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by Muhammad Miftahussurur

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The roles of IL-17, IL-21 and IL-23 in the *Helicobacter pylori* Infection and Gastrointestinal Diseases: a review

Running title: IL-17, IL-21 and IL-23 Axis in *H. pylori* Infection and GI Diseases

Astri Dewayani[1,2], Kartika Afrida Fauzia[3,4,5], Ricky Indra Alfaray[3,4], Langgeng Agung Waskito[3], Dalla Doohan[3], Yudith Annisa Ayu Rezkitha[3,6], Abdurachman Abdurachman[2], Yoshio Yamaoka[4,7,8,9], Muhammad Miftahussurur[3,7*]

[1]Department of Infectious Disease Control, Faculty of Medicine, Oita University, Yufu 879-5593, Japan

[2]Department of Anatomy and Histology, Universitas Airlangga, Surabaya 60131, Indonesia

[3]Institute of Tropical Disease, Universitas Airlangga, Surabaya 60115, Indonesia.

[4]Department of Environmental and Preventive Medicine, Oita University Faculty of Medicine, Yufu 879-5593, Japan.

[5]Department of Public Health and Preventive Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya 60131, Indonesia

[6]Faculty of Medicine, University of Muhammadiyah Surabaya, Surabaya, 60113, Indonesia.

[7]Gastroentero-Hepatology Division, Department of Internal Medicine, Faculty of Medicine-Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya, 60286, Indonesia

[8]Department of Medicine, Gastroenterology and Hepatology Section, Baylor College of Medicine, Houston, TX 77030, USA

[9]Global Oita Medical Advanced Research Center for Health (GO-MARCH), Yufu 879-5593, Japan

Corresponding authors:

Muhammad Miftahussurur, MD., PhD

Gastroentero-Hepatology Division, Department of Internal Medicine, Faculty of Medicine-

Dr. Soetomo Teaching Hospital, Universitas Airlangga, Surabaya

Jalan Mayjend Prof. Dr. Moestopo No. 6-8 Surabaya 60286, Indonesia.

Tel: +6231-502-3865; Fax: +6231-502-3865

E-mail: muhammad-m@fk.unair.ac.id

ABSTRACT

Introduction: Millions of people have been successfully infected by *Helicobacter pylori*, yet only a small proportion of infected individual will develop into an adverse outcome from chronic gastritis to gastric cancer. The advance development of the disease has been well linked with chronic inflammation establishment which significantly impacted by adaptive and humoral immunity response.

Areas covered: From cellular immunity view, this review will try to clarify the intricate axis between IL-17, IL-21, IL-23 with *H. pylori* and other gastrointestinal diseases pathogenesis.

Expert opinion: To take account, CD4 helper T (Th)-17 cells with a hallmark pleiotropic cytokine IL-17 can affect antimicrobial activity and pathogenic immune response in gut environment. These circumstances cannot be separated with the existence of affiliated cytokines, including IL-21 and IL-23 which take part in maintaining Th17 as well as accommodating humoral immune cells. Comprehensive understanding of the dynamic interaction between molecular host responses in *H. pylori* infection and gastrointestinal diseases progress may help to take the next step forward in further immune-based therapy that continue to develop.

Keywords: CD4 T cell, *Helicobacter pylori*, Gastrointestinal, T helper-17, adaptive immunity, inflammation

1. Introduction

Helicobacter pylori infection became a global concern since it affects more than half of the human population and proven to initiate carcinogenesis pathway [1]. *H. pylori* has a high recombinant rate, makes it one of the bacteria with high variety, especially in the virulence profile [2]. For example, *H. pylori* strains are more pathogenic in the presence of *cag*A gene than in the absence one [3], which the variation might explain the diverse symptoms and disease. Although most patients are asymptomatic, but approximately 10% develop peptic ulcer, 1-3% gastric cancer, and 0.1% mucosa-associated lymphoid tissue (MALT) lymphoma [4]. However, the risk to obtain the diseases after *H. pylori* infection is also associated with the geographical area and ethnicity [5]. Asian countries such as Japan, Korea, Mongolia, have the highest gastric cancer prevalence in the world [6]. These finding indicated that the outcomes of infection relying on host-pathogen interaction, inflammatory responses, host genetic diversity, and environment factors.

Chronic inflammatory reaction in *H. pylori* infection leads to the damage of the gastric mucosa. The interaction between Th cell and antigen presenting cells (APCs) during the infection time will skews adaptive immune cell into Th-polarizing-cytokines. Studies related *H. pylori* specific gastric mucosal T cell responses was usually Th1 predominant, but recently Th17, markedly by IL-17, is believed as one of the driving immune cells in *H. pylori* infection [7, 8]. Murine model demonstrated IL-17A and IL-17 F cytokines are playing role in neutrophil recruitment in mucosal immunity to extracellular pathogen. Although it is advantageous for host defense [9], the neutrophil activation and recruitment become the cellular point in *H. pylori* inflammation lesion [10].

IL-17 has many associated cytokines such as IL-1β, IL-6, IL-21, and IL-23. Studies affirmed IL-17, IL-21, and IL-23 are related with autoimmune diseases, allergy, and pathogen immunity [9, 11, 12]. The IL-17/IL-21 axis and IL-17/IL-23 axis are involve in

maintaining Th17 expansion, antimicrobial even multiple inflammatory and hemapoietic effects on epithelial, endothelial, and fibroblast cells [13, 14]. Together, the cytokines intertwine correspondence in gastritis process. IL-21 itself has pleiotropic action on adaptive and innate immune cells such as increasing pro-inflammatory cytokines release from macrophage, enhancing proliferation of lymphoid cells and promoting B cell differentiation. The IL-23 expression in *H. pylori* infection patients is elevated and positively correlated with the degree of neutrophils and monocytes infiltration [15].

