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Roles of Plasmacytoid Dendritic Cells in Gastric Cancer

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Gastric cancer (GC) is the fifth most common neoplasm and the third most deadly cancer in humans worldwide. *Helicobacter pylori* infection is the most important causative factor of gastric carcinogenesis, and activates host innate and adaptive immune responses. As key constituents of the tumor immune microenvironment, plasmacytoid dendritic cells (pDCs) are increasingly attracting attention owing to their potential roles in immunosuppression. We recently reported that pDCs have vital roles in the development of immunosuppression in GC. Clarifying the contribution of pDCs to the development and progression of GC may lead to improvements in cancer therapy. In this review, we summarize current knowledge regarding immune modulation in GC, especially the roles of pDCs in GC carcinogenesis and treatment strategies.

Keywords: gastric cancer, *Helicobacter pylori*, immune modulation, plasmacytoid dendritic cells, tumor microenvironment

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1 INTRODUCTION

Gastric cancer (GC) is one of the most common malignancies worldwide (1). GC has become relatively rare in the United States, but remains common in Asia (2); it is the third most commonly diagnosed cancer (10.6%) and the second most common cause of cancer-related death (13.6%) in China, and thus constitutes a serious health burden on society (3). *Helicobacter pylori* infection, high salt consumption, smoking, low fruit and vegetables consumption, and high alcohol consumption are risk factors for GC (4). As the early phase of GC is asymptomatic or has nonspecific symptoms, most patients are diagnosed at advanced stages. Therefore, effective strategies for early diagnosis, prevention, and treatment are needed.

The gastrointestinal mucosa, which forms the main interface between the human host and its environment, resists attacks from microorganisms, their products, and other toxins. Therefore, the immune system serves an essential purpose to maintain the defense property. The gastric mucosa consists of an epithelial layer, lamina propria, and mucosal muscle layer, which together form not only a simple physical barrier but also complex chemical and biological barriers. Innate and adaptive immunity synergistically contribute to the homeostasis of the gastric mucosa. When the balance of mucosal immunity is disrupted, certain gastric diseases may occur. Inflammation is a well-recognized risk factor for cancer. *H. pylori*-induced chronic inflammation in the gastric mucosa is a key step in the initiation of the development of GC, and eradication of *H. pylori* infection is recommended to prevent GC (5).

H. pylori stimulates gastric epithelial cells and recruits immune cells to the site of infection (6) (**Figure 1**). *H. pylori* infection is followed by upregulation of expression of various pro-inflammatory factors, including interleukin 1 (IL-1), IL-2, IL-6, IL-8, IL-12, tumor necrosis factor-α (TNF-α), and interferon γ (IFN-γ). Current evidence suggests that pro-inflammatory factors are critical participants in gastric carcinogenesis (7–9). However, the majority of *H. pylori* infected individuals do not develop GC (10) *H. pylori* infected patients with severe atrophy, corpus-predominant gastritis, and intestinal metaplasia are at high risk for intestinal-type GC, and patients with moderate atrophy and pangastritis are at high risk for diffuse-type GC, whereas isolated antral *H. pylori* infection or duodenal ulcer in *H. pylori* infected patients does not increase the risk of GC (11). Furthermore, British Society of Gastroenterology guidelines 2019 does not recommend surveillance in patients with gastric atrophy or gastric intestinal metaplasia limited just to the gastric antrum unless other risk factors are present (12).

Dendritic cells (DCs) are widely acknowledged as potent antigen-presenting cells (APCs), which are able to bridge innate and adaptive immunity. DCs can be classified into plasmacytoid DCs (pDCs) and conventional DCs (cDCs; also known as myeloid DCs). The pDCs have attracted increasing attention in recent years. Activated pDCs express various immunostimulatory and inhibitory molecules, secrete cytokines and chemokines, present antigens, and enhance the development and function of immune cells (13, 14). However, the precise roles of pDCs in gastric carcinogenesis and progression remain elusive. Here, we focus on current knowledge regarding immune modulation in GC, especially the role of pDCs in carcinogenesis and treatment strategies.

2 IMMUNOBIOLOGY OF PDCS

2.1 Characteristics of pDCs

Lennert and Remmele first described pDCs in 1958. They were found in the T cell zones of human lymph nodes and identified as

