3 (2014) 19.
[76] N. Capitani, G. Codolo, F. Vallese, G. Minervini, A. Grassi, F. Cianchi, A. Troilo, W. Fischer, G. Zanotti, C.T. Baldari, M. de Bernard, M.M. D'Elios, The lipoprotein HP1454 of Helicobacter pylori regulates T cell response by shaping T cell receptor signalling, Cell. Microbiol. (2019) e13006.
[77] A.J. Deutsch, E. Steinbauer, N.A. Hofmann, D. Strunk, T. Gerlza, C. Beham-Schmid, H. Schaider, P. Neumeister, Chemokine receptors in gastric MALT lymphoma: loss of CXCR4 and upregulation of CXCR7 is associated with progression to diffuse large B-cell lymphoma, Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc 26(2) (2013) 182–94.
[78] R. Guo, L. Chai, L. Chen, W. Chen, L. Ge, X. Li, H. Li, S. Li, C. Cao, Stromal cell-derived factor 1 (SDF-1) accelerated skin wound healing by promoting the migration and proliferation of epidermal stem cells, In Vitro Cell Dev Biol Anim 51 (6) (2015) 578–585.
[79] X. Xu, F. Zhu, M. Zhang, D. Zeng, D. Luo, G. Liu, W. Cui, S. Wang, W. Guo, W. Xing, H. Liang, L. Li, X. Fu, J. Jiang, H. Huang, Stromal cell-derived factor-1 enhances wound healing through recruiting bone marrow-derived mesenchymal stem cells to the wound area and promoting neovascularization, Cells Tissues Organs 197 (2) (2013) 103–113.
[80] S. Liekens, D. Schols, S. Hatse, CXCL12-CXCR4 axis in angiogenesis, metastasis and stem cell mobilization, Curr. Pharm. Des. 16 (35) (2010) 3903–3920.
[81] U.M. Domanska, R.C. Kruizinga, W.B. Nagengast, H. Timmer-Bosscha, G. Huls, E.G. de Vries, A.M. Walenkamp, A review on CXCR4/CXCL12 axis in oncology: no place to hide, Eur. J. Cancer 49 (1) (2013) 219–230.
[82] J.L. Owen, M. Mohamadzadeh, Macrophages and chemokines as mediators of angiogenesis, Front. Physiol. 4 (2013) 159.
[83] L.J. Xue, X.B. Mao, L.L. Ren, X.Y. Chu, Inhibition of CXCL12/CXCR4 axis as a potential targeted therapy of advanced gastric carcinoma, Cancer medicine 6 (6) (2017) 1424–1436.
[84] D.G. Duda, S.V. Kozin, N.D. Kirkpatrick, L. Xu, D. Fukumura, R.K. Jain, CXCL12 (SDF1alpha)-CXCR4/CXCR7 pathway inhibition: an emerging sensitizer for anticancer therapies? Clin. Cancer Res. 17 (8) (2011) 2074–2080.
[85] C. Zhao, X. Lu, X. Bu, N. Zhang, W. Wang, Involvement of tumor necrosis factor-alpha in the upregulation of CXCR4 expression in gastric cancer induced by Helicobacter pylori, BMC Cancer 10 (419) (2010) 419.
[86] W. Shibata, H. Ariyama, C.B. Westphalen, D.L. Worthley, S. Muthupalani, S. Asfaha, Z. Dubeykovskaya, M. Quante, J.G. Fox, T.C. Wang, Stromal cell-derived factor-1 overexpression induces gastric dysplasia through expansion of stromal myofibroblasts and epithelial progenitors, Gut 62 (2) (2013) 192–200.
[87] Y. Cheng, Y. Song, J. Qu, X. Che, N. Song, Y. Fan, T. Wen, L. Xu, J. Gong, X. Wang, C. Zhang, X. Qu, Y. Liu, The chemokine receptor CXCR4 and c-MET cooperatively promote epithelial-mesenchymal transition in gastric cancer cells, Transl. Oncol. 11 (2) (2018) 487–497.
[88] K. Sakitani, Y. Hayakawa, H. Deng, H. Ariyama, H. Kinoshita, M. Konishi, S. Ono, N. Suzuki, S. Ihara, Z. Niu, W. Kim, T. Tanaka, H. Liu, X. Chen, Y. Tailor, J.G. Fox, S.F. Konieczny, H. Onodera, A.R. Sepulveda, S. Asfaha, Y. Hirata, D.L. Worthley, K. Koike, T.C. Wang, CXCR4-expressing Mist1(+) progenitors in the gastric antrum contribute to gastric cancer development, Oncotarget 8 (67) (2017) 111012–111025.
[89] A. Shi, H. Shi, L. Dong, S. Xu, M. Jia, X. Guo, T. Wang, CXCR7 as a chemokine receptor for SDF-1 promotes gastric cancer progression via MAPK pathways, Scand. J. Gastroenterol. 52 (6–7) (2017) 745–753.
[90] Q. Xin, N. Zhang, H.B. Yu, Q. Zhang, Y.F. Cui, C.S. Zhang, Z. Ma, Y. Yang, W. Liu, CXCR7/CXCL12 axis is involved in lymph node and liver metastasis of gastric carcinoma, World J. Gastroenterol. 23 (17) (2017) 3053–3065.