While many factors can contribute, this review designs to elaborate the interaction of host immunity with *H. pylori* focusing on IL-17, IL-21 and IL-23. Understanding the relation between cytokines is needed for better comprehend of *H. pylori* infection pathogenesis and gastrointestinal-related inflammation diseases.

2. Bacterial antigen induced immune response

In order to colonize in extreme condition of human stomach, *H. pylori* produces numbers of bacterial virulence factors that play important role in immune invading mechanisms. The most well studied bacterial components of *H. pylori* are cytokine associated gene A (*cagA*) and vacuolating cytotoxin A (*vacA*). CagA is a part of a 40kb gene cluster famously known as cag pathogenicity island *cag*PAI that encodes Cag type IV secretion system (CagT4SS) which contributes to the pathogenicity of *H. pylori* [16]. The CagT4SS delivers *H. pylori* components into host through outer membrane protein (OMP) [17]. Evidences show the CagA product involves in T cells activation and induction of proinflammatory cytokines of the host cell resulting in more severe gastritis and higher prevalence of peptic ulcer or gastric cancer. Patients with *cagA*-positive strain had Th1-mediated cellular response in early carcinogenesis then dominated by Th2-mediated cell immunity in advance stage while there was no such tendency in *cagA*-negative patients [18]. The injection of *cagA* into gastric

mucosal also capable of inducing nuclear factor κB (NF-kB)-mediated IL-8 production [19]. *H. pylori* strain that possess complete *cag* PAI induce significantly higher levels of IL-8 [20]. The complexity of *H. pylori* influences on immune response via antigen presenting cells (APCs) representing by macrophage, DCs and B cells. The affect has been describes in DC maturation, altering antigen presentation, while other studies provide evidences "tolerogenic" DCs [21-23]. DCs-induced pro-inflammatory cytokines IL-6, IL-12, IL-1b, IL-23 express more in *in vitro* cultured with *H. pylori* [21, 24]. DC maturation regulator, transcription factor E2F1 is downregulated in DC maturation. *H. pylori* VacA sustain immature states of DC by retrieving E2F1. Moreover, VacA suppressed costimulatory factors (CD40, CD86, MHC-II) that might dampen T cells and promote tolerance [25]. Combined, these data pointing that functional *cag* PAI can impact host response resulting different phenotypes, although the differences in non-physiological level of purified antigen of virulent factors between studies may cause the discrepancy.

Urease protein in combination of subunit A (UreA) and subunit B (UreB) is another abundantly produced protein from *H. pylori*, take up to 5% bacterial cell protein. UreB is contribute on colonization and induce strong immune responses. CD4+ T cells from *H. pylori*-infected mice were co-cultured with recombinant UreB in the presence of macrophage as APC was potent enough to induce Th17 number as well as IL-17A levels. When given rUreB as immunization agent, it could prompt UreB-spesific Th17 cells and reduced bacterial colonization [26]. This shows urease as an important protein to induce Th17 response both in vitro and in vivo.

3. Overview of IL-17, IL-21 and IL-23

3.1 IL17

IL-17 consists of a related cytokines family (IL-17A-F) is majorly produced by specific subset of CD4 T helper (Th) 17 cells. In a lesser extent, Th17 also produces TNF-α, IL-6, IL-21, IL-22, and granulocyte macrophage-colony stimulating factor (GM-CSF) [13]. Th17 lineage develops independently from Th1 and Th2 differentiation.

To date, there are five receptors identified as IL-17 receptor family (Figure 1). This family comprises receptor subunits IL-17A, IL-17B, IL-17C, IL-17D and IL-17E. Many of the genes encoding the IL-17R family are associated with cluster on mouse chromosome 6 and 14, also human chromosome 3. From all of the information regarding IL-17R and its ligand, the receptor for IL-17D is yet to be known, as is the ligands for IL-17RD/SEF or an IL-17RA/IL-17RD pairing if it is successfully proven to be exist [27, 28]. This information might be evolved and their correlation with molecular pathways in development of Th17 cells in human become clearer in future.

The molecular pathways regulating Th17-cells development in humans have not been fully explicated, but studies in murine indicate the Th17 cell differentiation is driven by transcription factor retinoic acid-related orphan receptor gamma-t (RORγ) in the presence of IL-6 and TGF-β1 then expanded by IL-23 [29, 30]. There are similarities among Th17 member, but IL-17F has the highest amino acid homology with IL-17A and both cytokines might be secreted as IL-17A/F heterodimer [10].

Similar to the innate immune receptors such as IL-1R and toll-like receptors (TLRs), IL-17A activates NF-κB, a well-known transcription factor correlated with inflammation process [31]. IL-17A can activate p50 and p65 subunit of the classical NF-κB pathway. This activation leads to NF-κB inducing kinase (NIK) mediation events in the non-classical pathway [32]. IL-17 is capable of activating NF-κB and c-Jun N-terminal kinase (JNK) in the presence of TNF receptor associated factor 6 (TRAF6). Supporting this finding, several studies also have concluded a critical role for TRAF6 as an adaptor for various signal such as

TNFRs as well as IL-1 receptor including IL-17R [33]. A study exhibited that in embryonic fibroblasts (EFs) of TRAF6 deficient mice, IL-17 incapable to activate the IkappaB kinases (IKKs) and JNK. This concludes the lack of TRAF6 seems to be the crucial point for the failure to respond to IL-17 while transient transfection of TRAF6 expression plasmid into the TRAF6-deficient cells could reverse the effect [34].

