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Intersections between innate immune response and gastric cancer development

INTRODUCTION

Globally, gastric cancer (GC) is the fifth most commonly diagnosed malignancy. Although there has been a reduction in its incidence, its poor prognosis makes it the fourth leading cause of cancer related deaths per year[1], and around 86% of all GC cases in 2018 occurred in countries with a high or very high Human Development Index, where 60% of the total cases occurred in Eastern and South-Eastern Asia[2]. GC development is a multistep process initiated by the transition of normal mucosa to non-atrophic gastritis. This superficial gastritis may progress to atrophic gastritis, then intestinal metaplasia and finally to dysplasia and adenocarcinoma[3]. Overall, GC is viewed as the consequence of a multifactorial process involving environmental factors (socioeconomic status, smoking and alcohol consumption), dietary habits (diet rich in salt and poor in antioxidants) and intrinsic factors (ethnicity, genetic background, age and gender)[4,5]. Recently, a meta-analysis and prospective cohort study demonstrated in the Chinese population, that healthy lifestyle factors such as abstention from smoking, non-consumption of alcohol, low consumption of preserved foods, and frequent intake of fresh fruits and vegetables - all of them in combination- reduce significantly the relative and absolute risk of incident GC although the individual carries a high polygenic risk of GC based on the presence of 112 single-nucleotide polymorphisms[6]. This observation suggests that some intrinsic host factors, like the genetic background, may be secondary to external or environmental aspects during GC onset.

Most of the malignant gastric tumors correspond to the histological type of adenocarcinoma (approximately 90%), with a lower percentage of lymphomas of the

mucosa-associated lymphoid tissue, leiomyosarcomas and other rarer tumors[7,8]. The adenocarcinomas have been divided classically into two histological subtypes: diffuse and intestinal, each of which have differences in their presentations depending on the anatomic subsite, age when diagnosed, sex, race, demographical distribution and socio-economic situation[7-9]. More recent molecular and genomic classifications have defined four major genomic subtypes of GC: The Epstein-Barr virus (EBV) infected tumors; genomically stable tumors; chromosomally unstable tumors; and tumors with microsatellite instability (MSI)[5], all of them with a poor prognosis and different molecular profiles.

It is very well documented that GC is strongly associated with infectious agents such as the bacterium *Helicobacter pylori* (*H. pylori*) and, recently, the EBV[5]. Approximately 15%–20% of human cancers are provoked by cancer-causing viruses[10]; however, the specific role of EBV in GC development is not clear as yet. Although the World Health Organization has categorized *H. pylori* as a group 1 carcinogen[11], the role of other bacteria in causing cancer is controversial; studies have shown that some bacteria, such as *Fusobacterium nucleatum*[12], and *Porphyromonas spp.*[13,14] play a role in the development of colon, oral and other digestive cancers. Nevertheless, all those microorganisms can promote a local inflammatory status and a parallel activation of protumoral pathways.

Innate immunity represents the first barrier against pathogens, and epithelial cells of the gastric mucosa are the first line of immunity against, for example, a *H. pylori* infection. In response to an infection, many physiological adaptations are observed, such as an increase in vascular diameter and permeability along with an overexpression of cell-adhesion molecules on endothelial cells, promoting the extravasation of myeloid cells into the inflamed site of infection. The characteristics of an inflamed microenvironment are low levels of glucose and a scarcity of oxygen due to an altered metabolism, increased oxygen consumption by neutrophils, and reduced oxygen supply due to disrupted perfusion[15]. It is within such a hypoxic microenvironment that immune cells kill and prevent the spread of invading microorganisms. Accumulating evidence suggests that chronic inflammation, either non-infectious such as in autoimmune disorders or, as a

result of pathogen infection, is connected to cancer development. At the same time, the crosstalk between innate and adaptive immunity is critical for the successful eradication of different pathogens and tumor cells.

The aim of this review is to provide an overview of innate immune activation in the context of gastrointestinal malignancies, focusing on the premalignant lesions of the epithelium and the gastric tumor microenvironment. During the transition from atrophic gastritis to the final carcinoma, some microorganisms will play a determinant role promoting the neoplastic transformation or contributing with a particular tumor phenotype. This work compiles studies related to Toll-like receptors (TLRs), neutrophils, cytokines and pathogens, as crucial players during the precancerous cascade and the cancer onset (Figure 1), allowing the correlation of those aspects with clinical and socioeconomic variables.

STARTERS AND MEDIATORS OF THE INNATE IMMUNE RESPONSE IN GASTRIC TISSUE

Gastro-intestinal epithelial cells express several TLRs, that can respond to exogenous infectious ligands or pathogen-associated molecular patterns (PAMPs). TLRs are the most important class of pattern recognition receptors (PRRs), these transmembrane proteins present a distinctive Leucine-Rich Repeat extracellular domain that confers specificity to their ligands[16], and a cytoplasmic signaling domain homologous to that of the interleukin 1 receptor (IL-1R), termed the toll/IL-1R homology domain[17]. Up to now, the TLR family consists of ten (TLR1-TLR10) and twelve (TLR1-TLR9 and TLR11-TLR13) members identified in humans and mice respectively[18]. These receptors are expressed in various immune cells, including macrophages, Dendritic cells (DCs), B cells, specific types of T cells, and even in non-immune cells such as fibroblasts and epithelial cells; their activation leads to the induction of inflammatory cytokines, chemokines, antigen-presenting molecules, and costimulatory molecules[15,17,19].

