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Landscape of B lymphocytes and plasma cells in digestive tract carcinomas

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Abstract

Digestive tract carcinomas are the most commonly occurring cancers worldwide, but their prognosis with traditional treatments remains poor. T lymphocytes are well-recognized as crucial components of effective anti-tumor immunity, and current immunotherapeutic strategies concentrate mainly on T-cell-mediated immunity reinforcement, whereas the role of B lymphocytes and plasma cells (PCs) has been neglected in the past, and it is only recently that these cells have been considered as key players in the tumor microenvironment (TME). In this review, we describe the complex dual role of B lymphocytes and PCs in promoting and inhibiting tumor progression in the TME of digestive tract carcinomas, and we demonstrate their prognostic value. Furthermore, we highlight their controversial function in cancer and nominate them as additional therapeutic targets for the development of new treatment interventions that might alter the dismal prognosis of digestive tract tumors.

Keywords B lymphocytes, plasma cells, digestive tract carcinomas

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Introduction

Digestive tract carcinomas are among the 5 most common cancers in both men and women and are the most frequent causes of cancer-related death worldwide [1]. Immunotherapy now represents a cornerstone of cancer therapy and has changed the landscape of oncology. However, patients with digestive tract carcinomas usually do not benefit from it as much as patients with other solid malignancies, such as melanoma or lung cancer, and chemotherapy remains the backbone of systemic treatment in the majority of these cancers [2]. Furthermore, identifying patients who will benefit from immunotherapy remains a key challenge, and future investigation is needed to shed light on the complexity of the tumor microenvironment (TME), understand its function and discover additional therapy options.

The dynamic relationship between the adaptive immune system and cancer development has been well described over the past few decades, and tumor-infiltrating lymphocytes (TILs) are known to play an indispensable role in controlling tumor progression. Existing data have reported that high CD8+ T lymphocyte (T cell) density is associated with an antitumor response and better survival [3]. On the other hand, regulatory T cells (Tregs) are recognized as the main T cell subsets with an immunosuppressive role and are related to poor prognosis in cancer [4]. While T cells are considered crucial players in the tumor "battlefield", and current immunotherapeutic strategies focus extensively upon T cell-mediated immunity reinforcement, B lymphocytes (B cells) are not just bystanders in the TME but are considered active participants that can orchestrate the immune response [5]. However, B cells are less well investigated and have mainly been studied only during the last decade.

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In this review, we summarize the dual role of B cells and plasma cells (PCs) in TME and discuss their prognostic significance in digestive tract carcinomas. Additionally, we explore their curative implications in cancer and whether their manipulation may actually lead to a future therapeutic advantage.

Normal B cell development and maturation

B cells are the central components of the humoral immunity, and their early development originates from hematopoietic stem cells in the bone marrow under the influence of factors such as interleukin (IL)-7, secreted by stromal cells [6]. In the bone marrow microenvironment, immature B cells that possess B cell receptors (BCRs), as a result of effective V(D)J recombination, undergo negative selection, by which autoreactive immature B cells either are eliminated by apoptosis or change their antigen specificity by receptor editing. During this process, a second immunoglobulin light chain is generated with a possibility to reduce self-reactivity [6]. Although autoreactive B cells are edited by these mechanisms before exiting the bone marrow, a considerable proportion of mature B cells possess self-reactive BCRs [4]. In neoplastic states, there is a disruption of peripheral tolerance, and it has been shown that the most common target antigens of tumor infiltrating B cells (TIL-Bs) are self-proteins [3]. After exiting the bone marrow, B cell maturation occurs in secondary lymphoid organs (SLOs) in T cell-dependent and T cell-independent processes [6]. Specifically, after antigen recognition by the BCR of naïve B cells and interaction with T follicular helper cells in SLOs, germinal centers are formatted where B cells can proliferate, differentiate and turn into activated B cells [3]. Some of the B cells further differentiate into PCs, which release immunoglobulins IgA, IgG and IgM, or memory B cells, which regulate long-term specific immune responses [4]. In the gastrointestinal (GI) tract, B cell maturation and differentiation take place in gut regional lymph nodes, gut-associated lymphoid tissues (GALT) and, mainly, in Peyer's patches (PPs), which are the predominant GALT [7].