Th17-associated cytokines has been described in a growing list of diverse autoimmune diseases, such as multiple sclerosis, Chron's disease, psoriasis, or arthritis. Mice with IL-17, IL-23p19, or IL-12/IL-23p40 deficiency are resistant to EAE, IBD, or CIA, while the absence of Th1 affiliation, IL-12 or IFN-γ signaling worsens disease [35]. In brief, the function of each member of IL-17 is unique but still not well understood. IL-17A was believed to have function for autoimmune pathology, neutrophil recruitment and extracellular pathogen immunity. IL-17B-IL-17D was hypothesized had function in pro-inflammatory activities. IL-17E can induce Th2 and suppress Th17. IL-17F and IL-17A/F, which the ligand was yet to be found, believed to have role in neutrophil recruitment and immunity to extracellular pathogen [28]. Overall, the most widely studied member of the IL-17 family was IL-17A. This might be because IL-17A plays a critical role for host defense against microbial infection and tissue inflammation.

3.2 IL-21

IL-21 is another cytokine produced by Th17, also by T follicular helper (Tfh) cells, NK and Th1 cells [36]. It has close structural similarities with IL-15, IL-2 and IL-4 and mediates its function via a heterodimeric receptor that composed of IL-21R and the common γ-chain [37]. IL-21 signaling leads to the activation of JAK-STAT signal, or MAPK in some cells. IL-21 take role in activation, proliferation and survival of both $CD4^+$ T cells and B cells, functional

activity of CD8 T cells and NK cells, suppress Treg differentiation, or inhibit function of DC. Studies shows IL-21 correlate with chronic autoimmune diseases or EAE [38]. IL-21 can synergize with TGF-β1 to induce murine Th17 independently of IL-6 [39] through similar condition by upregulated IL23R and RORγt expression on naïve T cells and impeded the development of TGF-β-induced FOXP3^{+} Treg cells [40].

IL-21 receptor was discovered in 2000 as an orphan type I cytokine receptor. IL-21R is expressed in many cells, including immune cells (T cells, B cell, DC, NK) and non-immune cells (epithelial cells, fibroblast, and endothelial cells). The similarity of IL-21 to IL-2, IL-4, and IL-15, suggested the possibility that IL-21 might share an important receptor part on the common cytokine receptor γ chain (γc) which encoded by IL2RG, the gene found to be mutated in humans with X-linked severe combined immunodeficiency (XSCID) [41]. Similar with the other γc family cytokines in activating Jak1 and Jak3, where IL-21R interacting with Jak1 and Jak3 interacts with γc (Figure 2) [42, 43].

3.3 IL-23

IL-23, a heterodimer of IL-23p19 subunit and an IL-12p40 subunit, is produced by antigen presenting cells (APCs) including macrophages, dendritic cells, and neutrophils. IL-23 has several homologies with IL-6 and granulocyte colony-stimulating factor (G-CSF). The IL-23 receptor (IL-23R) itself composed of IL-12R β1 combined with IL-23R, a specific receptor which resembles IL-6gp130 (Figure 3) [44, 45]. The IL-23 signaling pathway is similar to that of IL-12, with a preponderant role for STAT3 [44].

The function of IL-23 resembles the function of IL-12 in linking innate responses and adaptive immunity. Both cytokines are increased in intestinal inflammation, however IL-12 stimulates IFNγ and Th1 lineage whereas IL-23 does not directly stimulate IFNγ but acts on memory cells and enhances Th17. In vitro studies show IL-23 is not driving naïve CD4 T

cell toward Th17 phenotype, but later in Th17 development, the focus is in regulating IL-17 secretion through at STAT3 dependent pathway [13, 35] or collaborate with other pathways indirectly affects Th17 survival. In the absence of TGF-β, IL-23 in conjunction with other pro-inflammatory cytokines IL-1β and IL-6 helps promoting the differentiation of Th17 [46, 47]. Other function that unique from this cytokine is that IL-23 acts also as an end-stage effector cytokine through direct action on macrophages [48].

4. The role of IL-17, IL-21 and IL-23 in gastrointestinal tract

Th17-associated cytokines has been well demonstrated for both protective and pathogenic functions in gut environment. The IL-17 protective role have been shown to be important for controlling *Citrobacter rodentium* oral infection [49]. In another case, mice dextran sulphate sodium (DSS) induced colitis model had exacerbated inflammation after IL-17A neutralization. IL-17A and IL-22 is believed helps strengthen tight-junction formation by inducing the expression of claudins in intestinal epithelial cells, stimulating mucin production, and enhance goblet cell restitution [14]. The synergize function also activates the expression of S100A8 and S100A9 (component of calprotein, lipocalin, and β-defensin protein) in epithelial [50]. Whereas IL-17F is suggested exacerbates inflammation DSS model. Mice deficient in IL-17F develop milder symptoms and present lower mRNA expression comparable to wild-type controls [14].