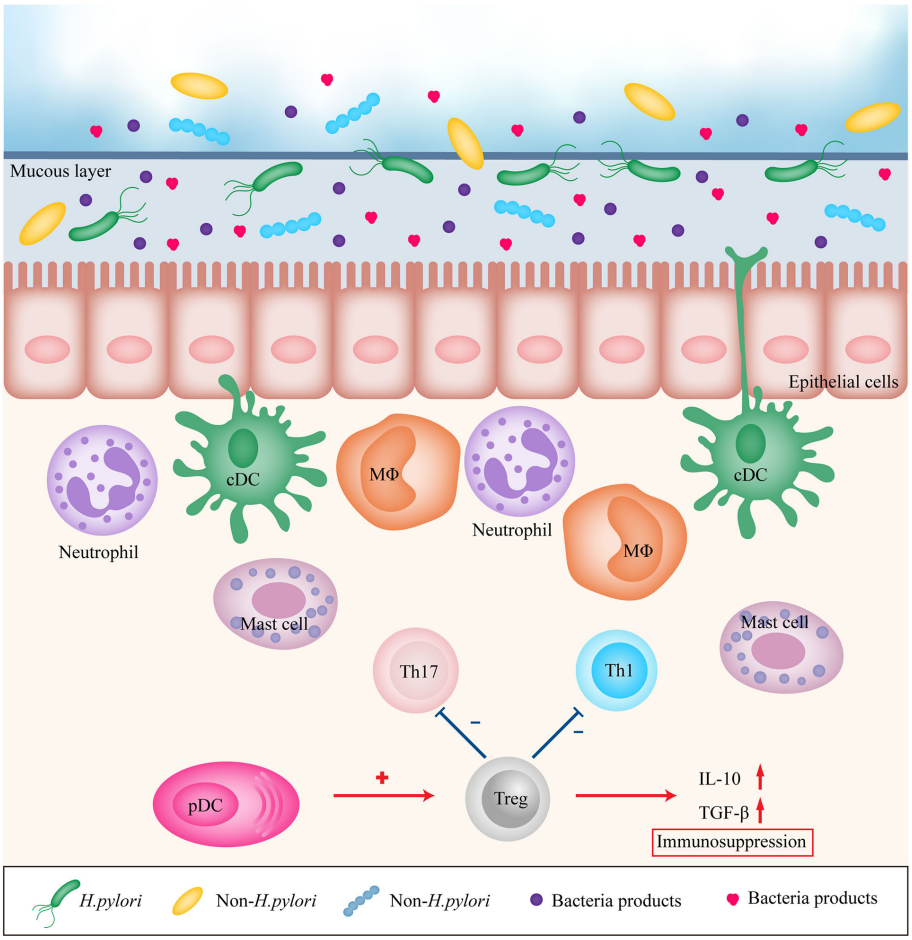

FIGURE 1 | Immune modulation in gastric mucosa during inflammation. *H. pylori*, other bacteria and their products stimulates gastric epithelial cells and recruits immune cells to the site of infection, leading to persistent chronic inflammation. However, pDCs may recruit Treg cells to promote immunosuppression. Treg, regulatory T cell; Th1, T helper cell type 1; Th17, T helper cell type 17; DC, dendritic cell; MΦ, macrophage; pDC, plasmacytoid dendritic cell; IL-10, interleukin 10; TGF-β, transforming growth factor-β.

T-associated plasma cells based on their morphological features (15). Over the past few decades, there have been significant new insights into pDCs. pDCs have a round morphology with an eccentric nucleus, harboring well-developed rough endoplasmic reticulum, Golgi apparatus, and many mitochondria (16), which account for about 0.1% of peripheral blood mononuclear cells (17). Human pDCs are phenotypically characterized by the presence of CD4, CD68, ILT3, IL-3 receptor α-subunit (IL-3R; also known as CD123), blood DC antigen 2 (BDCA-2; also known as CD303), CD304, and major histocompatibility class (MHC) II (18, 19).

pDCs originate from hematopoietic stem cells in the bone marrow (BM). pDCs can develop from IL-7R$^+$ lymphoid precursor cells *via* the lymphoid pathway and are also derived from common DC progenitors *via* the myeloid pathway (20, 21). Fms-like tyrosine kinase 3 (Flt3) and its ligand (Flt3L) have critical roles in the developmental processes of pDCs (22–24). Flt3 and Flt3L activate signal transducer and activator of transcription 3 (STAT3) to promote the expression of the basic helix-loop-helix transcription factor E2-2/Tcf4, leading to the promotion of pDC development. Together, E2-2, E2a, and HEB make up the E protein family, which can form homo- or heterodimers to bind to cognate DNA sequences called E boxes (CANNTG), and subsequently activate or repress their target genes (25). E2-2 is essential for pDC development and the pDC-mediated IFN response in both mice and humans (26). However, granulocyte-macrophage colony-stimulating factor (GM-CSF) inhibits pDC development *via* STAT5-mediated expression of inhibitor of DNA binding 2 (ID2), which is an inhibitor of E2-2 (27).

Previously, pDCs were thought to be long-lived compared with cDCs based on the relatively slow rate of BrdU labeling by splenic pDCs (28, 29). However, parabiotic experiments in mice revealed that the turnover of pDC pools in the spleen and lymph nodes is more rapid than that of cDCs (30). Zhan et al. indicated that the slower rate of BrdU labeling of spleen pDCs may reflect the time required for pDCs labeled with BrdU to migrate to the spleen, rather than a longer lifespan of pDCs (31). The lifespan of pDCs is also short and is regulated by genetic and environmental factors (31). The underlying regulation mechanisms regarding the longevity of pDCs are not well understood, and further studies are needed.