B cell function in the TME

Regarding the TME, it has been demonstrated that B cells exist in several different states, such as naïve, activated, memory, and germinal center (in the context of tertiary lymphoid structures) B cells, and PCs [4]. B cells in the TME may exert their function via different effector mechanisms, such as antigen presentation and priming of T cell responses, immune cell recruitment via cytokine production, activation of innate immunity via complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cell-mediated phagocytosis (ADCP) and immunosuppression related to the presence of regulatory B cells (Bregs) [2]. Regarding the specificities of detected antibodies in cancer patients, although antibodies recognizing cancer-associated and cancer-specific antigens have been reported, the majority of them are autoreactive, recognizing non-mutated self-proteins [2].

Current evidence suggests that B cells can promote or inhibit tumor progression, and they are recognized as biomarkers of both bad and good prognoses in cancer [2]. The TME contains a mixed B cell subset population, and the balance between their responses may determine whether these cells can have a pro- or anti-tumorigenic impact.

Antitumor function of B cells and PCs

B cells and PCs participate in antitumor immune responses through several mechanisms. Indeed, recent data report that B cells negatively control tumor development, and the presence of CD20+ TIL-Bs in non-small lung adenocarcinoma, cervical and ovarian cancer is associated with better survival and a lower risk of relapse [5]. Recent studies have shown that the presence of B cells in the form of lymph node-like aggregates named tertiary lymphoid structures (TLS) correlates with hot tumors and better survival (Fig. 1,2) [3]. The level of organization of TLS represents a spectrum from small B-cell aggregates, with some dispersed T lymphocytes (primers), to highly organized structures that contain secondary B cell follicles with germinal centers (secondary) and a perifollicular T zone with conventional dendritic cells and high endothelial venules (HEVs) [3]. In most studies the presence of TLS, especially mature, secondary ones, has been associated with a favorable prognosis in many different tumor types and is a significant predictor of the response to immune checkpoint blockade [3]. In addition, the presence of HEVs represents a gate for further lymphocyte recruitment into the TME, contributing to potent antitumor responses and a positive prognosis [2]. Moreover, B cells promote antitumor immunity through their role as antigen-presenting cells (APCs) to CD4+ and CD8+ T lymphocytes, leading to their activation and proliferation [6]. Another protective function of B cells is the secretion of cytokines such as interferon (IFN)γ and IL-12 that drive cytotoxic immune responses and polarize T cells toward Th1 or Th2 differentiation [2]. Furthermore, B cells can directly attack tumor cells using granzyme B and through the TRAIL/Apo-2L-related pathway [4]. Finally, tumor cells can trigger a humoral response by expressing specific antigens (neoantigens). Consequently, B cells differentiated into PCs produce antibodies that kill tumor cells through complement activation, phagocytosis by macrophages and activation of NK cells [6]. In fact, a high PC density is correlated with better clinical outcomes in patients with melanoma, non-small cell lung carcinoma, ovarian cancer and head and neck squamous carcinoma [3].

Protumor function of B cells and PCs

B cells, on the other hand, are also crucial mediators of tumor development. Indeed, high B cell and PC levels have been related to progression in bladder cancer, a higher relapse