[91] N. Li, H. Xu, Y. Ou, Z. Feng, Q. Zhang, Q. Zhu, Z. Cai, LPS-induced CXCR7 expression promotes gastric cancer proliferation and migration via the TLR4/MD-2 pathway, Diagn. Pathol. 14 (1) (2019) 3.
[92] D.M. Ma, D.X. Luo, J. Zhang, SDF-1/CXCR7 axis regulates the proliferation, invasion, adhesion, and angiogenesis of gastric cancer cells, World journal of surgical oncology 14 (1) (2016) 256.
[93] D.K. Finch, R. Ettinger, J.L. Karnell, R. Herbst, M.A. Sleeman, Effects of CXCL13 inhibition on lymphoid follicles in models of autoimmune disease, Eur. J. Clin. Investig. 43 (5) (2013) 501–509.
[94] K. Yamamoto, S. Nishiumi, L. Yang, E. Klimatcheva, T. Pandina, S. Takahashi, H. Matsui, M. Nakamura, M. Zauderer, M. Yoshida, T. Azuma, Anti-CXCL13 antibody can inhibit the formation of gastric lymphoid follicles induced by Helicobacter infection, Mucosal Immunol. 7 (5) (2014) 1244–1254.
[95] G. Zhang, R. Ducatelle, E. De Bruyne, M. Joosten, I. Bosschem, A. Smet, F. Haesebrouck, B. Flahou, Role of gamma-glutamyltranaspeptidase in the pathogenesis of Helicobacter suis and Helicobacter pylori infections, Vet. Res. 46 (2015) 31.
[96] Y. Nakashima, H. Isomoto, K. Matsushima, A. Yoshida, T. Nakayama, M. Nakayama, J. Hisatsune, T. Ichikawa, F. Takeshima, T. Hayashi, K. Nakao, T. Hirayama, S. Kohno, Enhanced expression of CXCL13 in human Helicobacter pylori-associated gastritis, Dig. Dis. Sci. 56 (10) (2011) 2887–2894.
[97] V.J. Hofman, C. Moreilhon, P.D. Brest, S. Lassalle, K. Le Brigand, D. Sicard, J. Raymond, D. Lamarque, X.A. Hebuterne, B. Mari, P.J. Barbry, P.M. Hofman, Gene expression profiling in human gastric mucosa infected with Helicobacter pylori, Modern pathology: an official journal of the United States and Canadian Academy of Pathology, Inc 20 (9) (2007) 974–989.
[98] S. Winter, C. Loddenkemper, A. Aebischer, K. Rabel, K. Hoffmann, T.F. Meyer, M. Lipp, U.E. Hopken, The chemokine receptor CXCR5 is pivotal for ectopic mucosa-associated lymphoid tissue neogenesis in chronic helicobacter pylori-induced inflammation, Journal of molecular medicine (Berlin, Germany) 88 (11) (2010) 1169–1180.
[99] O. Galamb, B. Gyorffy, F. Sipos, E. Dinya, T. Krenacs, L. Berczi, D. Szoke, S. Spisak, N. Solymosi, A.M. Nemeth, M. Juhasz, B. Molnar, Z. Tulassay, Helicobacter pylori and antrum erosion-specific gene expression patterns: the discriminative role of CXCL13 and VCAM1 transcripts, Helicobacter 13 (2) (2008) 112–126.
[100] K. Troppan, K. Wenzl, P. Neumeister, A. Deutsch, Molecular pathogenesis of MALT lymphoma, Gastroenterol. Res. Pract. 2015 (2015) 102656.
[101] L. Mazzucchelli, A. Blaser, A. Kappeler, P. Scharli, J.A. Laissue, M. Baggiolini, M. Uguccioni, BCA-1 is highly expressed in Helicobacter pylori-induced mucosa-associated lymphoid tissue and gastric lymphoma, J. Clin. Invest. 104 (10) (1999) R49–R54.
[102] K. Nobutani, M. Yoshida, S. Nishiumi, Y. Nishitani, T. Takagawa, H. Tanaka, K. Yamamoto, T. Mimura, Y. Bensuleiman, H. Ota, S. Takahashi, H. Matsui, M. Nakamura, T. Azuma, Helicobacter heilmannii can induce gastric lymphoid follicles in mice via a Peyer's patch-independent pathway, FEMS Immunol. Med. Microbiol. 60 (2) (2010) 156–164.
[103] F. Xu, D. He, J. Liu, Q. Ni, Y. Lyu, S. Xiong, Y. Li, Genetic diversification of chemokine CXCL16 and its receptor CXCR6 in primates, Dev. Comp. Immunol. 85 (2018) 86–94.
[104] Y.P. Lv, P. Cheng, J.Y. Zhang, F.Y. Mao, Y.S. Teng, Y.G. Liu, H. Kong, X.L. Wu, C.J. Hao, B. Han, Q. Ma, S.M. Yang, W. Chen, L.S. Peng, T.T. Wang, Q.M. Zou, Y. Zhuang, Helicobacter pylori-induced matrix metallopeptidase-10 promotes gastric bacterial colonization and gastritis, Sci. Adv. 5 (4) (2019) eaau6547.
[105] B. Kronsteiner, J. Bassaganya-Riera, N. Philipson, R. Hontecillas, Novel insights on the role of CD8+ T cells and cytotoxic responses during Helicobacter pylori infection, Gut Microbes 5 (3) (2014) 357–362.