IL-21 and IL-23 as associated cytokines not only linked with Th17 but also cross-regulated with classical IFNγ-produced Th1. The role of IL-21 in Th17 and Th1 is prominent in chronically inflamed areas. In Chron's disease (CD) tissue, IL-21 was produced mostly by CD4+ T cells co-expressing IFNγ and small amount from Th17 [51]. Ulcerative colitis (UC) patients displayed excessive IL-21 in mucosal sample, leads the colonic epithelial cells to produce macrophage inflammatory protein (MIP)-3a or called CCL20, a chemokine

upregulated in IBD patients or mice with chemically-induce colitis. Molecular signaling IL-21 activates ERK 1/2 and p38 mytogen activated protein (MAP) kinase, whereas blockade those pathways significantly inhibited MIP-3a. Thus, IL-21 deficient mice are protected from colitis through reduction of Th17 and Th1 as well as MIP-3a/CCR6 interactions displaying the attraction of pathogenic Th17 cells into inflamed tissues [51, 52]. Other than sustaining immune cells responses, IL-21 is capable to enhance the production of Matrix metalloproteinases (MMPs). Elevated expression MMP-1, MMP-2, MMP-3, and MMP-9 by fibroblasts, and MMP-2 and MMP-9 by gastric epithelial cells following IL-21 induction may contribute to extra-vascularization, inflammation, and remodeling of the extracellular matrix (ECM) [11].

There is an increase levels of IL-23 and Th17 cytokines in intestinal mucosa, plasma and serum of IBD patients and polymorphism in IL-23 or IL-17 pathways has been associated with increasing risk [53, 54]. From molecular view, IL-23 favors pathogenic Th17 phenotype compared to cells cultured under TGF-β and IL-6 due to IL-23 incapability to induce IL-10 production for immune suppression [55]. Using $Rag^{-/-}$ mice colitis model treated with IL-$23R^{-/-}$ $CD45RB^{high}$ $CD4^{+}$ cells alone could elevate IL-10 production, while co-transfer with wild-type T cells abrogated the action. Implicating the capability of IL-23 responsive T cells to reduce IL-$23R^{-/-}$ T cells response to produce IL-10 in colonic mucosal. The $Rag^{-/-}$ recipients IL-$23R^{-/-}$ donor T cells also had increased $Foxp3^{+}$ regulatory T (Treg) cells that important for maintaining intestinal homeostasis[56]. Another evidence of pathogenic role is suggesting from the IL-23 ability to stimulates IFNγ production by human memory T cells or in the *H. hepaticus* colitis model. The p19 subunit found to regulate mucosal rather than systemic immune responses in the colitis model [12]. In addition, one study shows the early protective function of IL-17A in gut mucosa barrier produced by IL-$23R^{+}$ $ROR\gamma t^{+}$ T cells but IL-23 independent. IL-17A regulating occludin protein cellular

localization and Act-1 activation during DSS injury, while IL-23 requiring RORγt for transactivation to promote IL-17F. Neutralizing IL-23 but not IL-17A minimized the tissue inflammation [57]. These findings denote that IL-23 may promote intestinal inflammation via T cells function and restraining mucosal-protective population.

5. Th17 Roles in *H. pylori* infection

In the early colonization, *H. pylori* modulates immature "tolerogenic" DCs that skews Th17/Treg balance towards Treg (Figure 4). Tregs may reduce inflammation and provide pathogen persistent [58]. Th17 cells function is still contradictive although tend to display pro-inflammatory function in *H. pylori* disease context. IL-17 required to help bacterial clearance though the levels produced may insufficient for extensive clearance and cause IL-17-mediated-diseases from the inflammation [58]. The IL-17 family could induce numerous immune regulatory and pro-inflammatory related to local tissue such as antimicrobial peptides (b-defensin and S100 protein), chemokines (CXCL1, CXCL-5, CCL-2, CCL-20) and MMPs. The increased production of chemokines can cause inflammation-associated neutrophil infiltration [50, 59].

Mouse model demonstrated elevated IL-17 through the Th17 responses then precede Th1 mediate mucosal inflammation. Th17 later contributes to chronic inflammation thus favors pathogen infection [8]. In human cases, there is an elevated level of IL-17 and IFNγ in *H. pylori* infection patients gastric mucosa, adding with upregulation of Th17-related genes expression (IL-6, IL-23 p19, IL-12/IL-23 p40, TGF-b1) [7]. The elevation of IL-23 and IL-12 indicated the Th1/Th17 mixed responses [10].

IL-17 expression is reported to be positively correlated with IL-8 level in *H pylori*-colonized biopsies. Antigens from *H. pylori* stimulates epithelial cells, endothelial cells, and macrophages production of IL-8 and growth-regulated oncogene-alpha that produce

chemotactic gradient for attracting neutrophils into the gastric mucosa. IL-17 secreted by Th17 stimulates gastric epithelial cells to release IL-8, while blocking IL-8 can impede the migration effects [13]. This consequence of infection by active synthesis of IL-8 in conjunction of IL-17 might be involved in gastric ulcer development.

Stimulation of IL-17A by Th17 can also be influenced by IL-1β. One study showed IL-1β levels remained high in individuals with past *H. pylori* and correlate with persistent specific Th-17 responses [60].

6. IL-17 and IL-21 axis in *H. pylori* infection

IL-21 is increasing in *H. pylori* infection case and also found higher in gastric cancer mucosa tissues [61, 62]. To the proinflammatory side, molecular signaling shows STAT1 and STAT3 are important in Th17 and Th1. $CD4^+$ T cells of $IL21^{-/-}$ *H. pylori*-infected mice had lower phosphorylation of STAT1 and STAT3 than wild-type. Moreover, this led to lower expression of *tbx21* and *rorc*, gene encode Tbet and RORγ. IFNγ and IL-17 can induce chemokine expression and neutrophil that needs in controlling bacterial burden. Thus IL-21 deficiency had lower IFNγ and IL-17 were protected from chronic gastritis despite having more bacterial colonization [38]. IL-21 could also signal through epithelial cells to induce chemokine CCL20. Alongside with *H. pylori* similar effect, the CCL20/CCR6 interaction increase T cells subset mobilization [63]. On the other hand, being a pleiotropic cytokine, *in vitro* assay shows recombinant IL-21 has immunomodulatory effect on *H. pylori* cocultured DCs by reducing proinflammatory cytokines (IL-1b, IL-6, IL-12, and IL-23) [64]. In addition, IL-21 induces MMP-2 and MMP-9 production in vivo via NF-κB activation might related with chronic inflammation [61].