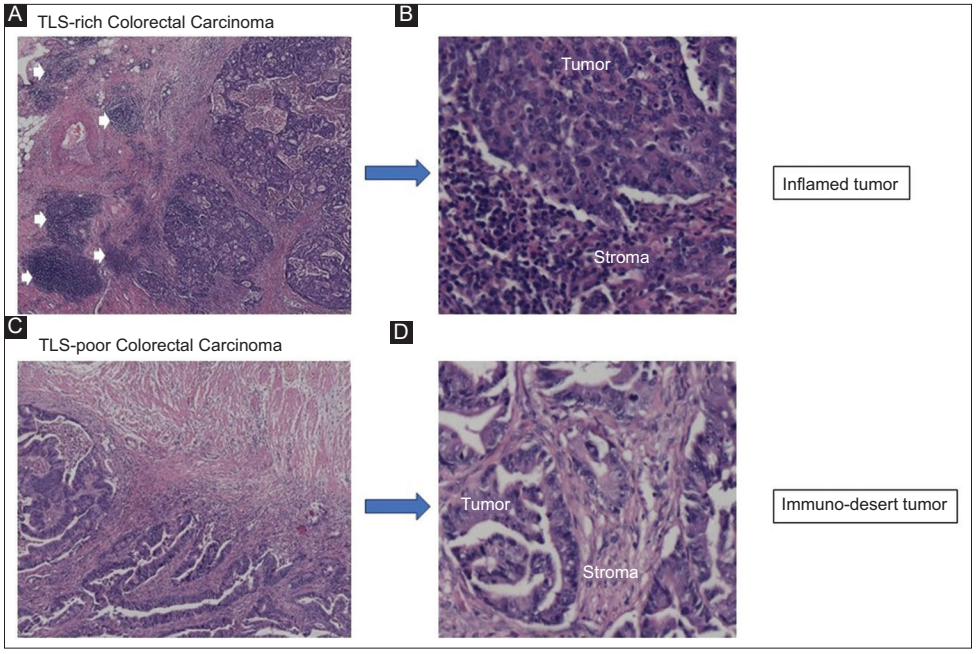

Figure 1 The background concept regarding the role of tertiary lymphoid structures (TLS) in shaping tumor-specific immune responses. Upper panel: A case of colorectal carcinoma (CRC) with high densities of TLS in the invasive front (A, white arrows) that display an inflamed immune phenotype with increased densities of lymphocytes and plasma cells, both in the stroma and inside tumor islets (B). Lower panel: A case of TLS-poor CRC without any lymphoid aggregates present in the tumor bed (C) that display an immuno-desert phenotype with rare stromal lymphocytes (D)