[106] T.A. Sebrell, M. Hashimi, B. Sidar, R. Wilkinson, L. Kirpotina, M.T. Quinn, Z. Malkoc, P.J. Taylor, J.N. Wilking, D. Bimczok, A novel gastric spheroid co-culture model reveals chemokine-dependent recruitment of human dendritic cells to the gastric epithelium, Cellular and molecular gastroenterology and hepatology 8 (1) (2019) 157–171.
[107] J.J. Jin, F.X. Dai, Z.W. Long, H. Cai, X.W. Liu, Y. Zhou, Q. Hong, Q.Z. Dong, Y.N. Wang, H. Huang, CXCR6 predicts poor prognosis in gastric cancer and promotes tumor metastasis through epithelial-mesenchymal transition, Oncol. Rep. 37 (6) (2017) 3279–3286.
[108] W. Hu, Y. Liu, W. Zhou, L. Si, L. Ren, CXCL16 and CXCR6 are coexpressed in human lung cancer in vivo and mediate the invasion of lung cancer cell lines in vitro, PLoS One 9 (6) (2014) e99056.
[109] B. Chung, A.A. Esmaeili, S. Gopalakrishna-Pillai, J.P. Murad, E.S. Andersen, N. Kumar Reddy, G. Srinivasan, B. Armstrong, C. Chu, Y. Kim, T. Tong, J. Waisman, J.H. Yim, B. Badie, P.P. Lee, Human brain metastatic stroma attracts breast cancer cells via chemokines CXCL16 and CXCL12, NPJ breast cancer 3 (2017) 6.
[110] D. Aldinucci, N. Casagrande, Inhibition of the CCL5/CCR5 axis against the progression of gastric cancer, Int. J. Mol. Sci. 19 (5) (2018).
[111] T. Kudo, H. Lu, J.Y. Wu, D.Y. Graham, A. Casola, Y. Yamaoka, Regulation of RANTES promoter activation in gastric epithelial cells infected with Helicobacter pylori, Infect. Immun. 73 (11) (2005) 7602–7612.
[112] B. Cha, J.W. Lim, K.H. Kim, H. Kim, 15-Deoxy-D12,14-prostaglandin J2 suppresses RANTES expression by inhibiting NADPH oxidase activation in Helicobacter pylori-infected gastric epithelial cells, Journal of physiology and pharmacology: an official journal of the Polish Physiological Society 62 (2) (2011) 167–174.
[113] M. Oleastro, A. Menard, The role of Helicobacter pylori outer membrane proteins in adherence and pathogenesis, Biology (Basel) 2 (3) (2013) 1110–1134.
[114] T.A. Nagy, S.S. Allen, L.E. Wroblewski, D.K. Flaherty, J.C. Slaughter, G. Perez-Perez, D.A. Israel, R.M. Peek Jr., Helicobacter pylori induction of eosinophil migration is mediated by the cag pathogenicity island via microbial-epithelial interactions, Am. J. Pathol. 178 (4) (2011) 1448–1452.
[115] S. Krauss-Etschmann, E. Sammler, S. Koletzko, N. Konstantopoulos, D. Aust, B. Gebert, B. Luckow, D. Reinhardt, D.J. Schendel, Chemokine receptor 5 expression in gastric mucosa of Helicobacter pylori-infected and noninfected children, Clin. Diagn. Lab. Immunol. 10 (1) (2003) 22–29.
[116] T. Kikuchi, K. Kato, S. Ohara, H. Sekine, T. Arikawa, T. Suzuki, K. Noguchi, M. Saito, Y. Saito, H. Nagura, T. Toyota, T. Shimosegawa, The relationship between persistent secretion of RANTES and residual infiltration of eosinophils and memory T lymphocytes after Helicobacter pylori eradication, J. Pathol. 192 (2) (2000) 243–250.
[117] S.H. Ko, J.I. Jeon, Y.J. Kim, H.J. Yoon, H. Kim, N. Kim, J.S. Kim, J.M. Kim, Helicobacter pylori outer membrane vesicle proteins induce human eosinophil degranulation via a beta2 integrin CD11/CD18- and ICAM-1-dependent mechanism, Mediat. Inflamm. 2015 (2015) 301716.
[118] A.R. Sima, H.R. Sima, H. Rafatpanah, H. Hosseinnezhad, K. Ghaffarzadehgan, N. Valizadeh, M. Mehrabi Bahar, H.R. Hakimi, A. Masoom, A. Noorbakhsh, N. Razavi Satvati, H.R. Raziee, Serum chemokine ligand 5 (CCL5/RANTES) level might be utilized as a predictive marker of tumor behavior and disease prognosis in patients with gastric adenocarcinoma, Journal of gastrointestinal cancer 45 (4)

(2014) 476–480.
[119] L. Yang, B. Wang, J. Qin, H. Zhou, A.P.N. Majumdar, F. Peng, Blockade of CCR5-mediated myeloid derived suppressor cell accumulation enhances anti-PD1 efficacy in gastric cancer, Immunopharmacol. Immunotoxicol. 40 (1) (2018) 91–97.
[120] H. Saeki, K. Tamaki, Thymus and activation regulated chemokine (TARC)/CCL17 and skin diseases, J. Dermatol. Sci. 43 (2) (2006) 75–84.