Epithelial cells from the gastric mucosa are considered as the first line of innate immunity against gastrointestinal pathogens, including *H. pylori* infection, and the PRRs have shown a wide range of expression in normal and pathological tissue (Table 1).

Human gastric epithelial cells and tumor cells were found to express both TLR2 and TLR4 and both receptors are described as responsible for the *H. pylori* lipopolysaccharides (LPS) recognition. However, the results are contradictory and have not accurately probed the role of those receptors due both to the diversity of the host's immune system and the pathogenicity of the *H. pylori* strain[20,21]. TLR2 is the most extensively expressed gene among all the TLRs in gastric tumors and high levels of TLR4 are associated with a higher risk of GC[22-24].

On the other hand, TLR3 and TLR4 have been implicated in several disorders related to the gastroesophageal reflux disease spectrum and largely documented, including the expression of both receptors and expression of their downstream products, such as cyclooxygenase-2, IL-8, nuclear factor-κB (NF-κB), and nitric oxide in human tissue samples and *ex vivo* cell cultures from the esophagus, the esophageal-gastric junction and the stomach[25].

TLR5 is expressed within the esophageal epithelium and has been shown to increase in a stepwise manner with progression from normal to dysplastic and eventually neoplastic states[26]. In addition, it is well documented that TLR5 is present in both primary gastric epithelial cells and gastric tumor cell lines[22,24,27]; however, the role of TLR5 during the gastric precancerous cascade is not clear yet.

TLR5 is responsible for flagellin recognition, *H. pylori* flagellin seems to be a less potent stimulator compared with other flagellins[28] but has a significant role in long-term bacterial persistence. The lack of TLR5 activity in response to *H. pylori* flagellin is caused mainly by the amino acid residues variation R89, L93, and E114 described as hotspots for binding TLR5 which, replaced with threonine (R89T), lysine (L93K), and aspartate (E114D) in *H. pylori* flagellin, lead to receptor evasion[29]. TLR5 instead recognizes CagL and CagY, two proteins from the type IV secretion system (T4SS) of *H. pylori*, and both have immunoregulatory properties[30,31]. A high TLR5 expression has been suggested to

have a better prognosis amongst young GC patients in an early stage of disease, and this better outcome may be associated with a non-distant metastasis and an intestinal-type cancer[32].

TLR9, the only TLR with both anti- and pro-inflammatory roles, is involved in the recognition of *H. pylori* DNA, and the promotion or suppression role of TLR9 will depend on the gastric environment[22]. TLR9 expression has been shown to be up-regulated in *H. pylori* infected gastric tissue compared with non-infected tissue, and it was not related to the presence of tumor cells, suggesting that increased TLR9 expression was specifically associated with *H. pylori* infection[33]. It is reported that TLR9 interaction with *H. pylori* and *H. pylori* DNA, triggers an IL-8 secretion response mediated by the NF-κB pathway[34].

The role of TLR9 in cancer is not absolutely clear, but patients with stage II of GC and a high TLR9 expression had a better prognosis than cases with lower levels[32].

Other TLRs have been described, TLR1, TLR7, TLR8, and TLR10, but further studies are required in order to understand their role in GC and in *H. pylori* infected individuals, as well as other pathogens[22,23,35]. However, high levels of TLR10 expression have been observed in gastric biopsy samples from subjects with *H. pylori* and, when NCI-N87 gastric cells were co-cultured with the bacteria, both TLR10 and TLR2 mRNA levels were upregulated[35]. Those results suggest that TLR10 is a functional receptor and that TLR2/TLR10 heterodimer functions in *H. pylori* LPS recognition[35].

From a cellular perspective, neutrophils are the most abundant white blood cells in human blood and also considered as part of the first line of defense against infections by pathogens[36]. These cells have the ability to capture and destroy invading microorganisms and participate as mediators of inflammation. Phagocytosis and formation of neutrophil extracellular traps are part of the cellular mechanisms for pathogen elimination, as well as granules releasing[36-38].

Neutrophils extracellular traps (NETs) formation, known as NETosis is a process of releasing extracellular web-like structures, and is described as a coat consisting of decondensed chromatin filaments, histones and antimicrobial proteins[39]. NETosis is a

mechanism of innate immunity to contain and prevent microbial spread, and eliminate bacterial[40].

H. pylori can activate different cells of innate immunity, including neutrophils, and these activated cells recognize *H. pylori* infection through different receptors, such as TLR2, TLR4, and TLR9[34,41,42]. TLR5 has not been detected in neutrophils localized in the lamina propria during *H. pylori* gastritis[24]. The activation and recruitment of neutrophils is stimulated by *H. pylori* neutrophil-activating protein, or HP-NAP[37,43]. TLR2 interacts with HP-NAP for the secretion of IL-8[41]. However, the interaction between neutrophils and *H. pylori* appears to be complex and contradictory and shows the development of different mechanisms of immune evasion, including NET degradation, the increase in bacterial resistance mediated by the modification of proteins or surface polysaccharides, or the suppression of NET formation[44].

H. pylori has shown a selective alteration of neutrophils function mediated by the inactivation of NADPH Oxidase and superoxide release[45]. In addition, the bacterium performs lipid A modification mediated by lipid A phosphatases to resist the polymyxin, an antimicrobial peptide[46]. Another study remarked on the presence of an outer membrane-associated nuclease that can degrade extracellular DNA, where the ability to degrade exogenous DNA was originally proposed as a purine source uptake mechanism[47], but it could also have the potential role of degrading NETs[48].