2.2 Innate and Adaptive Immune Responses by pDCs

Distinct Toll-like receptors (TLRs) recognize different microbial components (32). TLR7 and TLR9 are key players in the sensing of pathogens by pDCs. Following ligand binding, the cytoplasmic Toll/IL-1 receptor (TIR) domains of TLR7 and TLR9 interact with signaling adaptor myeloid differentiation primary-response gene 88 (MyD88), triggering the activation of IRF7 to produce large amounts of type I IFNs (33, 34). IRF5 is critical for the induction of production of pro-inflammatory cytokines by the MyD88–nuclear factor kappa B (NF-κB) pathway (35). Type I IFNs comprise a large family of cytokines, consisting of IFN-α, IFN-β, IFN-ϵ, IFN-κ, and IFN-ω (36). It is widely accepted that type I IFNs have important roles in anti-viral immunity, both *in vitro* and *in vivo*. Type I IFNs also function as links between innate and adaptive immune responses. Type I IFNs can act directly or indirectly on multiple immune cells, including natural killer (NK) cells, T cells, B cells, DCs, and phagocytic cells (37–41).

Direct type I IFN signaling can play a critical part in clonal expansion of CD4$^+$ and CD8$^+$ T cells in certain infections (39, 42, 43). Moreover, type I IFNs can substitute T cells help *via* direct promotion of the survival and differentiation of CD8$^+$ T cells during viral infections (44). pDCs can regulate the development of both T helper cell type 1 (Th1) and Th2 responses, depending on a variety of factors (45). pDCs stimulated with a virus and CD40L can efficiently drive Th1 cell polarization through the synergistic effects of IL-12 and type 1 IFNs (46). The virus converts the CD40L-mediated Th2 chemokine profile of pDCs into a potent Th1 mediator profile *via* the IFN-γ autocrine loop (47). Type 1 IFNs also limit the development of Th17 and negatively regulate Th17-mediated immune responses (48, 49). IFN-α inhibits spontaneous apoptosis of CD4$^+$ and CD8$^+$ T cells (50). It has been reported that pDCs regulate B cell responses *via* production of type 1 IFNs and IL-6, and by direct cell-to-cell contact (40). Data suggest that IFN-α secreted by pDCs makes B cells more responsive to T cell help and subsequently facilitates proliferation and differentiation of B cells with a T-cell-dependent pattern (51).

In addition to generating abundant amounts of type I IFNs, pDCs also act as APCs to activate adaptive immune responses. Owing to their expression of MHC molecules and costimulatory molecules CD40, CD80, and CD86, pDCs are thought to possess antigen presenting capacity (52). Activated pDCs have the potential to persistently synthesize, ubiquitinate, and turn over the MHC II–peptide complexes (41). This ability enables pDCs to consistently process and present endogenous self or viral antigens following activation, while the efficiency of presenting exogenous antigens is relatively low compared with those of cDCs (41).

In recent years, it has been suggested that pDCs can perform cross-presentation for efficient activation of T cells. Human circulating pDCs have similar ability to BDCA3$^+$ cDCs to cross-present soluble and cell-associated tumor antigens to cytotoxic T cells, albeit pDCs take up less antigens than cDCs (53). Moreover, pDCs preserve exogenous antigens for a prolonged period of time and upregulate MHC I and II molecules after stimulation, which indicates the essential role of pDCs in cross-presenting extracellular antigens (53). Human pDCs can capture antigens in the form of microvesicles such as exosomes and apoptotic bodies (54). A recent study found that cross-presenting pDCs require pDC-derived exosomes to transfer antigens from pDCs to cDCs for cross-priming of naive CD8$^+$ T cells (55).

Intriguingly, the ability of pDCs to induce peripheral tolerance in different situations has been well established; this function is predominantly realized through induction of regulatory T (Treg) cells (56–58). pDCs could cargo antigens to draining lymph nodes and transfer antigens to lymph node-resident APCs, leading to abortive proliferation of cognate CD4$^+$ T cells and inducing tolerance (59). In addition, peripheral pDCs transport peripheral antigens in a central chemokine receptor 9-dependent manner to

the thymus and subsequently delete the antigen-reactive thymocytes to promote immune tolerance (60). Recent studies have indicated that pDCs contribute to immune tolerance by expressing indoleamine 2,3-dioxygenase, inducible co-stimulator ligand (ICOS-L), OX40L, PD-L1, and granzyme B (61–65).

2.3 pDCs in GC

There are limited number of studies about the role of pDCs in GC (**Table 1**), and there is a deficiency of experiments (such as animal models of GC) to confirm the role of pDCs in GC. In peripheral blood, the increased numbers of pDCs, Treg cells, and ICOS$^+$ Treg cells were found in GC patients when compared with healthy controls (66, 69). The enrichment of circulating pDCs was detected in GC patients with advanced stages and lymph node metastasis (69). Even though the number of circulating pDCs elevated, the plasma IFN-α level was decreased in GC patients (66). In breast cancer, the capacity of tumor-associated pDCs to produce type I IFN is substantially impaired, which in turn potentiates their capacity to promote the proliferation of tumor-associated forkhead box protein 3 (FOXP3)$^+$ Treg cells (74).