[121] S. Scheu, S. Ali, C. Ruland, V. Arolt, J. Alferink, The C-C chemokines CCL17 and CCL22 and their receptor CCR4 in CNS autoimmunity, Int. J. Mol. Sci. 18 (11) (2017).
[122] M. Quiding-Jarbrink, S. Raghavan, M. Sundquist, Enhanced M1 macrophage polarization in human helicobacter pylori-associated atrophic gastritis and in vaccinated mice, PLoS One 5 (11) (2010) e15018.
[123] Y. Mizukami, K. Kono, Y. Kawaguchi, H. Akaike, K. Kamimura, H. Sugai, H. Fujii, CCL17 and CCL22 chemokines within tumor microenvironment are related to accumulation of Foxp3+ regulatory T cells in gastric cancer, Int. J. Cancer 122 (10) (2008) 2286–2293.
[124] V.J. Craig, S.B. Cogliatti, I. Arnold, C. Gerke, J.E. Balandat, T. Wundisch, A. Muller, B-cell receptor signaling and CD40 ligand-independent T cell help cooperate in Helicobacter-induced MALT lymphomagenesis, Leukemia 24 (6) (2010) 1186–1196.
[125] X. Ni, T. Langridge, M. Duvic, Depletion of regulatory T cells by targeting CC chemokine receptor type 4 with mogamulizumab, Oncoimmunology 4 (7) (2015) e1011524.
[126] A.Y.S. Lee, H. Korner, The CCR6-CCL20 axis in humoral immunity and T-B cell immunobiology, Immunobiology 8(19) (2019) 30028-2.
[127] R. Ranasinghe, R. Eri, Pleiotropic immune functions of chemokine receptor 6 in health and disease, Medicines (Basel, Switzerland) 5 (3) (2018).
[128] A. Safa, H.R. Rashidinejad, M. Khalili, S. Dabiri, M. Nemati, M.M. Mohammadi, A. Jafarzadeh, Higher circulating levels of chemokines CXCL10, CCL20 and CCL22 in patients with ischemic heart disease, Cytokine 83 (2016) 147–157.
[129] A. Jafarzadeh, S. Bagherzadeh, H.A. Ebrahimi, H. Hajghani, M.R. Bazrafshani, A. Khosravimashizi, M. Nemati, F. Gadari, A. Sabahi, F. Iranmanesh, M.M. Mohammadi, H. Daneshvar, Higher circulating levels of chemokine CCL20 in patients with multiple sclerosis: evaluation of the influences of chemokine gene polymorphism, gender, treatment and disease pattern, Journal of molecular neuroscience: MN 53 (3) (2014) 500–505.
[130] Y. Zhuang, Y. Shi, X.F. Liu, J.Y. Zhang, T. Liu, X. Fan, J. Luo, C. Wu, S. Yu, L. Chen, P. Luo, G. Guo, Z. Liu, B. Tang, X.H. Mao, Y. Guo, Q.M. Zou, Helicobacter pylori-infected macrophages induce Th17 cell differentiation, Immunobiology 216 (1–2) (2011) 200–207.
[131] J.P. Chen, M.S. Wu, S.H. Kuo, F. Liao, IL-22 negatively regulates Helicobacter pylori-induced CCL20 expression in gastric epithelial cells, PLoS One 9 (5) (2014) e97350.
[132] Y.Y. Wu, H.F. Tsai, W.C. Lin, P.I. Hsu, C.T. Shun, M.S. Wu, P.N. Hsu, Upregulation of CCL20 and recruitment of CCR6+ gastric infiltrating lymphocytes in Helicobacter pylori gastritis, Infect. Immun. 75 (9) (2007) 4357–4363.
[133] H.F. Tsai, P.N. Hsu, Interplay between Helicobacter pylori and immune cells in immune pathogenesis of gastric inflammation and mucosal pathology, Cellular & molecular immunology 7 (4) (2010) 255–259.
[134] M. Garcia, J.C. Chomel, P. Mustapha, C.T. Tran, M. Garnier, I. Paris, N. Quellard, J. Godet, J. Cremniter, A. Bennaceur-Griscelli, J.C. Lecron, A.G. Turhan, C. Burucoa, C. Bodet, In vitro culture and phenotypic and molecular characterization of gastric stem cells from human stomach, Helicobacter 22 (2) (2017).
[135] H.F. Tsai, P.N. Hsu, Modulation of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-mediated apoptosis by Helicobacter pylori in immune pathogenesis of gastric mucosal damage, Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi 50 (1) (2017) 4–9.
[136] S. Kabir, The role of interleukin-17 in the Helicobacter pylori induced infection and immunity, Helicobacter 16 (1) (2011) 1–8.
[137] K.J. Laing, C.J. Secombes, Chemokines, Developmental & Comparative Immunology 28 (5) (2004) 443–460.
[138] C.R. Mackay, Chemokines: immunology's high impact factors, Nat. Immunol. 2 (2) (2001) 95–101.
[139] Y.Y. Wu, C.T. Hsieh, G.J. Tsay, J.T. Kao, Y.M. Chiu, D.C. Shieh, Y.J. Lee, Recruitment of CCR6(+) Foxp3(+) regulatory gastric infiltrating lymphocytes in Helicobacter pylori gastritis, Helicobacter 24 (1) (2019) e12550.