Although NETosis was described as an antimicrobial process, it has been described in other pathologies, including cancer. The first study that provided evidence on NET in cancer was Berger-Achituv *et al*[49] studying the Ewing sarcoma. The authors proposed NET as a pro-tumor effect and the possibility of using this parameter as a poor prognostic biomarker[49].

Regarding GC, the first study was reported by Yang *et al*[50], the authors found the correlation of NET formation with TNM status and a significant increase in the formation of fibrin and thrombin, however, the focus was on peripheral circulation. More recently, the formation of NETs within the gastric tumor microenvironment including immunofluorescent staining of Neutrophil Elastase (NE) and citrullinated-histone 3[51,52]

showed that NETs are more abundant in the tumor core than in the adjacent non-tumor tissue[51,52], and the plasma from GC patients revealed the capacity of NET formation in vitro[52]. NETs measured in peripheral blood have been shown to be significantly correlated with GC and staging, and its levels decrease after surgery[50-52].

A very recent report showed that abdominal infectious complications after gastrectomy would stimulate neutrophils to release NETs both in peripheral blood and abdominal cavity, facilitating GC metastasis *in vitro* and *in vivo* dependent on transforming growth factor (TGF)-β signaling[53]. The formation of NETs has an important role in the epithelial-mesenchymal transition and gastric tumor progression, because NETosis may induce proliferation, invasion, migration, and a mesenchymal phenotype, in addition to its immune role, which makes it difficult to be therapeutically targeted.

ACCOMPLICE CELLS AND MEDIATORS OF AN ANTI-TUMOR RESPONSE

Additionally, the macrophages have been demonstrated to be important cells for the innate immune system in healthy and tumor tissue. Within the tumor microenvironment (TME), macrophages are known as tumor-associated macrophages (TAMs) and play a key role in the recognition and clearance of foreign and damaged cells, as well as in tumor development and the response to several cancer therapies.

Macrophages can infiltrate solid tumors modulating T cell activity within the TME, and often undergo phenotype polarization in response to stimuli or inhibitory factors, either to pro-inflammatory (M1) or anti-inflammatory (M2) subtypes, which cause immune response or immune escape of the tumors respectively[54-57]. The general consensus is that TAMs are usually pro-tumorigenic. These cells are recruited by tumor-derived chemokines and produce low levels of inflammatory cytokines, promote Th2-T cell response, favor wound healing, and increase angiogenesis and metastases[55,56].

IL-6 and tumor necrosis factor (TNF)-α are both pro-inflammatory cytokines, exerting pro-tumoral functions, including the promotion of angiogenesis and metastasis, and these molecules can be secreted by myeloid cells and leukocytes under different

conditions and stimuli[54-56]. In parallel to classic immunomodulators such as cytokines and chemokines, some microRNAs (miR) have shown a significant impact on macrophages activity[57]. miR-125b, miR-127, miR-155, miR-181 and miR-451 are significantly upregulated in M1 macrophages, whereas miR-125a-5p, miR-146a, miR-145-5p, miR-143-3p are highly expressed in M2 macrophages[58,59].

miR-155 directly targets the expression of the IL-13 receptor α1, thereby inhibiting STAT6 activation and promoting M1 polarization[59]. miR-155 knockdown in myeloid cells induces faster tumor growth, reduction of M1-macrophages and enrichment of pro-tumor cytokines within the TME[60]. In addition, miR-125b overexpression enhanced responsiveness to interferons (IFN)-γ, through the targeting of IRF4 and increased expression of pro-inflammatory cytokines[58,61].

miR-187, miR-146a, let-7e, and miR-92a are considered anti-inflammatory miRs because they downregulate IL-6 and TNF-α in human macrophages by targeting the TLRs signaling[57,62]. The NF-κB-dependent miR-146a expression is induced in monocytes and macrophages upon triggering of TLR4 to act as a modulator of the inflammatory response[61]. miR-155 is key to modulating genes related to M2/pro-Th2 phenotype in macrophages, and includes CCL18, SERPINE, CD23 and DC-SIGN[56]. In addition, other microRNAs will modulate directly or indirectly the NF-κB or TLR activity, such as miR9, miR-21, miR-29b, and those can be expressed and released by both TAMs and solid tumors in exosomes[57,62-65]. Due to the inflammatory microenvironment and oncogenic mutations, a significant number of human cancers have constitutive miRs deregulation affecting NF-κB activity, cytokine production and hallmarks of cancer such as apoptosis, proliferation and tumor survival[57,62,65].

Previous studies demonstrated that Gastric Epithelial Cells (GECs) function as antigen presenting cells by constitutively expressing MHC class II[66]. Interestingly, *H. pylori* infection induces up-regulation of costimulatory molecules (CD86 and CD80) among GECs[66], suggesting its potential to be used as a local bridge between innate and acquired immunity; however, the capacity to play a role secreting cytokines and polarizing macrophages requires further studies.

The inhibition of the polarization of pro-inflammatory macrophages can accelerate the development of precancerous lesions in GC[67]. In addition, when TAMs spread in the peritoneum of GC patients, these cells normally are polarized to an anti-inflammatory subtype (M2), which can promote the growth and progression of GC when the tumor exists[68]. In fact, high densities of TAMs are associated with poor survival in GC patients[68,69].

INTRINSIC AND EXTRINSIC MODULATORS OF INFLAMMATION AND PRECANCEROUS LESIONS

Currently, there is enough evidence based on epidemiological, molecular and pathological studies that persistent infection with *H. pylori* is a risk factor for the development of gastric adenocarcinoma[70-73], estimating an increment in the relative risk by 3–6 times in infected people which might represent over 80% of all distal GC cases and some with proximal gastric tumors[1,74,75]. The prevalence of *H. pylori* infection is extraordinarily high, infecting 50% of the world's population[1,76-78].