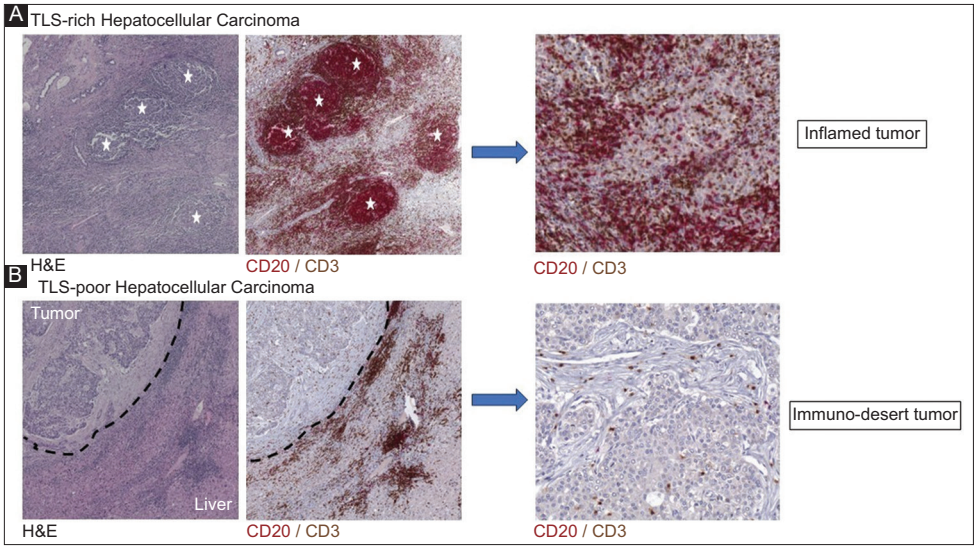

Figure 2 Tertiary lymphoid structures (TLS) and tumor immune microenvironment in hepatocellular carcinomas (HCC). A (Upper panel). A case of TLS-rich HCC, with high densities of mature TLS with germinal centers (white stars) that display an inflamed immune phenotype with increased numbers of CD20+ B lymphocytes (red) and CD3+ T lymphocytes (brown). B (Lower panel). A case of TLS-poor HCC (upper left part), with dispersed TLS only in the liver parenchyma (lower left part) that is related to the underlying chronic hepatitis. Only rare CD20+ B lymphocytes and CD3+ T lymphocytes infiltrate the stroma and tumor islets (immuno-desert phenotype)

rate of prostate carcinoma after prostatectomy, and worse survival in renal cell and ovarian carcinoma [3]. Immune complexes formed by tumor-specific antibodies are associated with a poor outcome by inducing chronic inflammation, tissue remodeling, and angiogenesis with the activation of myeloid cells [3]. Furthermore, B cells increase angiogenesis by activating STAT3 pathways and promoting tumor growth [3]. The protumor impact of B cells is largely associated with the presence of Bregs. These cells are characterized by the production of suppressive cytokines, such as IL-10, IL-35 and tumor growth factor (TGF)-β, and inhibitory ligands, such as PD-L1 [4]. Consequently, Bregs may lead to cancer progression by inhibiting helper and cytotoxic T cells to eradicate tumors, and by converting CD4+ T cells into Tregs [2-4].

Methods

Search strategy

We conducted a literature search of articles in the PubMed/Medline electronic database related to the function and prognostic effect of TIL-Bs and PCs in digestive tract carcinomas, covering a period from January 2000 to September 2023. In addition, the reference lists of retrieved articles were checked manually for related articles. We explored the literature for studies involving any type of the B lineage, including naïve B cells, memory B cells, plasmablasts and PCs. Additionally, we used the key words "B cells", "B lymphocytes", "plasma cells", "gastrointestinal cancer", "digestive tract tumors", "digestive tract carcinomas", "gastrointestinal tumors", "gastrointestinal carcinoma", "esophageal carcinoma", "gastric carcinoma", "pancreatic carcinoma", "colorectal carcinoma", "liver cancer", "hepatocellular carcinoma", "cholangiocarcinoma" and "prognosis". The search terms were combined with the Boolean operators AND/OR. The key words were used in all possible combinations to obtain the maximal number of articles. All articles selected for inclusion were critically evaluated.

Study selection

In the first step of study selection, we ruled out irrelevant studies by assessing the titles and abstracts of the articles. Subsequently, we screened the full texts of the selected studies, and articles that met the following criteria were included: (1) qualitative, quantitative, and mixed-method original articles; (2) reviews, case series, randomized control trials; (3) studies that used immunohistochemistry to detect TIL-Bs and PCs in tumors, gene expression signatures that are exclusively or closely associated with the B-cell lineage and flow cytometry to identify these cells in cell suspensions of tumor tissues; and (4) studies that provided the standard prognostic endpoints of overall survival and/or progression free survival. For the identification of B cells, CD20 and to a lesser extent CD19 were widely used, as they are expressed in mature B cells but lost upon differentiation to PCs, while for PCs CD138 is the most frequently used marker. The literature search was restricted to the English language. Case reports, studies with a sample size below 20, and anywhere the full text could not be acquired, were excluded. A total of 81 clinicopathological studies that fulfilled the inclusion criteria were retrieved via database search (Table 1).

After the first screening, all the full text copies were evaluated independently by 2 of the authors (KD and PGF) for eligibility. Any disagreements between the 2 reviewers were resolved by discussion and consensus.