[140] P. Sipponen, H.I. Maaroos, Chronic gastritis, Scand. J. Gastroenterol. 50 (6) (2015) 657–667.
[141] I.V. Pinchuk, K.T. Morris, R.A. Nofchissey, R.B. Earley, J.Y. Wu, T.Y. Ma, E.J. Beswick, Stromal cells induce Th17 during Helicobacter pylori infection and in the gastric tumor microenvironment, PLoS One 8 (1) (2013) e53798.
[142] H. Ohata, S. Kitauchi, N. Yoshimura, K. Mugitani, M. Iwane, H. Nakamura, A. Yoshikawa, K. Yanaoka, K. Arii, H. Tamai, Progression of chronic atrophic gastritis associated with Helicobacter pylori infection increases risk of gastric cancer, Int. J. Cancer 109 (1) (2004) 138–143.
[143] T. Rajkumar, N. Vijayalakshmi, G. Gopal, K. Sabitha, S. Shirley, U.M. Raja, S.A. Ramakrishnan, Identification and validation of genes involved in gastric tumorigenesis, Cancer Cell Int. 10 (2010) 45.
[144] G. Han, D. Wu, Y. Yang, Z. Li, J. Zhang, C. Li, CrkL meditates CCL20/CCR6-induced EMT in gastric cancer, Cytokine 76 (2) (2015) 163–169.
[145] H. Ohtani, T. Nakayama, O. Yoshie, In situ expression of the CCL20-CCR6 axis in lymphocyte-rich gastric cancer and its potential role in the formation of lymphoid stroma, Pathol. Int. 61 (11) (2011) 645–651.
[146] J. Liu, N. Zhang, Q. Li, W. Zhang, F. Ke, Q. Leng, H. Wang, J. Chen, H. Wang, Tumor-associated macrophages recruit CCR6+ regulatory T cells and promote the development of colorectal cancer via enhancing CCL20 production in mice, PLoS One 6 (4) (2011) e19495.
[147] A. Jafarzadeh, H. Fooladseresht, K. Minaee, M.R. Bazrafshani, A. Khosravimashizi, M. Nemati, M. Mohammadizadeh, M.M. Mohammadi, A. Ghaderi, Higher circulating levels of chemokine CCL22 in patients with breast cancer: evaluation of the influences of tumor stage and chemokine gene polymorphism, Tumour biology: the journal of the International Society for Oncodevelopmental Biology and Medicine 36 (2) (2015) 1163–1171.
[148] E. Stromberg, A. Edebo, B.S. Lundin, P. Bergin, M. Brisslert, A.M. Svennerholm, C. Lindholm, Down-regulation of epithelial IL-8 responses in Helicobacter pylori-infected duodenal ulcer patients depends on host factors, rather than bacterial factors, Clin. Exp. Immunol. 140 (1) (2005) 117–125.
[149] K. Enarsson, A. Lundgren, B. Kindlund, M. Hermansson, G. Roncador, A.H. Banham, B.S. Lundin, M. Quiding-Jarbrink, Function and recruitment of mucosal regulatory T cells in human chronic Helicobacter pylori infection and gastric adenocarcinoma, Clinical immunology (Orlando, Fla.) 121 (3) (2006) 358–368.
[150] J.W. Griffith, C.L. Sokol, A.D. Luster, Chemokines and chemokine receptors: positioning cells for host defense and immunity, Annu. Rev. Immunol. 32 (2014) 659–702.
[151] J.M. Taylor, M.E. Ziman, D.R. Canfield, M. Vajdy, J.V. Solnick, Effects of a Th1- versus a Th2-biased immune response in protection against Helicobacter pylori challenge in mice, Microb. Pathog. 44 (1) (2008) 20–27.
[152] M.S. Al-Balushi, E.A. Said, S.S. Hasson, J.Z. Al-Busaidi, I. Al-Reesi, M. Idris, W. Al-Ghafri, M. Al-Kalbani, A.A. Al-Jabri, High levels of IgA antibodies to Helicobacter pylori among Omani women during pregnancy and after delivery, Iranian journal of immunology: IJI 13 (2) (2016) 114–123.
[153] M. Mohammadi, J. Nedrud, R. Redline, N. Lycke, S.J. Czinn, Murine CD4 T-cell response to Helicobacter infection: TH1 cells enhance gastritis and TH2 cells reduce bacterial load, Gastroenterology 113 (6) (1997) 1848–1857.
[154] R. Srivastava, A. Kashyap, M. Kumar, G. Nath, A.K. Jain, Mucosal IgA & IL-1beta in Helicobacter pylori infection, Indian journal of clinical biochemistry: IJCB 28 (1) (2013) 19–23.
[155] B. Marotti, A. Rocco, P. De Colibus, D. Compare, G. de Nucci, S. Staibano, F. Tatangelo, M. Romano, G. Nardone, Interleukin-13 mucosal production in Helicobacter pylori-related gastric diseases, Dig. Liver Dis. 40 (4) (2008) 240–247.
[156] A. Mueller, J. O'Rourke, P. Chu, A. Chu, M.F. Dixon, D.M. Bouley, A. Lee, S. Falkow, The role of antigenic drive and tumor-infiltrating accessory cells in the pathogenesis of helicobacter-induced mucosa-associated lymphoid tissue lymphoma, Am. J. Pathol. 167 (3) (2005) 797–812.