H. pylori is a Gram-negative bacterium which colonizes the human stomach and promotes a full immune response locally and sustainably[19,79,80]. Strains of *H. pylori* are grouped into two broad families tentatively named type I and type II, which are based on whether they express or not the vacuolating cytotoxin (VacA) and the CagA antigen (cytotoxin-associated gene A)[81].

One of the major determinants of *H. pylori*'s virulence is the cag pathogenicity island (cag PAI)[82-84]. This cagPAI is a 40-kb DNA region surrounding the *cagA* gene that contains about 27-31 genes that encode a bacterial type IV secretion system acting as a syringe-like structure, which allows for the delivery of bacterial effector molecules into host gastric epithelial cells[85]. During infection with *H. pylori*, CagA is translocated into epithelial cells, and it is tyrosine-phosphorylated in the EPIYA motifs by the proto-oncogene tyrosine-protein kinase Src and the members of the Abelson family of non-receptor tyrosine kinases[86,87], which results in the interaction with various intracellular

signaling pathways, triggering changes in the cytoskeleton, in the morphology and in the mobility of the host cells[86,87].

Compared with cagA– strains, *H. pylori* cagA+ strains significantly increase the risk of developing severe gastritis, atrophic gastritis, peptic ulcer disease and distal GC. In fact, people infected with cagA+ strains have higher degrees of gastric inflammation and epithelial cell damage than people from whom cagA- strains have been isolated[88]. People infected with cagA+ *H. pylori* strains have an enhanced expression of IL-1α, IL-1β, and IL-8 in gastric biopsies compared to uninfected persons or patients infected with cagA- strains[89]. Keeping that consideration in mind, proinflammatory cytokines will be up-regulated by a local infection; however, the magnitude of that systemic response and the profile of released cytokines and chemokines will depend also on host factors.

Regarding host factors, many polymorphisms in genes related to inflammation and innate immunity, such as cytokines and MHC molecules, have been reported to be associated with increased risk of GC[90-92]. Among the cytokines with polymorphisms that have been associated with GC are IL-1β, IL-1Rβ, IL-4, IL-6, IL-10, TNF-α, and TNF-β[93-97]. Based on ethnic backgrounds, two sets of haplotypes for IL-1β and IL-10 have been related to increased risk for GC[93-95]; specifically, IL-1β-1464G/-511C/-31T and IL-10-1082G/-819C/952C for Asians and IL-1β-1464C/-511T/-31C and IL-10-1082A/-819T/952T for Caucasians[95].

Canedo *et al*[96] found that IFN-γ receptor 1 -56C/T polymorphism is a relevant host susceptibility factor for GC development associated with *H. pylori* infection. Polymorphism in the promoter region of the gene coding for IL-10 and TGF-β has been also described in the Mexican population in relation to susceptibility to GC[97]. There is a need for extended studies in different populations and in larger patient groups, particularly in regions of Latin America where the burden of GC is more severe. In recent years, NF-κB has been widely studied in inflammation, immunity and cancer, but its roles are still unclear[98-100]. NF-κB is a master transcription factor activated downstream of the TLR and cytokines such as TNF-α and IL-1β[98]. In contrast to the canonical NF-κB pathway, the noncanonical NF-κB activation responds to specific

stimuli, including ligands from the TNFR superfamily members such as LTβR, BAFFR, CD40 and RANK[99].

In GC, *H. pylori* is associated with increased expression of the proinflammatory NF-κB[101-104]. It has been shown that the induction of NF-κB mediated by *H. pylori* induces the expression of activation-induced cytidine deaminase, which has been demonstrated to induce nucleotide modifications in *TP53* gene in gastric cell models[105] and suggests that the accumulation of those *TP53* gene alterations might contribute to the development of gastric neoplasia.

As an example, *in vitro* studies showed that programmed death (PD)-1 is increased among gastric epithelial cells after *H. pylori* infection and its immunosuppressive functions on T-cells may contribute to carcinogenesis[106]. Evidence from small studies observed an up-regulation of PD-1 and programmed cell death-ligand 1 (PD-L1) in human *H. pylori*-related gastric carcinoma[107].

In addition, *H. pylori* has shown other effects within the gastrointestinal epithelium not associated with inflammation but compromising the genome stability, for example, reduced levels of transcripts for DNA mismatch repair (MMR) proteins such as MutS, MutL RAD51, FEN1, POLD1, and LIG1[108-110], and this phenotype might be more severe in cases cagA+ *H. pylori*[110]. However, the deficiency MMR in gastric tumors was recently shown to predict clinical response to pembrolizumab[111], demonstrating also the expansion of antigen-specific T cells reactive to tumor-derived neoantigens, suggesting that further studies are required to understand the interaction between pathogens and genomic features as biomarkers.

CROSSTALK BETWEEN VIRAL INFECTION AND INNATE IMMUNITY ACTIVATION

The EBV is a ubiquitous virus, member of the subfamily of human Gammaherpesvirinae[112] and can infect several cell types, including B-lymphocytes, epithelial cells, and fibroblasts[113]. EBV is the main pathogenic factor for nasopharyngeal carcinoma. However, studies find that EBV infection is also associated with the

development of T-cell lymphoma and EBV-associated GC[114]. Although the infection rate of EBV is extraordinarily high, reaching over 90% of the adult population worldwide[115,116], the incidence rate of EBV-positive GC remains low, representing around 9% of characterized stomach adenocarcinomas[117], these EBV-positive tumors display recurrent PIK3CA mutations, extreme DNA hypermethylation, and amplification of JAK2 and both PD-L1 and PD-L2[5].