Other than Th17, IL-21 produced within the germinal center in lymph nodes or Peyer's patches is demonstrated autocrine loop for Tfh cells generation. In addition, B cells

proliferate needed IL-21 responsiveness and might help to switch isotype or increased the antibody production [65]. In human and mice, *H. pylori* infection stimulates strong specific IgG and IgA antibodies in blood and gastric mucosa. IL-17RA$^{-/-}$ mice shows an impaired negative feedback of Th17 from IL-17A and IL-21 in higher expression in the stomach. At the chronic infection these mice have more abundant of B cells infiltration and lymphoid follicles in gut following enhancement of anti-*H. pylori* antibodies. These may implicate IL-21 drives B cells in antibody response of IL-17RA$^{-/-}$ mice [66]. In accordance, *H. pylori*-infected IL-21 deficient mice lack of *H. pylori* specific antibody response in serum [38].

The importance of antibodies level is still in question, B cell in gastric lumen has adapted to produce secretory IgA and IgM to facilitate the bacterial clearance or toxin neutralization. Even so, *H. pylori* is using several different receptors that one antibody ligand would not be effective for protection. Its importance in gastritis pathogenesis can be account from the capability of monoclonal antibodies against *H. pylori* to recognize an epitope on mice and humans gastric epithelial [67]. Mice injected with these antibodies generated gastritis and caused mild erosions [68]. Interestingly, study using B cell deficient mice showed *H. pylori*-specific Abs production had lesser the inflammation but prolonged the eradication time [69]. However, the lack of B cells does not diminish gastritis.

These pointing the possibility biomarker from the specific Abs to help predict patient outcome. In addition, while showing impact on B cell proliferation, it is less unknown on IL-21 correlation with MALT lymphoma in gastric as it is account in parotid gland of Sjorgen patient [70].

7. IL-17 and IL-23 axis in H. pylori infection

The relationship between IL-17 and IL-23 tend to the pathogenic side. The function of Th17 cells itself different between diseases depend the cytokines activation in upstream pathway. It

is stated that Th17 activated by TGFβ and IL-6 promote barrier tissue integrity, mucosal defense and mitigate the pathogenic responses, while IL-23 drives Th17 cells to produce tissue inflammation in chronic infection, granuloma formation and autoimmunity [71].

Previous result shows IL-23 highly express in *H. pylori*-colonized mucosa patient with or without CagA [7]. *H. pylori* colonization leads to the activation APCs especially DCs as center role in the induction of adaptive immune responses that produce cytokines involved in Th17, Treg differentiation. Khamri et al., demonstrated the *H. pylori* cultured-DCs able to induce IL-23 and significantly boost IL-17 from $CD4^+$ T cells compared to untreated DCs. They also showed that IL-23-positive DCs were presented in human infected samples [72]. *H. pylori* neutrophil-activating protein (*H. pylori*-NAP) triggers IL-23 production from neutrophils and monocytes.

IL-23 shows minor contribution to the development of chronic gastritis in *H. pylori* infection mouse model after 3-4 months post infection but not in acute inflammation. The IL-$23^{-/-}$ mice had significant lowered IL-17 and IFNγ after chronic infection [73]. On the other hand, *H. pylori* co-culture with BMDCs can induce mRNA of IL-6, IL-1β and IL-23p19 that might drive IL-17 expression via STAT3 [73]. Treatment of human lamina propia mononuclear cells (LPMC) with anti-IL-23 will inhibit pSTAT3 which damped IL-17 production [7]. There are some possible mechanisms of STAT3 regulates IL-17. One possibility IL-23 through Jak2 activate STAT3 and NF-kB that both directly binds to IL-17 promoter hence enhance transcriptional activity [74]. Another way is STAT3 facilitates IL-17 differentiation regulator, RORγt [75]. STAT3 could also enhance IL-23R expression, hence amplifying the feedback that maintain IL-17/IL-23 pathway [7].

This conclude *H. pylori* evading mechanism by modulating DCs phenotype. In response to colonization, DCs secreted IL-23 has autocrine role in attracting neutrophil as well as maintaining Th17 differentiation.

8. IL-17 roles in gastric cancer development

The exact causes of gastric cancer are still poorly understood, but it has been widely studied that the metastatic progression relies upon inflammation. Accumulating evidence indicates Th-17/Treg proportion found to be increased in gastric cancer patients [76]. The Th17/Treg plasticity is shown from the capability of Treg turn into Th17 or vice versa where coexpressing both Treg and Th17 (Foxp3 and RORgt) signature genes shares in same cell. TGF-β dose dependent alongside IL-6, IL-21, IL-23 inhibit Foxp3 expression [77]. Furthermore, it also proven that IL-17A is strong candidate of immunology inflammatory immunological response leading to cancer. The concept of microbiota induce cancer by an inflammatory immunological pathway related IL-17A could be found in *H. pylori* induce gastritis which precedes most of gastric cancer case worldwide [78].