[157] P. Yang, G. Qiu, S. Wang, Z. Su, J. Chen, F. Kong, L. Lu, T. Ezaki, H. Xu, The mutations of Th1 cell-specific T-box transcription factor may be associated with a predominant Th2 phenotype in gastric cancers, International journal of immunogenetics 37 (2) (2010) 111–115.
[158] X. Liu, K. Cao, C. Xu, T. Hu, L. Zhou, D. Cao, J. Xiao, L. Luo, Y. Guo, L. Huang, GATA-3 augmentation down-regulates Connexin43 in Helicobacter pylori associated gastric carcinogenesis, Cancer biology & therapy (just-accepted) 16 (6) (2015) 987–996.
[159] H.-H. Cheng, G.-Y. Tseng, H.-B. Yang, H.-J. Wang, H.-J. Lin, W.-C. Wang, Increased numbers of Foxp3-positive regulatory T cells in gastritis, peptic ulcer and gastric adenocarcinoma, World J Gastroenterol: WJG 18 (1) (2012) 34.
[160] A. Bassagh, M. Hayatbakhsh Abasi, T. Larussa, M. Ghazizadeh, M. Nemati, E. Mirkamandar, A. Jafarzadeh, Diminished circulating concentration of interleukin-35 in Helicobacter pylori-infected patients with peptic ulcer: its association with FOXP3 gene polymorphism, bacterial virulence factor CagA, and gender of patients, Helicobacter 23 (4) (2018) e12501.
[161] L.-L. Chang, S.-W. Wang, I.-C. Wu, F.-J. Yu, Y.-C. Su, Y.-P. Chen, D.-C. Wu, C.-H. Kuo, C.-H. Hung, Impaired dendritic cell maturation and IL-10 production following H. pylori stimulation in gastric cancer patients, Appl. Microbiol. Biotechnol. 96 (1) (2012) 211–220.
[162] S. Raghavan, M. Quiding-Jarbrink, Immune modulation by regulatory T cells in Helicobacter pylori-associated diseases, Endocr Metab Immune Disord Drug Targets 12 (1) (2012) 71–85 (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders).
[163] C.A. Figueiredo, C.R. Marques, R. dos Santos Costa, H.B.F. da Silva, N.M. Alcantara-Neves, Cytokines, cytokine gene polymorphisms and Helicobacter pylori infection: friend or foe? World J Gastroenterol: WJG 20 (18) (2014) 5235.
[164] K. Robinson, R. Kenefeck, E.L. Pidgeon, S. Shakib, S. Patel, R. Polson, A.M. Zaitoun, J.C. Atherton, Helicobacter pylori-induced peptic ulcer disease is associated with inadequate regulatory T cell responses, Gut 57 (10) (2008) 1375–1385.
[165] R. Rad, L. Brenner, S. Bauer, S. Schwendy, L. Layland, C.P. da Costa, W. Reindl, A. Dossumbekova, M. Friedrich, D. Saur, H. Wagner, R.M. Schmid, C. Prinz, CD25+/Foxp3+ T cells regulate gastric inflammation and Helicobacter pylori colonization in vivo, Gastroenterology 131 (2) (2006) 525–537.
[166] S. Raghavan, M. Fredriksson, A.M. Svennerholm, J. Holmgren, E. Suri-Payer, Absence of CD4+CD25+ regulatory T cells is associated with a loss of regulation leading to increased pathology in Helicobacter pylori-infected mice, Clin. Exp. Immunol. 132 (3) (2003) 393–400.
[167] M. Kaparakis, K.L. Laurie, O. Wijburg, J. Pedersen, M. Pearse, I.R. van Driel, P.A. Gleeson, R.A. Strugnell, CD4+ CD25+ regulatory T cells modulate the T-cell and antibody responses in helicobacter-infected BALB/c mice, Infect. Immun. 74 (6) (2006) 3519–3529.
[168] I. Wertel, J. Surowka, G. Polak, B. Barczynski, W. Bednarek, J. Jakubowicz-Gil, A. Bojarska-Junak, J. Kotarski, Macrophage-derived chemokine CCL22 and regulatory T cells in ovarian cancer patients, Tumour biology: the journal of the International Society for Oncodevelopmental Biology and Medicine 36 (6) (2015)

4811–4817.
[169] Y.Q. Li, F.F. Liu, X.M. Zhang, X.J. Guo, M.J. Ren, L. Fu, Tumor secretion of CCL22 activates intratumoral Treg infiltration and is independent prognostic predictor of breast cancer, PLoS One 8 (10) (2013) e76379.
[170] K. Enarsson, A. Lundgren, B. Kindlund, M. Hermansson, G. Roncador, A.H. Banham, B.S. Lundin, M. Quiding-Järbrink, Function and recruitment of mucosal regulatory T cells in human chronic Helicobacter pylori infection and gastric adenocarcinoma, Clin. Immunol. 121 (3) (2006) 358–368.
[171] Y.M. Yang, A.L. Feng, C.J. Zhou, X.H. Liang, H.T. Mao, B.P. Deng, S. Yan, J.T. Sun, L.T. Du, J. Liu, Q.J. Wang, M.R. Neckenig, Q.F. Yang, X. Qu, Aberrant expression of chemokine receptor CCR4 in human gastric cancer contributes to tumor-induced immunosuppression, Cancer Sci. 102 (7) (2011) 1264–1271.