The EBV-positive GC has been characterized by an increased expression of PD-L1, and a sustained immune-infiltration, which is indicative of the presence of stable T-cells and supports the use of an immune checkpoint inhibitor for the treatment of this GC subtype[118,119]. In addition, most EBV-positive GCs show MSI which has also been associated with inflammation and local immune activation[120-123]. Previous groups have shown that high density of intra-tumoral or stromal CD8+ T cells with high percentage of PD-L1 expression seems to be associated with a worse progression-free survival and overall survival[118,120,124]. However, a recent study demonstrated that EBV-positive GC patients treated with immunotherapy showed favorable responses[125], suggesting that viral status represents a potential predictive biomarker for using immune-checkpoint inhibitors; however the balance between pro-inflammatory and immunosuppressive signals together with a concomitant viral infection requires more studies to clarify its role as a biomarker.

Type I and type II IFN are central to both combating virus infection and modulating the antiviral immune response[126]. The cytokine IFN-γ is mainly produced by T Cell CD4+ and natural killers to activate macrophages. The ligation to its receptor triggers an activation of the Janus-Activated kinases, JAK1 and JAK2, and subsequently the activation of STAT1 and interferon regulatory factor 1 (IRF1). STAT1 and IRF1 are activated by phosphorylation and translocated to the nucleus to regulate the *IFN-γ* gene expression[127].

Crucial to the induction of type I IFN is the recognition of viral PAMPs by PRRs, among which, the cyclic GMP-AMP synthase-stimulator of interferon genes modulates the antiviral response triggered by DNA viruses and retroviruses[128]. In addition, most

viruses, including EBV, stimulate innate immune response during primary infection predominantly by activating the expression of TLRs, such as TLR2, TLR3, TLR4, TLR7, TLR8, and TLR9[129]. TLR2 is likely activated by EBV surface glycoprotein gp350[130] and the nonstructural protein dUTPase[131], while EBV-encoded small RNAs released from EBV-infected cells are detected by TLR3[132]. Furthermore, EBV can activate monocytes and plasmacytoid DCs through cooperative action of TLR9 and TLR2[133].

Activation of PRRs by EBV-PAMPs triggers JAK-STAT-mediated IFN response and different branches of innate immune signaling including NF-κB pathway; inflammasome activation; and programmed cell death such as apoptosis and necroptosis[134]. However, innate immunity is a double-edge sword as the induction of pro-inflammatory responses and activation of programmed cell death might release a burst of virions and may therefore facilitate the spread of infection[135].

Recently, IFN-γ has been the subject of studies due to its immune role in cancer development, especially in GC. There are several signaling pathways of innate immunity during GC development in which interferon is involved, such as in proliferation, metastasis, and advancement of GC through the upregulation of integrin β3-mediated NF-κB signaling[136]. Serum levels of IFN-γ are elevated in GC which may promote systemic and local responses[137] at the same time, for example: peroxisome proliferator-activated receptor delta, a ligand involved in physiologic processes in cell metabolism, proliferation, and inflammation[138] together with IFN-γ signaling creates an inflammatory tumor-promoting microenvironment enabling villin-expressing gastric progenitor cells transformation and gastric tumorigenesis[139]. Furthermore, natural killer (NK) cells play a role in innate immunity against cancer cells. Lee *et al*[140] reported that IFN-γ produced by the activated NK decreases in GC patients compared with healthy donors. This low level of IFN-γ-NK could be used as a non-invasive biomarker for carcinogenesis in GC[140].

Some reports including latinamerican cohorts have shown that concentrations of IFN-γ and IL-10 are significantly higher in GC cancer than in non-oncological cases, and within the GC group, IFN-γ levels are increased at the early stages (I/II) and remain

higher in late stage (IV)[141]. Interestingly, increased levels of viral capsid antigen antibodies are significantly associated with elevated serum levels of IFN-γ, particularly in the intestinal type of GC[142]. Therefore, IFN-γ is suggested as a biomarker for assessing GC risk; however, this molecule is known to mediate gastric damage or immune antipathogen responses, as well as the expression of some negative immune checkpoint molecules.

The PD-L1 expression is activated by several cytokines, of which IFN-γ is the strongest[143]. In a melanoma cell line model, PD-L1 has shown to be mainly regulated by the type II interferon receptor signaling pathway through JAK1 and JAK2, several STATs including STAT1/STAT2/STAT3, to converge on the binding of IRF1 to the PD-L1 promoter[144]. Later, Chen *et al*[145] treated with IFN-γ thirty-four cultured human tumor lines, including 18 melanomas (MEL), 12 renal cell carcinomas (RCC), 3 squamous cell carcinomas of the head and neck (SCCHN), and 1 non-small-cell lung carcinoma, and as wildtype control the authors considered isolated peripheral blood monocytes. The results indicated that PD-L1 was constitutively expressed on 1/17 cultured MELs, 8/11 RCCs, 3/3 SCCHNs, and on monocytes; however the inhibition of STAT1 but not STAT3 was more critical to reduce IFN-γ-induced PD-L1 protein expression on tumor cells[145]. Other authors have provided evidence of a crosstalk between JAK2-STAT1 and PI3K-AKT pathways in response to IFN-γ in lung adenocarcinoma[146]. Transcriptome analysis demonstrated that tumor tissues expressing IFN-γ display gene expression associated with suppressed cell cycle progression and expansion, which was not observed in PD-L1 negative tumors. In lung adenocarcinoma cells IFN-γ induces the activation of JAK2-STAT1 and PI3K-AKT pathways, showing that the activation of JAK2-STAT1 is responsible for the anti-proliferative effect of IFN-γ, and the inhibition of PI3K downregulates PD-L1 expression and enhances the anti-proliferative effect of IFN-γ[146]. In addition to the cytokine regulation, a lncRNA (long non-coding RNA) named Interferon-stimulated non-coding RNA 1 (INCR1) has been described as a major regulator of IFN-γ signaling in tumors by post-transcriptional modulation of PD-L1 and JAK2 expression[147]. INCR1 is expressed as an antisense RNA from the PD-L1/PD-L2