TABLE 1 | Studies on pDCs in patients with gastric cancer.

Author	Year	Sample	Results	References
Xiao-Mei Huang et al.	2014	☙ Peripheral blood 51 patients, 30 healthy individuals ☙ Tissue samples 91 patients	☙ The numbers of pDCs, Tregs, and ICOS$^+$ Tregs in peripheral blood were increased in GC patients compared with healthy donors. ☙ In tissue, Tregs and ICOS$^+$ Tregs were found distributing mainly in carcinoma tissue, whereas pDCs were mainly found in peritumor tissue. ☙ The Foxp3$^+$ICOS$^+$/Foxp3$^+$ cell ratio in carcinoma and peritumor tissue were higher than that in normal tissue. ☙ There were more ICOS$^+$ Tregs in tumor and peritumor tissue of late-stage GC patients. ☙ There was a positive correlation between pDCs and ICOS$^+$ Tregs in peripheral blood and peritumor tissue from GC patients.	(66)
Fangxuan Li et al.	2014	☙ Tumor and normal tissues were obtained from 77 stomach cancer patients	☙ The higher pDCs percentage was associated with larger tumor size. ☙ The ratio of myeloid DCs/pDCs was significantly lower in tumor tissues.	(67)
Hirotsugu Nagase et al.	2016	☙ Peripheral blood was drawn from 40 GC patients and 5 healthy donors ☙ The surgically resected fresh cancer tissues of 40 GC, 10 colorectal cancers, 10 ovarian cancers, and 10 melanomas were obtained	☙ ICOS$^+$ Foxp3$^+$ CD4$^+$ T cells were abundantly observed in the late stages of gastric cancer. ☙ The expression of ICOS in Foxp3$^+$ cells was closely related to pDCs and their expression of ICOS-L and TLR9 as well as *H. pylori* infection.	(68)
Weihuang Liu et al.	2018	Peripheral blood samples ☙ 32 patients with GC ☙ 35 healthy volunteers	☙ Patients with GC were identified to have substantially higher numbers of peripheral pDCs and mDC1s. ☙ There was a trend of elevated circulating pDCs with advanced stages and lymph node metastasis in GC.	(69)
Zongxin Ling et al.	2019	A cohort of 64 GC patients without preoperative chemotherapy was enrolled retrospectively, and 60 normal, 61 peritumoral and 59 tumoral tissues were obtained	☙ From different microhabitats, BDCA2$^+$ pDCs and Foxp3$^+$ Tregs were observed positively correlated, and increased in tumoral and peritumoral tissues compared to normal ones. ☙ The diversity, composition and function of gastric mucosal microbiota also changed more significantly in tumoral tissues than those in normal and peritumoral ones. ☙ *Stenotrophomonas* and *Selenomonas* were positively correlated with BDCA2$^+$ pDCs and Foxp3$^+$ Tregs, respectively, while *Comamonas* and *Gaiella* were negatively correlated with BDCA2$^+$ pDCs and Foxp3$^+$ Tregs, respectively.	(70)
Xiaosun Liu et al.	2019	☙ Peripheral blood from 41 GC patients ☙ Carcinoma tissue, peritumor tissue and normal gastric mucosa from 87 GC patients	☙ Both ICOS$^+$Foxp3$^+$ Treg cells and pDCs in peripheral blood and tumor tissue could predict poor clinical outcome in GC patients.	(71)
Munetoshi Hinata et al.	2020	☙ 40 EBV-Negative GC ☙ 41 EBVaGC	☙ A high number of BDCA2$^+$ DCs was correlated with tumor invasion depth and was inversely proportional to the number of CD1a-positive cells in EBVaGC. ☙ The ratio of BDCA2$^+$ DCs to immature DCs was similarly low in the group with a high number of Langerhans- and CD1a-positive DCs.	(72)
Zhenlin Wang et al.	2021	☙ Samples from TCGA-STAD cohort and GSE62254 cohort ☙ A total of 594 patients	☙ The infiltration of pDCs positively associated with GC prognostic index in the TCGA-STAD cohort. ☙ The infiltration of pDCs positively associated with GC prognostic index in the GSE62254 cohort.	(73)

pDCs, plasmacytoid dendritic cells; ICOS, inducible co-stimulator; GC, gastric cancer; Foxp3, Forkhead box protein 3; DCs, dendritic cells; ICOS-L, inducible co-stimulator ligand; TLR9, Toll-like receptors 9; mDC1s, myeloid CD1c+ dendritic cells; BDCA2, blood DC antigen 2; EBV, Epstein-Barr virus; EBVaGC, EBV-associated gastric carcinoma; TCGA-STAD, the Cancer Genome Atlas Stomach Adenocarcinoma.