Th17 responses in the pathogenesis of gastric cancer seeing through the transcription factor RORg mRNA significantly increase is correlated with IL-17, IL-6, TGF-β, and IL-23[79] and those corresponding with the severity [80]. Gastric myofibroblast (GMF) as APC from both *H. pylori*-exposed and GC patients had elevated mRNA IL-6, TGF-β, and IL-21 to maintain Th17 induction [62]. This suggesting that mucosal contact from chronic inflammation effect with *H. pylori* infection contributed to Th17 production and gastric cancer development. Moreover, the Th17 immunity still lasts in serum even after bacterial eradication. The tenacity of IL-17A and IL-17F exposure is suggested to increase the risk of cancer [81].

Several studies already proved the theory of IL-17/IL-23 axis plays part in inflammation-related malignancies, such as gastric neoplasms. Furthermore, epidemiological analyses showed that Asian patients with selected polymorphisms in genes coding for both IL-17 and IL-23 might have an altered risk for developing gastric cancer [82].

The pro-tumorigenic interrelation with IL-8 that produced by many types of cancers. IL-8 can trigger differentiation of Th17 cells through simultaneous activation of STAT3 with IL-6 and IL-17 can induce IL-8 from epithelial which augmented neutrophil migration. Moreover, IL-17 displaying the ability to produce pro-angiogenic factors including VEGF, prostaglandin E1 (PGE1), PGE2 and macrophage inflammatory protein-2 (MIP-2) by fibroblasts and tumor. This relation pointing IL-17 stimulation of vascular endothelial cell migration and cord formation can enhanced angiogenesis and tumor growth [83].

9. Interleukin Polymorphism and the development of gastrointestinal cancer

Interleukin could be expressed in a different level that leads to different inflammatory effect which influence the severity of diseases. Several factors from host could cause the expression variation such as age, gender, the presence of autoimmune disease, and Single Nucleotide Polymorphism (SNPs) that presented as a nucleotide variation between the allele [84]. The SNPs could partially explain the different susceptibility to diseases among the patients. IL-17, IL-21 and IL-23 polymorphism and their association in many diseases were reported.

Several studies reported that the subjects with high expression of IL-17 had a better prognosis compared to the low expression, but some studies reported otherwise. Despite the controversial, the SNP is believed to code the variation of expression that associated with the gastric cancer. A metanalysis evaluated the association of IL-17 rs1974226, rs2275913, rs3819024, rs4711998, and rs8193036 in the 1126 gastric cancer and 1221 cancer free control [85] . In this study, rs3819024 with AA allele was associated with the decreased GC risk. The stratification study showed that IL-17 rs1974226 AA was associated with GC risk in older age (>59 years-old). The higher GC risk was associated independently with rs1974226 for AA compared to GG+GA. GC risk was also significantly associated with the rs2275913 for GA+AA compared to AA. The variation of rs2275913 was located in the genes of IL-17A

which also called IL-17A G197A polymorphism. The updated meta-analysis by Elshazli et al including 7,660 cases and 9,409 controls, showed similar results for rs2275913 c-197G >A [86] . Another polymorphism in IL-17A was in the rs3748067 c1249C >T that also associated with GC risk as reported in the meta-analysis [87] [86]. Polymorphism in IL-17F rs763780 was associated with the susceptibility of patients to the gastric cancer. The association of IL17A rs2275913G>A and IL-17F rs763780C>T polymorphisms with the other gastrointestinal cancer such as hepatocellular carcinoma and colorectal cancer were also evaluated. However, there were no statistically significant association, indicating a cancer-type-specific function [88]. They also found that the polymorphism was significantly associated with gastric cancer in the Asian ethnic, but not in the Caucasians [88]. These results indicate the strong role of host factor to the susceptibility to gastric cancer.

Interleukin gene polymorphism was detected in the IL-21 rs907715, rs2221903, and rs12508721. Recent study investigated the association of those SNPs with gastric precancerous lesion in 588 cases and 290 healthy controls but only *IL-21* rs907715 CC+C was associated with the atrophy and the intestinal metaplasia [89]. The polymorphism can alter the regulation of transcription, protein translation and also the cell proliferation.

To date, the SNPs of IL-23 genes and its association with gastric cancer was not established. However, SNPs in the IL-23 receptor (IL-23R) was reported. In a study with 479 cases and 483 controls, patients with *IL-23R* rs1884444 GG and rs6682925 CC genotype had less survival. This survival was worse in older groups of patients with *IL-23R* rs1884444 GG. Similarly, the female participants with rs6682925 CC also had worse survival. This result showed a possible utility to of interleukin gene polymorphism to stratify the risk of patients to gastric cancer and choose the treatment strategy in addition to *H. pylori* infection.

10. Conclusion

Th17 has been displayed significant contribution in autoimmune disease processes and inflammation in GI tract. IL-17 as the main cytokine from Th17 cell has a pleiotropic effect in defensive and pathogenic gut homeostasis. In *H. pylori* infection, IL-17 is necessary for bacterial clearance, however the dual side gave rise to inflammation-induced diseases. Together with IL-21 and IL-23, those play role in inflammation site formation directly or indirectly. From reviewing previous sources, this study led us to identify the lack of understanding parts between cytokines and intestinal mucosa. Since its important role in the gastroduodenal diseases, a comprehensive dynamic of IL-17 modulation needs to be considered carefully for the clinical outcome of gastritis and gastric cancer patients.

Expert opinion

It is always quite fascinating in understanding immune response that involved in each step of pathogenesis. Gastrointestinal diseases both autoimmune and *H. pylori*-related infection has similarity concerning inflammation. Other than Th1, another subset namely Th17 arises role in mediating that process. Correlation of IL-17 levels and inflammation rate in gastritis dan gastric ulcer of *H. pylori* patients have been proven though the double-edge sword of Th17 and associated cytokines function is still controversial. Research concerning Th17 differentiation has been done in human and animal model. However, the requirement factors in human Th17 differentiation need to be carefully interpreted since most studies were using peripheral blood, considering more antigen exposure in particular subjects, thus it may not be naïve in starting population rather than isolated from cord blood or spleen. Understanding proliferation and differentiation of human T cell subsets in naïve and committed cells will help in a grasp of manipulates Th17 cell responses.