Locus and has been detected in human samples across multiple tumor types, and its levels increase after IFN-γ stimulation, correlating with PD-L1 but not PD-L2 expression[147].

Regarding GC, PD-L1 has shown a wide and very variable range of expression based on technique and cutoff, however, it seems to be absent in non-tumor gastric tissue[148-151]. Imai *et al*[152] showed IFN-γ treatments enhanced the expression of intracellular and membranous PD-L1 expression in GC cell lines, this upregulation of PD-L1 induced by IFN-γ was associated with the JAK-STAT but not the MAPK and PI3K-AKT pathway activation[152,153]. PD-L1 overexpression mediated by IFN-γ is also seen in GC with positive EBV[154]. Polymorphism in PD-L1 related to GC has also been described. PD-L1rs2297136 was positively correlated with a higher proportion of PD-L1 protein and could be employed as a tool of prognosis in GC patients[155,156].

A recent study suggested the role of ISG12a as a tumor suppressor in gastrointestinal tissue[157,158]. ISG12 or interferon alpha-inducible protein 27 promotes β-catenin proteasomal degradation by inhibiting the degradation of ubiquitinated Axin, thereby suppressing the canonical Wnt/β-catenin signaling pathway[158]. Reduced levels of ISG12a were observed in gastrointestinal cancer, such as hepatocellular cancer and GC, and it was associated with an immune-suppressive tumor microenvironment. The authors argue that β-catenin is a transcription factor for PD-L1, and the inhibition of Wnt/β-catenin signaling by ISG12a sensitives tumor cells to NK cell-mediated killing[157]. Therefore, the balance between the induction or suppression of IFN-stimulated genes[159], such as ISG12a, may accelerate the malignant transformation of cancer cells and lead to a poor prognosis in gastrointestinal cancer[157,160].

NON-BIOLOGICAL FEATURES AS IMMUNE AND PREMALIGNANT MODULATORS

GC is currently accepted as the consequence of a multifactorial process, involving pathogen infection and the virulence of some strains (as *H. pylori*), environmental factors, dietary habits, and host intrinsic factors, as we have discussed above; however,

socioeconomic factors, such as education level and occupation, have shown to be determinant during the progression of the premalignant cascade of GC and the patient outcome after the cancer onset[161-163].

Asia accounts for 71% of GC cancer worldwide, in which China's incidence is 44.1%. The high incidence in China is marked by the rural population, and their exposure to carcinogens through diet and the environment and the *H. pylori* infection *per se*[164]. The incidence of GC in Europe is heterogeneous; while the highest incidence is in Central and Eastern Europe, the lowest incidence is in Western and Northern Europe, which correlates with a higher detection of *H. pylori* in Eastern Europe compared to Western Europe[165], as well as an observed higher consumption of red and processed meat resulting in an increased risk of GC[166].

After Europe, Latin American countries have shown a high incidence of gastric malignancies, among the associated risk factors are infection with *H. pylori*, diet and habits such as smoking, consumption of salt, alcohol and meat, as well as ethnicity and age[167]. Some authors have suggested for Latin America a close correlation between GC incidence and altitude, based on the presence of a mountainous geography, such as the Sierra Madre, Cordillera de Centroamerica and the Cordillera de los Andes[168]. However, the mortality and incidence rates for gastric malignancies in the Chilean population is statistically higher than the average rates in the rest of Latin America, becoming the second cause of death from cancer in Chile, affecting 11.6 per 100000 inhabitants and causing around 3000 deaths per year[1]. That incidence seems to correlate mainly with socioeconomic status, Mapuche ethnicity, and the age at the primary *H. pylori* infection[169].

Surprisingly, most of the countries with the highest incidence of GC are not those with low incomes (Table 2). In fact, it seems that the vicious circle between precancerous lesions, inflammation and GC onset is caused by the low level of education within the population. A study performed within the Swedish population, which considered all the economically active population, showed an increased risk factor of GC in workers engaged in manual-labor occupations and in industry. The statistics were standardized

for categories of occupation and adjusted by age, period and region, and confirmed that overall manual-workers and farmers had the highest risk of GC, including male miners and quarry workers[162]. The European Prospective Investigation into Cancer and Nutrition cohort included about 520000 participants mostly aged 35–70 years and, after an average follow-up of 6.5 years, reported 268 cases with adenocarcinoma of the stomach. Higher education was significantly associated with a reduced risk of GC with a hazard ratio (HR) of 0.64 (95%CI: 0.43–0.98) and, as was expected from other reports, that effect was more pronounced for cancer of the cardia (HR: 0.42) as compared to non-cardia GC (HR: 0.66)[163].