In tissue, the higher pDCs percentage was related to larger tumor size (67). $BDCA2^+$ pDCs were homogeneously distributed in the GC tissue, but the number of $BDCA2^+$ pDCs was significantly high in Epstein-Barr virus-associated gastric carcinoma (EBVaGC) as compared with EBV-negative GC (72). In EBVaGC, a high number of $BDCA2^+$ pDCs was associated with diffuse histology and tumor invasion depth (72). Moreover, pDCs were mainly distributed in peritumor tissue, whereas Treg cells and $ICOS^+$ Treg cells were mainly distributed in tumor tissue (66). The similar distribution pattern of pDCs has been reported in cervical carcinomas (75). There was a positive correlation between pDCs and $ICOS^+$ Treg cells in peripheral blood and peritumor tissue of GC patients, suggesting that pDCs may promote the differentiation of naïve $CD4^+$ T cells into $ICOS^+$ Tregs (66). Both tumor and peritumor tissue had higher $Foxp3^+ICOS^+/Foxp3^+$ cell ratio when compared with normal tissue (66). The number of $ICOS^+$ Treg cells in tumor and peritumor tissue increased with the progress of tumor stage in patients (66). $Foxp3^+ICOS^+$ Treg cells utilize distinct cytokines, for example IL-10, and thereby contribute to immunosuppression (76). The level of IL-10 increased from normal tissue to tumor tissue, mirroring the distribution of $ICOS^+$ Treg cells (66). Therefore, pDCs may recruit $ICOS^+$ Treg cells to promote immunosuppression of GC. A prospective study analyzing blood samples from 41 GC patients and tissue samples from 87 GC patients indicated that $ICOS^+Foxp3^+$ Treg cells and pDCs could predict poor prognosis of GC (71). Wang et al. analyzed data from the Cancer Genome Atlas Stomach Adenocarcinoma (TCGA-STAD) cohort and GSE62254 cohort, suggested that the higher risk score demonstrated a significantly lower overall survival time, and revealed positive correlation between increased risk score and infiltration of pDCs in GC (TCGA-STAD: $P < 0.001$, $R = 0.49$; GSE62254: $P < 0.001$, $R = 0.39$) (73). In other tumors, the prognostic values of pDC and Treg cells have also been evaluated (77, 78).

The human microbiome is essential for maintaining health, and a growing number of studies indicate a link between dysbiosis of the microbiome and diseases. Until the discovery of *H. pylori*, the stomach was long been thought to be sterile because of its highly acidic environment (79). As technology has developed, the mystery of the gastric microbiome has gradually been uncovered. The microbial load of the stomach is approximately 10^2–10^4 colony-forming units/ml (80). The most common phyla in gastric mucosa under normal conditions include *Proteobacteria*, *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Fusobacteria* (81). In healthy humans, the acidic gastric environment inhibits the over proliferation of microorganisms and reduces the risk of infection. *H. pylori* infection modulates the stomach environment. *H. pylori*-induced chronic inflammation triggers the loss of acid-secreting parietal cells, resulting in an increase in gastric pH, which promotes colonization by other bacteria (82). Although microbial dysbiosis has been observed during gastric carcinogenesis, there is currently no uniform pattern of alteration of the gastric microbiome. Alterations of the stomach microbiome promote the development of gastric diseases. Non-*H. pylori* bacteria promote gastric carcinogenesis by inducing inflammatory responses, modulating immune responses, triggering DNA damage, and promoting epithelial–mesenchymal transition (83–88).

As it is well known, *H. pylori* infection is associated with GC initiation, which leads to active inflammation and immune responses including the changes of pDCs. One study compared pDCs in *H. pylori*-infected children and noninfected controls and demonstrated upregulated expression of HLA-DR on circulating pDCs, and increased density of pDCs in gastric epithelium mucosa in *H. pylori*-infected children (89). Gastric mucosal microbiota analysis from 64 GC patients showed that the diversity, composition, and function of gastric mucosal microbiota was significantly different in tumor tissues compared with normal and peritumoral tissues, and $BDCA2^+$ pDCs and $Foxp3^+$ Tregs were positively correlated from different microhabitats (70). BDCA-2 is a novel type II C-type lectin that potently suppresses the production of IFN-α/β in pDCs (90). The changes in gastric mucosal microbiota and immune cells reflect the disturbance of the homeostasis of gastric mucosal immunity. In addition, *Stenotrophomonas* and *Selenomonas* were positively associated with $BDCA2^+$ pDCs and $Foxp3^+$ Tregs, respectively, whereas *Comamonas* and *Gaiella* were negatively associated with $BDCA2^+$ pDCs and $Foxp3^+$ Tregs, respectively (70). The gastric mucosal microbiota may play a part in modulating numbers of $BDCA2^+$ pDCs and $Foxp3^+$ Tregs to impair gastric mucosal immunity. Another study on the immune microenvironment of GC indicated close relationships among the expression of ICOS in $Foxp3^+$ tumor-infiltrating lymphocytes and pDCs, the expression of ICOS-L and TLR9 of pDCs, and *H. pylori* infection (68).