The stimulation in microenvironment can change T cell polarization depends as seen in acute or chronic standpoint. There is a possibility Foxp3 Treg can become Th17 under

microenvironment influence and this plasticity also displayed on Th17/Treg in human patients, yet the exact underlying mechanism of interconversion in co-expression T cells still poorly understood. *H. pylori* has infected humans for almost 60.000 years and evolved escaping strategies to elude immune system in their colonization time. The enigma of remodeled immune balance can be seen from how patient with ulcer has better *H. pylori* clearance than chronic gastritis. The of abundant immunosuppressive Treg for colonization in chronic gastritis state could not efficiently eradicate the infection with less symptom. On the other hand, in gastric ulcer the balance more to the proinflammatory as well as the increase of IL-23 and IL-21 helping Th17 to induce severe pathological lesions but *H. pylori* can be handle better with antibiotic and proton-pump inhibitor [90-92]. This related with recent studies displayed a negative correlation of H. pylori dan IBD incident. It remains controversial as several studies stated that H. pylori infection protective against the IBD progress [93, 94] while small numbers revealed no significant correlation [95]. The infection could elevates TGF-β but lower IL-17A, IL-17F, IL-6, IL-21, IL-23 level thus tend to immunosuppressive Treg balance that crosstalk with colon environment in DSS-colitis model [96].

Besides that, genetic factors play role in alteration of cytokine alongside with environmental factors in carcinogenesis. Polymorphism in IL-17 exhibit a link with *H. pylori* infection which is one of the predisposition of GC development through increasing activity dan inflammation score [97]. Moreover, cascade signaling such as TLR could also increase the susceptible [98]. China population study discuss IL-21 polymorphism with risk of precancerous lesion [89], but limited number of studies on IL-21 cannot describe the bigger picture. These indicating immune response-related pathogenesis or altered of related cytokines following the polymorphism.

In the time ahead, the exact mechanism of immune response regulatory to become protective or pathogenic and vice versa will continue to be untangled. Th-17 and IL-23

pathways variants associated with risk of intestinal inflammation condition, thus the use of cytokine inhibitor in gastrointestinal diseases has been clinically trial studied. Selective IL-23 and Th17 agents such as briakinumab, secunikumab or brazikumab have been tried to IBD patient in phase 2 trial may elicit promising result yet still controversial. Some clinical trial of dermatology dan rheumatology patient under cytokine inhibitor therapy reported newly cases of IBD [99, 100]. A meta-analysis revealed the incidence rates of IBD cases from anti-IL-17 of 0.37 (95% CI: 0.12,0.61) of the entire treatment with no significant differences between indications [101]. Pathogenicity IL-17A capable of inducing apoptosis of parietal cells from mouse gastric mucosa as similarly seen in chronic inflammation. Neutralizing IL-17A reduce atrophy severity than untreated mice although did not reverse completely [102]. Further ahead, these cytokines might become adjuvant treatment in solid tumor such as GC. However, which cytokine has potent role in GC even targeting cytokine signaling complex to help maximize efficacy and reduce side-effect remain to be elucidated.

Article Highlights

- Th17 with IL-17 as hallmark cytokine emerges as key regulator in gut inflammation. IL-17 can activate proinflammatory pathways NF-κB and JNK.
- The associated cytokines namely IL-21 and IL-23 play role in maintaining Th17 proliferation. Interrelation of IL-17/IL-21/IL-23 attracts neutrophil migration, change extracellular matrix (ECM), and alters mucosa protective defenses.
- *H. pylori* can amend immune response throughout their immune escape mechanism using antigen or protein part.
- There is a dysregulation of Th17/Treg balance in pathogenesis of *H. pylori* infection and IBD that later could shape the disease outcome.

- Variant polymorphism in IL-17, IL-21 and IL-23 display association with risk of precancerous lesion or gastric cancer.

Author Contributions

Conceptualization, AD; writing—original draft preparation, AD; writing—review and editing, KAF, RIA, LAW, DD, YAAR; visualization, RIA; supervision, AA, YY, MM; project administration, MM. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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Figure Legends