A survey to address GC risk factors and endoscopic screening within the North American population showed that ethnicity, cultural habits and immigration patterns are potentially useful to identify high-risk persons from multicultural areas within the USA[170]. The authors identified that dietary habits during teenage years (15-18) and education below high school level may represent signs of risk of GC in older people of foreign birth[170]. Most recently, based on the previous research, a secondary analysis showed that education level was the single most reliable measure of GC risk among three variables of socioeconomic status including, education, income, and occupation, which are the most commonly used for health outcomes such as cancer survival[171]. Similar results were observed in a seroepidemiologic study in Japan where the *H. pylori* positive rate increased at 1% per year for people born after 1950 but was comparatively constant for people with birth dates before 1950[171]. Based on the authors, the apparent decreased prevalence of *H. pylori* post-war was accompanied by the Westernization of the country and subsequently by a reduction in the frequency of atrophic gastritis and the incidence of gastric carcinoma during the most modern times[171,172].

The infection status in adults is considered to be influenced by socioeconomic status in childhood; however, given the massive improvement in hygiene and the economic environment around the world, it has contributed to the variation in the trends in incidence and death rates of GC among the countries mentioned above. Based on other authors, the education in *H. pylori* eradication and gastric malignancies is largely due to

unplanned prevention caused by the widespread adoption of technology and improved manufacturing practices of the food industry. In a similar way, the prevalence of *H. pylori* infection may be reduced owing to improvements in sanitary and housing conditions based on education at early ages by primary schools and in adult life by primary health workers.

Where the intersection between education and immunity is not evident, by intuition a limited knowledge regarding gastrointestinal health and eradication of *H. pylori* infection might dramatically influence the development of GC. Therefore, the inflammatory process induced by a pathogen or even an incipient neoplasm may not receive enough attention, progressing finally to an advanced disease with limited therapeutic opportunities and uncertain outcome for the patient.

CONCLUSION

During the transition from premalignant lesions of the gastric epithelium to the final carcinoma, some microorganisms will play a determinant role promoting the neoplastic transformation or contributing with particular tumor phenotype and its heterogeneity, together with different mutagenic agents and genomic aberrations. This review provides an overview on innate immune activation in the context of gastrointestinal malignancies and compiles studies related to TLRs, neutrophils, cytokines and pathogens, as crucial players during the precancerous cascade and the cancer onset, allowing the correlation of those aspects with clinical and socioeconomic variables.

As shown in the graphical abstract, intersections between innate immune response and GC development is driven by common mediators, such as NF-κB and IFN-γ molecular pathways, cellular processes (neutrophil and myeloid cells activation), and activators/inducers (PAMP, damage-associated molecular patterns, tumor-antigens). However, universal risk factors are identified affecting globally any human being which, depending on extrinsic and intrinsic host factors, might facilitate the progression of the precancerous cascade to GC.

Modern therapies such as adoptive cell therapy, vaccines, and especially immunotherapy using checkpoint inhibitors, which have not been mentioned in this work, have shown in clinical trials the role of restoring the balance in favor of the immune system against GC. In the words of Dunn *et al*[173] the observed benefits in GC may be based on (1) Elimination: NK cells and T lymphocytes (helper and cytotoxic) secrete interferon IFN-γ leading to a reduction of angiogenesis and proliferation of cancerous cells; moreover, macrophages and DC secrete cytokines that activate immune cells to phagocytize dead tumor cells; (2) Equilibrium: Residual cancerous cells remain in a dormant state because DC and cytotoxic T cells secrete IFN-γ and inhibitory cytokines (IL- 12) suppress them; and (3) Escape: Tumor cells change their features, up-regulating immune checkpoint pathways, which will be transmitted to the daughter cells, therefore escaping immunosuppression and proliferating, along with the apoptosis of the effector lymphocytes[173]. The success of those treatments relies on an efficient immune system, and of course an innate response able to promote priming and mobilization of newly activated immune cells; the presence of pathogens or their PAMPs, as well as molecules derived from the tumor itself will continuously modulate the tumor immune microenvironment. The shape of the tumor will also depend on the host background (genome stability, driver mutations and other gene variants) but in addition, the external environment shaped by the socioeconomic status of each person will determine the final outcome.

Innate immunity is the beginning, and certainly, will be part of the final response against tumors. All these observations require further investigation but it is clear that pathogens like *H. pylori* and EBV need to be assessed in GC based on their role as biomarkers and as potential mechanisms of resistance to therapy.

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Figure Legends

Figure 1 Graphical abstract. Intersections between innate immune response and gastric cancer development is driven by common mediators, such as molecular pathways (Nuclear factor-κB and interferons-γ), cellular processes (neutrophil and myeloid cells activation), and activators/inducers (Pathogen-associated molecular patterns, damage-associated molecular patterns, tumor-antigens). However, universal risk factors are identified affecting globally to any human being, which depending on extrinsic and intrinsic host factors might facilitate the progression of the precancerous cascade to gastric cancer. NF-κB: Nuclear factor-κB; IFN-γ: Interferons-γ; PAMPs: Pathogen-associated molecular patterns; DAMPs: Damage-associated molecular patterns; TLR: Toll-like receptors; ICM: Immune checkpoint molecules; GC: Gastric cancer; EBV: Epstein-Barr virus; *H. pylori*: *Helicobacter pylori*.