However, the specific effects of microbiota on pDCs remains unclear. The commensal microbiota can shape systemic levels of pDCs *via* a novel mechanism involving cytolytic $CD8^+$ T cells (91). Certain spherical lactic acid bacteria have various immunomodulatory effects on pDCs (92). When exposed to polysaccharide A of the gut commensal *Bacteroides fragilis*, pDCs stimulate IL-10 secretion by $CD4^+$ T cells and mediate immunoprotection (93). One study monocolonized mice with single microbial strains derived from humans and found that the fluctuations of pDCs in monocolonized mice were bidirectional: 38% of the bacteria tested increased colonic pDC proportions, whereas 8% reduced colonic pDC proportions (94). Interestingly, the frequencies of pDCs were variable even in mice colonized by the same organism (94). One study compared the pDCs in germ-free and specific-pathogen-free mice and found that microbiota controlled trafficking and peripheral localization of pDCs by inducing sustained level of CCL2 (95).

3 INNATE IMMUNE RESPONSES IN GC

3.1 Role of the Innate Immune Receptors in GC

H. pylori is a Gram-negative bacterium with a spiral shape (96). The structural and functional characteristics of *H. pylori* confer it

with the ability to resist acidic environments and colonize the host stomach (97). Persistent *H. pylori* infection initiates inflammatory responses of gastric mucosa, leading to atrophy of the glands, intestinal metaplasia, and GC (98). Immune responses to *H. pylori* infection are initiated by gastric epithelial cells and tissue-resident immune cells. The conserved pathogens' molecules, such as lipopolysaccharide (LPS), double-stranded RNA, flagellin, and CpG repeats, is also known as pathogen-associated molecular patterns (PAMPs). Recognition of PAMPs of *H. pylori* by pattern recognition receptors (PRRs) triggers the initial stage of the host immune responses to *H. pylori*. PRRs are predominantly expressed in epithelial cells, DCs, macrophages, monocytes, and neutrophils. It has been reported that PRRs, including TLRs, nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), and retinoic acid-inducible gene I-like receptors, are involved in gastric carcinogenesis (99–101).

3.1.1 TLRs in GC

As the major components of PRRs, TLRs play an essential part in *H. pylori* infection. Despite extensive study, the precise mechanism of TLRs is still controversial. TLR4 is the most studied TLR in *H. pylori* infection. TLR4 is activated by LPS of Gram-negative bacteria and subsequently triggers MyD88- and TIR-domain-containing adapter-inducing interferon-β-dependent signaling pathways, leading to the production of pro-inflammatory cytokines and type I IFNs (102). Accumulating evidence suggests that TLR2 has a significant role in recognition of *H. pylori* and induction of inflammatory responses. *H. pylori* infection upregulates the expression of TLR2 in gastric epithelial cells (103), whereas the expression pattern of TLR2 is not significantly altered after *H. pylori* eradication therapy (104). TLR9 mediates the recognition of *H pylori* DNA by DCs, inducing secretion of pro-inflammatory cytokines (105). Previous studies have demonstrated the high expression of TLR9 in GC (106, 107). The levels of *H. pylori*-induced TLR9 activation and expression are correlated with GC risk in different human populations (108). Nagase et al. hypothesized that chronic *H. pylori* infection might impact the expression of ICOS-L on pDCs *via* TLR9, leading to infiltration of $ICOS^+$ Treg cells into GC (68). However, one study indicated that TLR9 had anti-inflammatory effects to suppress *H. pylori*-induced gastritis in the early phase of infection *via* reduction of Th1 response modulated by IFN-α (109). Taken together, TLR9 possesses both pro-inflammatory and anti-inflammatory effects, and more studies are needed to elucidate the detailed contributions of TLR9 in gastric carcinogenesis. In addition to TLR9, TLR7 is involved in recognition of purified *H. pylori* RNA, leading to the secretion of pro-inflammatory cytokines (110).

3.1.2 NLRs in GC

In addition to TLRs, NLRs are involved in GC. NLRs are a type of intracellular PRRs, which can recognize not only PAMPs but also damage-associated molecular patterns (111). Much research has focused on the role during *H. pylori* infection of NOD1 and NOD2, which are expressed in gastric epithelial cells and APCs, where they recognize fragments of bacterial peptidoglycan (112). After recognizing γ-D-glutamyl-*meso*-diaminopimelic acid and muramyl dipeptide, respectively, NOD1 and NOD2 recruit receptor-interacting serine/threonine-protein kinase 2 through homotypic CARD–CARD interactions, resulting in the activation of NF-κB and mitogen-activated protein kinase pathways to induce robust pro-inflammatory responses (113–116).

3.2 Evasion From Recognition by PRRs

To survive, *H. pylori* employs multiple strategies to evade innate immune attack, including avoiding recognition by PRRs. LPS is a glycolipid present in the outer membrane of *H. pylori*, composed of lipid A, a core oligosaccharide, and O antigen (117). Compared with LPS of *Escherichia coli*, the LPS of *H. pylori* has lower immunological activity (118). During *H. pylori* infection, LPS modification contributes to persistent inflammation (117). Modification of the lipid A portion of LPS is used by *H. pylori* to escape immune recognition of TLR4 and evade the host innate immune response (119). Another example of evasion of recognition of PRRs is flagellin, which can be detected by TLR5 (120). *H. pylori* does not release flagellin, and the flagellin of *H. pylori* is less pro-inflammatory than that of *Salmonella typhimurium* (121).