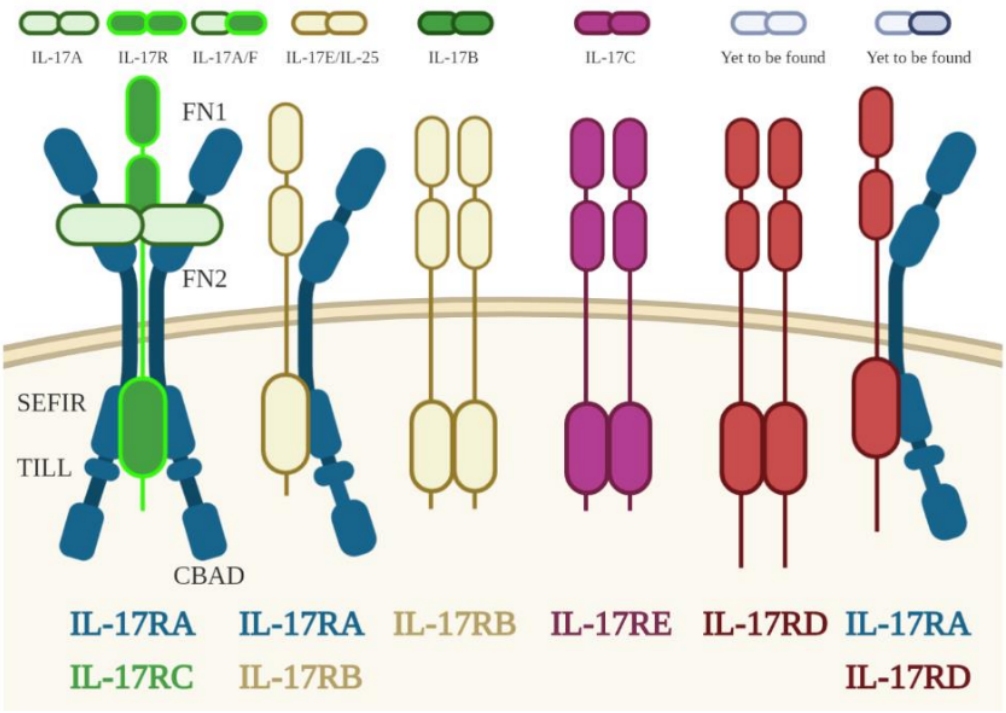

Figure 1. Illustration of IL-17 receptor family, receptor-ligands correlation and their main structural appearance. FN: fibronectin III-like domain; SEFIR: SEF/IL-17R-related signaling domain; TILL: TIR-like loop; CBAD: C/EBPβ activation domain.

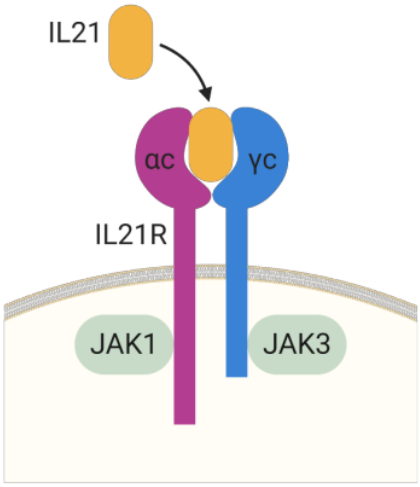

Figure 2. Illustration of IL-21 receptor and ligand. JAK: Janus Kinase

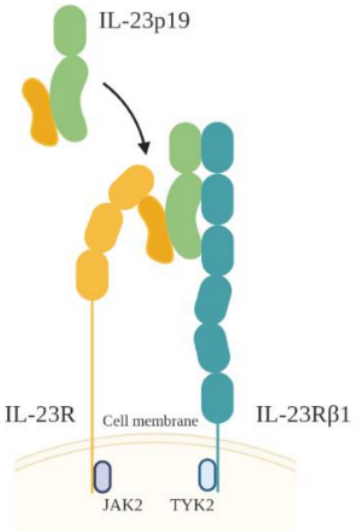

Figure 3. Illustration of IL-23 receptor and ligand

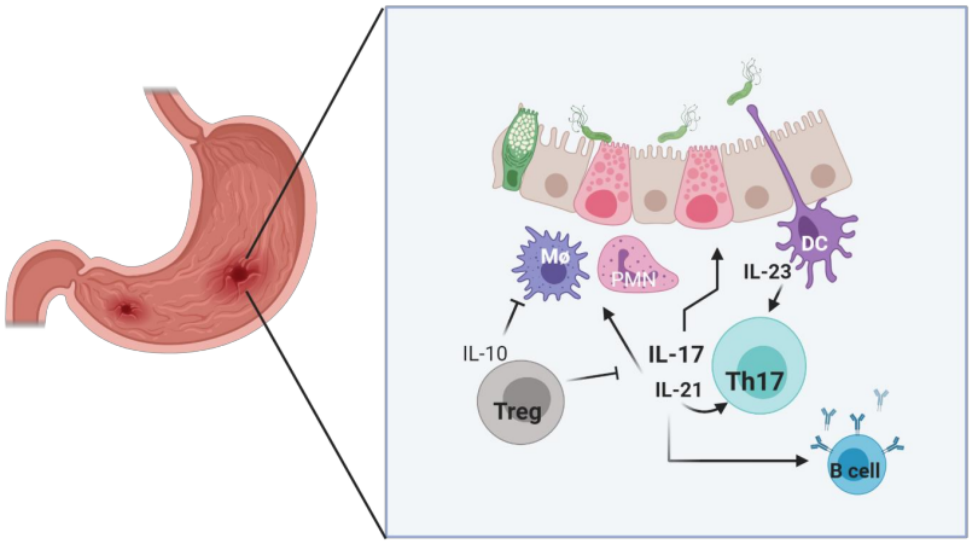

Figure 4. Illustration of immune cellular interaction in *H. pylori* infection. *H. pylori* is sensed by dendritic cell (DCs) and epithelial cells followed by the advent of $CD4^+$ T cells, PMN and macrophage to gastric mucosa for bacterial clearance. However, continuous activation might increase local inflammation. Bacteria could modulate escape mechanism and skew DCs to produce IL-23. Th17 equilibrium lean to the pathogenic side, releasing proinflammatory cytokines that recruited more PMNs. Regulatory T cells reported suppressing inflammatory effects of infection in gastric mucosal.

Treg, regulatory T cell; Th17, T helper produce IL-17; DC, dendritic cell; Mϕ, macrophage; PMN, polymononuclear neutrophil; B cell, lymphocyte produce antibody.

The roles of IL-17, IL-21 and IL-23 in the Helicobacter pylori Infection and Gastrointestinal Diseases: a review

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