Table 1 Expression of Toll-like receptors in esophageal and gastric epitheliums

PRR	Organ	Model	Method	Ligand	Observation	Reference
TLR1/2	Esophagus	Esophageal carcinoma and premalignant lesions.	IHQ	Triacyl lipopeptide	Receptor upregulation in tumor and dysplasia.	[22,171]
TLR2	Stomach; esophagus	Human ADC and premalignant lesions; *H. pylori* infection. Mice model and *in vitro* culture.	IHQ; RT-qPCR	Microbial lipopeptide	Receptor upregulation in tumor cores. Increased tumorigenesis; constitutive expression in TE-1 cell line.	[21,22,27,32,172-174]
TLR3	Stomach; esophagus	Human gastric and esophageal carcinoma.	IHQ; RT-qPCR	dsRNA	Increased receptor levels correlate with poor prognosis; increased expression on EAC-derived cell lines.	[25,174-176]
TLR4	Stomach; esophagus	Human ADC and premalignant lesions; *H.*	IHQ; RT-qPCR	LPS	Upregulation in tumor cores. Weak association with	[21,24,25,27,32,171,173-179,182]

		pylori infection; esophageal carcinoma.			clinicopathologic variables; high expression correlates with poor prognosis; upregulation of IL-8 and COX-2 in BE.	
TLR5	Stomach; esophagus	Human ADC and premalignant lesions. *H. pylori* infection.	IHQ	Flagellin	Highly expressed. Upregulation in tumor and older patients. Association with necrosis and tumor growth in the stomach; overexpression in dysplastic lesions of BE. No association with EAC prognosis.	[26,27,32,177]
TLR6	Esophagus	Esophageal carcinoma and human dysplasia.	IHQ; IF	Diacyl lipopeptide	Upregulated in tumor tissue.	[22,171]

TLR7	Stomach; esophagus	Human ADC and normal tissue.	IHQ; WB; RT-qPCR	ssRNA	Downregulated in gastric tumors; high levels correlate with a better outcome in GC; constitutive expression in TE-1 cell line; association between expression and tumor grade in ESCC.	[22,32,173, 174,176,18 0,183]
TLR9	Stomach; esophagus	Human ADC.	IHQ; RT-qPCR	ssDNA; dsDNA	Upregulated in early tumors. Correlation with better prognosis in GC; association with histopathologic al grade in ESCC and dysplasia; high expression in EAC correlates with advanced	[24,25,32-34,173,175, 176,181,18 4]

					tumor stage and metastasis.	
TLR10	Stomach	Human biopsy.	RT-qPCR	ssDNA; dsDNA	Upregulated by *H. pylori*.	[35]

PRR: Pattern recognition receptor; TLR: Toll-like receptors; IHQ: Immunohistochemistry; ADC: Adenocarcinoma; RT-qPCR: Reverse transcription and quantitative PCR; IF: Immunofluorescence; WB: Western blot; TE-1: Human cell line derived from esophageal cancer; ESCC: Esophageal squamous cell carcinoma; BE: Barrett's esophagus; EAC: Esophageal adenocarcinoma; GC: Gastric cancer; *H. pylori*: *Helicobacter pylori*.

Table 2 Gastric cancer incidence and socioeconomic indicators per country

Country	Estimated cases	Crude rate	ASR (World)[1]	Cum. risk	HDI classification
Japan	138470	109.5	31.6	9.35	Very high
Korea	28713	56	27.9	6.51	Very high
Brunei Darussalam	55	12.6	13.5	5.93	Very high
Russia	37364	25.6	13.5	3.29	Very high
Chile	4208	22	13.1	4.17	Very high
Lithuania	864	31.7	13	3.4	Very high
Estonia	379	28.6	12.3	3.2	Very high
Latvia	530	28.1	12	3.01	Very high
Portugal	2950	28.9	11	2.99	Very high
Slovakia	1210	22.2	10.7	3.12	Very high
Mongolia	860	26.2	32.5	7.71	High
China	478508	33.1	20.6	5.24	High
Iran	14656	17.4	17.5	6.58	High
Kazakhstan	3357	17.9	15.8	3.47	High

Belarus	2739	29	15.4	3.5	High
Peru	6300	19.1	15.2	5.16	High
Colombia	8214	16.1	12.8	3.61	High
Costa Rica	952	18.7	12.8	4.12	High
Samoa	20	10.1	12.8	3.75	High
Azerbaijan	1453	14.3	12.7	3.42	High
Tajikistan	1301	13.6	23.4	6.96	Medium
Kyrgyzstan	1027	15.7	19.7	5.01	Medium
Cabo Verde	82	14.7	18.4	5.88	Medium
Bhutan	118	15.3	17.7	3.88	Medium
Viet Nam	17906	18.4	15.5	3.57	Medium
Sao Tome and Principe	18	8.2	14.7	2.06	Medium
Myanmar	7235	13.3	13.7	3.58	Medium
Lao	675	9.3	12.9	3.17	Medium
Guatemala	1637	9.1	12.2	3.93	Medium
Turkmenistan	583	9.7	11.8	2.37	Medium
Haiti	1184	10.4	13.5	4.58	Low
Mali	1097	5.4	12.8	2.96	Low
Afghanistan	2149	5.5	12.4	3.18	Low
Zimbabwe	641	4.3	9.4	3.24	Low
Papua New Guinea	474	5.3	9.2	3.17	Low
Rwanda	587	4.5	8.1	1.61	Low
Yemen	966	3.2	7.1	2.68	Low
Senegal	597	3.6	7	1.66	Low
Benin	429	3.5	7	2.29	Low
Mauritania	143	3.1	5.6	1.46	Low

[1]Top10 countries with the highest age-standardized incidence rates per 100000 inhabitants, per each human development index classification. Source: Globocan 2020, access by https://gco.iarc.fr. ASR: Age-standardized incidence rates; HDI: Human development index.

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