3.3 Role of the Immune Cells in GC

3.3.1 Macrophage

Macrophages are essential responders in innate immune responses and are among the most abundant tumor-infiltrating immune cells in solid tumors. Macrophages are classified into two groups, M1 and M2 macrophages. The classically activated M1 macrophages mediate pro-inflammatory effects. Activated M1 macrophages produce high levels of IL-1β, IL-6, IL-12, IFN-γ, TNF-α, CXCL9, and CXCL10 (122, 123). These molecules promotes the polarization and recruitment of Th1 cells to amplify type 1 responses and mediates the destruction of pathogens and tumor cells (124). By contrast, alternatively activated M2 macrophages impart anti-inflammatory properties by producing IL-4, IL-10, and transforming growth factor β1 (TGF-β1), which have pro-tumorigenic functions (125–127). Tumor-associated macrophages (TAMs) predominantly have M2 characteristics, which are correlated with poor prognosis in a variety of tumors (128, 129).

During *H. pylori* infection, macrophages are critical to the severity of gastric inflammation, possibly owing to cytokine secretion and/or antigen presentation (130). A single-cell gene expression study revealed that macrophages were enriched in GC tissue compared with normal tissue, and the gene expression profiles of macrophages were heterogenous, that is, they were not confined to a binary M1/M2 designation (131). Other bacteria in addition to *H. pylori* are involved in immune modulation in GC. The abundance of *Propionibacterium acnes* is significantly increased in GC tissues and is related to TNM stages of GC patients. *P. acnes* induces M2 polarization of macrophages through TLR4/PI3K/Akt signaling to promote progression of GC (132). The crosstalk between macrophages and GC

cells or other immune cells contributes to shaping the immunosuppressive microenvironment and to GC progression (133–135). Furthermore, macrophages interact with mesenchymal stromal cells in GC. GC-derived mesenchymal stromal cells utilize cell-to-cell contact, paracrine effects, or extracellular vesicle transfer to induce the polarization of M2 macrophages, thereby prompting proliferation, invasion, and metastasis of GC (129, 136). A meta-analysis revealed that infiltration of M2 macrophages and total TAMs could be negative prognostic factors in GC, whereas M1 macrophage infiltration could be correlated with favorable survival rates (137). However, another study observed high infiltration of M2 macrophages in signet ring cell carcinoma and mucinous adenocarcinoma, which was associated with a favorable prognosis (138).

3.3.2 Neutrophils

Neutrophils are an important component of the innate response and are the first responders to infection and inflammation. Neutrophils are enriched in GC tissue, and correlate with poor prognosis in GC (139, 140). Tumor-associated neutrophils (TANs) have been reported to participate in cancer initiation and progression *via* several mechanisms (141). GC-derived GM-CSF activates neutrophils and induce the expression of PD-L1 *via* Janus kinase-STAT3 signaling pathway, leading to the suppression of T cell function to promote GC progression (140). TANs also produce cytokines, such as IL-1β, IL-6, IL-8, IL-17a, and IL-23, to facilitate migration and invasion of GC (139, 142, 143).

3.3.3 Mast Cells

Mast cells are another important BM-derived hematopoietic cells and widely distributed throughout the body (144). There are a substantial number of infiltrating mast cells in GC, which is correlated with tumor progression and predict shorter overall survival (145). Mast cells produce numerous mediators including pre-formed granule-associated mediators, newly generated lipid mediators, and a wide variety of cytokines and chemokines to exercise their biological functions (144). Tumor-derived TNF-α induces PD-L1 expression on intratumoral mast cells, which subsequently inhibits T cell function to suppress antitumor immunity in GC (145). Tumor-derived adrenomedullin activates mast cell degranulation, leading to the release of IL-17a to promote tumor progression (146). The mast cells-derived IL-17a also contributes to the tumor fibrosis in peritoneal dissemination in GC (147).

Taken together, the results of previous studies indicate both pro- and anti-oncogenic activities of immune cells in GC. However, the interaction between pDCs and other critical innate immune cells in GC still remains obscure, which is an important future research direction. Accumulating evidence suggests that tumor-infiltrating immune cells could be used to predict the prognosis of patients with GC. Although the molecular mechanism of immune cells in GC has not yet been fully elucidated, their potential therapeutic value is being investigated vigorously.

4 pDCs-BASED IMMUNOTHERAPY IN CANCER

Traditional approaches for cancer treatment, including surgery, chemotherapy, and radiation therapy, are not always satisfactory. Therefore, effective therapies for cancer are urgently needed. In recent years, the close relationship between cancer and the immune system has attracted increasing attention. pDCs are not abundant in peripheral blood or in the tumor microenvironment, but they represent potential targets for cancer immunotherapy owing to their interactions with other immune cells.