[172] D.K. Chang, E. Peterson, J. Sun, C. Goudie, R.I. Drapkin, J.F. Liu, U. Matulonis, Q. Zhu, W.A. Marasco, Anti-CCR4 monoclonal antibody enhances antitumor immunity by modulating tumor-infiltrating Tregs in an ovarian cancer xenograft humanized mouse model, Oncoimmunology 5 (3) (2016) e1090075.
[173] Z. Yang, B. Zhang, D. Li, M. Lv, C. Huang, G.X. Shen, B. Huang, Mast cells mobilize myeloid-derived suppressor cells and Treg cells in tumor microenvironment via IL-17 pathway in murine hepatocarcinoma model, PLoS One 5 (1) (2010) e8922.
[174] M. Hernandez-Ruiz, A. Zlotnik, Mucosal chemokines, Journal of interferon & cytokine research: the official journal of the International Society for Interferon and Cytokine Research 37 (2) (2017) 62–70.
[175] K. Kiriya, N. Watanabe, A. Nishio, K. Okazaki, M. Kido, K. Saga, J. Tanaka, T. Akamatsu, S. Ohashi, M. Asada, T. Fukui, T. Chiba, Essential role of Peyer's patches in the development of Helicobacter-induced gastritis, Int. Immunol. 19 (4) (2007) 435–446.
[176] S.F. Khaiboullina, S. Abdulkhakov, A. Khalikova, D. Safina, E.V. Martynova, Y. Davidyuk, F. Khuzin, R. Faizullina, V.C. Lombardi, G.V. Cherepnev, A.A. Rizvanov, Serum cytokine signature that discriminates Helicobacter pylori positive and negative juvenile gastroduodenitis, Front. Microbiol. 7 (2016) 1916.
[177] M. Hansson, M. Hermansson, H. Svensson, A. Elfvin, L.E. Hansson, E. Johnsson, A. Sjoling, M. Quiding-Jarbrink, CCL28 is increased in human Helicobacter pylori-induced gastritis and mediates recruitment of gastric immunoglobulin A-secreting cells, Infect. Immun. 76 (7) (2008) 3304–3311.
[178] S. Raghavan, A.K. Ostberg, C.F. Flach, A. Ekman, M. Blomquist, C. Czerkinsky, J. Holmgren, Sublingual immunization protects against Helicobacter pylori infection and induces T and B cell responses in the stomach, Infect. Immun. 78 (10) (2010) 4251–4260.
[179] Z. Tu, R. Xiao, J. Xiong, K.M. Tembo, X. Deng, M. Xiong, P. Liu, M. Wang, Q. Zhang, CCR9 in cancer: oncogenic role and therapeutic targeting, J. Hematol. Oncol. 9 (2016) 10.
[180] P.K. Sharma, R. Singh, K.R. Novakovic, J.W. Eaton, W.E. Grizzle, S. Singh, CCR9 mediates PI3K/AKT-dependent antiapoptotic signals in prostate cancer cells and inhibition of CCR9-CCL25 interaction enhances the cytotoxic effects of etoposide, Int. J. Cancer 127 (9) (2010) 2020–2030.
[181] T. Mohan, L. Deng, B.Z. Wang, CCL28 chemokine: an anchoring point bridging innate and adaptive immunity, Int. Immunopharmacol. 51 (2017) 165–170.
[182] Y. Ohue, H. Nishikawa, Regulatory T (Treg) cells in cancer: can Treg cells be a new therapeutic target? Cancer Sci. 110 (7) (2019) 2080–2089.
[183] K. Hieshima, Y. Kawasaki, H. Hanamoto, T. Nakayama, D. Nagakubo, A. Kanamaru, O. Yoshie, CC chemokine ligands 25 and 28 play essential roles in intestinal extravasation of IgA antibody-secreting cells, Journal of immunology (Baltimore, Md.: 1950) 173 (6) (2004) 3668–3675.
[184] M. Quiding-Jarbrink, H. Lonroth, I. Ahlstedt, J. Holmgren, A.M. Svennerholm, Human gastric B cell responses can be induced by intestinal immunisation, Gut 49 (4) (2001) 512–518.
[185] L. Ren, Y. Yu, L. Wang, Z. Zhu, R. Lu, Z. Yao, Hypoxia-induced CCL28 promotes recruitment of regulatory T cells and tumor growth in liver cancer, Oncotarget 7 (46) (2016) 75763–75773.
[186] P. Mustapha, I. Paris, M. Garcia, C.T. Tran, J. Cremniter, M. Garnier, J.P. Faure, T. Barthes, I.G. Boneca, F. Morel, J.C. Lecron, C. Burucoa, C. Bodet, Chemokines and antimicrobial peptides have a cag-dependent early response to Helicobacter pylori infection in primary human gastric epithelial cells, Infect. Immun. 82 (7) (2014) 2881–2889.
[187] T.T. Nguyen, S.J. Kim, J.M. Park, K.B. Hahm, H.J. Lee, Repressed TGF-beta signaling through CagA-Smad3 interaction as pathogenic mechanisms of Helicobacter pylori-associated gastritis, J. Clin. Biochem. Nutr. 57 (2) (2015) 113–120.