The strategies to create antitumor immunity include pDC vaccination. DC-based vaccines have shown benefits in multiple tumor types. Vaccination of metastatic melanoma patients using naturally occurring pDCs has been confirmed to be safe and to induce antigen-specific $CD4^+$ and $CD8^+$ T-cell responses (148). Dey Mahua et al. compared the immune response generated by pDCs *vs*. cDCs in a DC-based vaccine strategy in a mouse glioma model; the results indicated that cDCs were more effective than pDCs in generating an anti-glioma Th-1 immune response (149). Nine patients with metastatic stage IV melanoma received cancer vaccines based on an allogeneic pDC line. Clinical observations demonstrated the capacity of the vaccines to prime and expand antitumor $CD8^+$ responses, and no significant side effects were observed (150). In melanoma, vaccination with pDCs or $CD1c^+$ DCs caused secretion of different chemokines and recruitment of different immune effector cells, in particular, pDCs induced a stronger influx of cytolytic lymphocytes than $CD1c^+$ DCs (151). Combining the two DC subsets may enhance the antitumor efficacy of the vaccine owing to the chemoattractive properties of pDCs and the superior T cell priming properties of $CD1c^+$ DCs (151). $CD1c^+$ DCs and pDCs were shown to cross-activate each other and enhance NK-cell-mediated killing of an NK-resistant tumor cell line, suggesting that combining human blood DC subsets could further improve anticancer vaccine efficacy (152). Other vaccines have been used for anti-tumor therapy *via* activation of pDCs. One study investigated the effects of tumor cells infected with a measles virus vaccine on human pDCs; the results suggested that the vaccine induced immunogenic tumor cell death, as well as triggering pDC maturation, IFN-α production, and tumor antigen cross-presentation (153). The combination of an infectious but replication-deficient herpes simplex virus 1 vaccine strain with pDCs induced strong cytotoxic activity against tumor cells (154). The pDC vaccine has not been validated in a large population of patients; additional studies with large numbers of subjects are required in the future. However, the pDC vaccine is a promising option for cancer treatment.

The antitumor activities of type I IFNs have been well established (38). However, the efficacy of the IFN treatment is unsatisfactory in humans, and it causes frequent and severe adverse events (155). Therapies that are more effective have been developed over the past decades. Immunotherapies based on type I IFNs can selectively deliver IFN activity to targeted cells to reduce the toxic side effects caused by systemic IFN activity

(156). It has been confirmed that the interactions between type I IFNs and DCs are critical to triggering antitumor responses (157, 158). As mentioned above, cancer patients show higher tumor infiltration of pDCs, impaired production of type I IFNs by pDCs, and enhanced capacity to promote Treg cell expansion. Therefore, re-activation of pDCs to trigger the production of type I IFNs is a potential therapeutic approach. TLR7 and TLR9 agonists have been used to activate tumor-associated pDCs and showed some clinical benefit (159–161). The combination of imiquimod, a TLR7 agonist, and GM-CSF gene-transduced tumor vaccines activates pDCs and enhances their immunologic antitumor effects (162). Conjugation of TLR7 agonist to GC antigen MG7-Ag tri-epitope performed antitumor effects, which effectively induced the secretion of TNF-α, IFN-γ, and IL-12, and enhanced antibody-dependent cell-mediated cytotoxicity and cytotoxic T lymphocyte activity (163). GC vaccines, which were synthesized by covalent attachment of TLR7 agonist with MG7-Ag tetra-epitope, combined with 5- fluorouracil chemotherapy decreased tumor sizes and increased long-term survival rates by improving T cell responses and decreasing myeloid-derived suppressor cells (MDSCs) (164). A study using mice bearing autochthonous gastric tumors or subcutaneous C26 tumors explored the mechanism of antitumor immunity of TLR9 ligand CpG. Although CpG treatment did not significantly reduce growth of autochthonous gastric tumors, the suppressive function of MDSCs was blocked. Subsequent work revealed that CpG application stimulated the production of IFN-α by pDCs, which induced the maturation of MDSCs and blocked MDSCs suppressivity (165).

Therefore, based on the immunological properties of pDCs, reactivation of pDCs and restoring the production of type I IFNs could improve the efficiency of cancer treatments.

5 CONCLUSIONS

Many questions concerning the tumor immune microenvironment still need to be resolved, especially the role of pDCs. pDCs have been reported to infiltrate into a variety of tumors, including GC, accompanied by impaired production of type I IFNs. Evidence suggests that pDCs have some therapeutic effects on cancers. However, further clinical research and experimental studies are required to determine their clinical value in cancer treatment.

AUTHOR CONTRIBUTIONS

ZL and JY designed the review and revised the manuscript. JY performed the literature search and wrote the manuscript. YC, XL, JZ, and FJ performed the literature search and analyzed the literature. ZL and JY prepared the manuscript figure and revised the manuscript. All authors contributed to the article and approved the submitted version.

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