[188] R.L. Ferrero, P. Ave, D. Ndiaye, J.C. Bambou, M.R. Huerre, D.J. Philpott, S. Memet, NF-kappaB activation during acute Helicobacter pylori infection in mice, Infect. Immun. 76 (2) (2008) 551–561.
[189] A. Sheh, Z. Ge, N.M. Parry, S. Muthupalani, J.E. Rager, A.R. Raczynski, M.W. Mobley, A.F. McCabe, R.C. Fry, T.C. Wang, J.G. Fox, 17beta-estradiol and tamoxifen prevent gastric cancer by modulating leukocyte recruitment and oncogenic pathways in Helicobacter pylori-infected INS-GAS male mice, Cancer Prev. Res. 4 (9) (2011) 1426–1435.
[190] K. Echizen, O. Hirose, Y. Maeda, M. Oshima, Inflammation in gastric cancer: interplay of the COX-2/prostaglandin E2 and Toll-like receptor/MyD88 pathways, Cancer Sci. 107 (4) (2016) 391–397.
[191] J. Ford, A. Hughson, K. Lim, S.V. Bardina, W. Lu, I.F. Charo, J.K. Lim, D.J. Fowell, CCL7 is a negative regulator of cutaneous inflammation following Leishmania major infection, Front. Immunol. 9 (2018) 3063.
[192] R.E. Ericksen, S. Rose, C.B. Westphalen, W. Shibata, S. Muthupalani, Y. Tailor, R.A. Friedman, W. Han, J.G. Fox, A.W. Ferrante Jr., T.C. Wang, Obesity accelerates Helicobacter felis-induced gastric carcinogenesis by enhancing immature myeloid cell trafficking and TH17 response, Gut 63 (3) (2014) 385–394.
[193] T. Kuzuhara, M. Suganuma, M. Kurusu, H. Fujiki, Helicobacter pylori-secreting protein Tipalpha is a potent inducer of chemokine gene expressions in stomach cancer cells, J. Cancer Res. Clin. Oncol. 133 (5) (2007) 287–296.
[194] C.F. Flach, M. Mozer, M. Sundquist, J. Holmgren, S. Raghavan, Mucosal vaccination increases local chemokine production attracting immune cells to the stomach mucosa of Helicobacter pylori infected mice, Vaccine 30 (9) (2012) 1636–1643.
[195] N. Karin, Chemokines and cancer: new immune checkpoints for cancer therapy, Curr. Opin. Immunol. 51 (2018) 140–145.
[196] O. Schillaci, M. Scimeca, D. Trivigno, A. Chiaravalloti, S. Facchetti, L. Anemona, R. Bonfiglio, G. Santeusanio, V. Tancredi, E. Bonanno, N. Urbano, A. Mauriello, Prostate cancer and inflammation: a new molecular imaging challenge in the era of personalized medicine, Nucl. Med. Biol. 68-69 (2019) 66–79.
[197] K. Fujita, T. Hayashi, M. Matsushita, M. Uemura, N. Nonomura, Obesity, inflammation, and prostate cancer, J. Clin. Med. 8 (2) (2019).
[198] M.T. Chow, A.D. Luster, Chemokines in cancer, Cancer immunology research 2 (12) (2014) 1125–1131.
[199] O. Bonavita, M. Massara, R. Bonecchi, Chemokine regulation of neutrophil function in tumors, Cytokine Growth Factor Rev. 30 (2016) 81–86.
[200] T. Tahara, T. Shibata, M. Nakamura, H. Yamashita, D. Yoshioka, I. Hirata, T. Arisawa, RANTES promoter genotype and gastric cancer risk in a Japanese population, Anticancer Res. 29 (10) (2009) 4265–4269.
[201] S.-K. Wang, H.-F. Zhu, B.-S. He, Z.-Y. Zhang, Z.-T. Chen, Z.-Z. Wang, G.-L. Wu, CagA+ H pylori infection is associated with polarization of T helper cell immune responses in gastric carcinogenesis, World J. Gastroenterol. 13 (21) (2007) 2923.

Abbreviations

AP-1: Activator protein-1
BabA: Blood group antigen binding adhesin A
CAFs: Cancer-associated fibroblasts
CagE: Cytotoxin associated gene E
GATA3: GATA Binding Protein 3
GECs: Gastric epithelial cells.
HP-NAP: The neutrophil-activating protein
JAK: Janus kinase
IRF: Interferon regulatory factor
MAdCAM-1: Mucosal address in cell adhesion molecule
MALT: Mucosa-associated lymphoid tissue
EMT: Epithelial-mesenchymal transition
MD-2: Myeloid differentiation factor 2
PBMCs: Peripheral blood mononuclear cells
PI3K: Phosphoinositide-3-kinase
NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells
MMP: Matrix metalloproteinase
NOD1: Nucleotide-binding oligomerization domain-containing protein 1
ROS: Reactive oxygen species
SHP2: SRC-homology 2 domain-containing phosphatase 2
siRNA: small interfering RNA
TAM: Tumor-associated macrophage
TILs: Tumor-infiltrating lymphocytes
TLR: Toll-like Receptor
VEGFR: Vascular Endothelial Growth Factor Receptor