Data extraction

A standardized form was used to extract data from the included studies. We attempted to retrieve the following data from all publications: year of publication, type of publication, author, country, tumor type, sample size, B cell detection method (immunohistochemistry, gene expressing profiling, flow cytometry), prognostic data (overall survival, progression-free survival) and predictive value of studies according to the treatment response (Table 1).

Esophageal carcinomas (ECs) and B cells

ECs are the eighth most common type of cancer and their current treatments rely on tumor eradication by surgery and chemoradiation [1]. Thus, it is critical to understand the role of the immune system in order to improve the poor prognosis of this malignancy. Unfortunately, the existing literature relating to the effect of B cells and PCs in the TME is limited and conflicting. One possible explanation is the presence of different B cell subsets with opposing functions. Indeed, Zhang *et al* demonstrated that, within esophageal squamous cell carcinoma (SCC), B cell clones vary between different tumor regions leading to an intratumor immune response [8]. Increasing evidence suggests that, in curatively treated patients with esophageal adenocarcinoma or SCC, high PC infiltration was associated with longer overall survival (OS), while tumors with CD20+ B cell aggregates had a better prognosis [9-12]. Similarly, some reports revealed that in esophagogastric junction adenocarcinoma, high PC density was correlated with significantly better outcomes, whereas for B cells, the effect was only obvious when TLS were present, and mainly at the invasive margin [13,14]. It was notable that the TIL antitumoral effects in SCC were mostly dependent on the functional interaction between T cells and B cells organized in TLS, resulting in a better prognosis [15-17]. In SCC, Lu *et al* investigated a new synergistic, protective mechanism between B cells and IL-17, suggesting that the latter promotes tumor cells' production of chemokines CCL2, CCL20 and CXCL13, which are associated with B cell recruitment [18]. Consequently, IL-17 increases both B cell antibody production and their direct tumor killing effects through Granzyme B and Fasl, contributing to a more favorable prognosis [18]. Recently, Guo *et al* reported that in advanced SCC, B cell density in the TME correlated with clinical benefit in patients receiving anti-PD-1/PD-L1-based immunotherapy [19].

In EC, B cells in contrast to their anti-tumor activities, may exhibit a negative regulative impact. Shi *et al* observed that the level of circulating Bregs in EC patients was significantly enhanced before surgery and then decreased following resection, confirming their protumor role [20]. Moreover, it has been described that EC-derived microvesicles facilitate B cells' differentiation into Bregs, which in turn suppress CD8+ T cell activity [21]. Peritumoral B cells can activate proangiogenic signals in hypoxic conditions with high HMGB1 protein expression, leading to a fatal prognosis [22]. The above indicates that B cells and PCs are essential players in EC microenvironment and their role should be fully characterized in order to optimize immunotherapeutic approaches.

Table 1 Prognostic and predictive impact of B cells, plasma cells and TLS in digestive tract carcinomas based on clinicopathological studies

Carcinoma type	Patient number	Detection method (IHC, GEP, FC)	Prognostic value (PFS, OS)			Predictive value (immunotherapy response)			References
			B cells	Plasma cells	TLS	B cells	Plasma cells	TLS	
Esophageal	2136	IHC [9,11,13,16-18,22] GEP [10-12,15,19,22] FC [14]	Favorable in most studies Poor only in 1 study [22]	Favorable	Favorable	Favorable [19]	NA	NA	[9-19,22]
Gastric	4234	IHC [9,23,25,27-29,34,35] GEP [24,26,29,30,32,33] FC [30]	Favorable in 3 studies [23,25,27] Poor in 3 studies [32-34]	Favorable in most studies Poor only in 1 study [35]	Favorable	NA	NA	NA	[9,23-30,32-35]
Colorectal	5545	IHC [36,37,39-42,44-47,49-54] GEP [38,43,48,49,52,55,59] FC [59]	Favorable	Favorable in most studies Poor only in 1 study [59]	Favorable	Favorable [55]	Favorable [55]	Favorable [55]	[36-55,59]
Pancreatic	1976	IHC [61-64,66-68,70,71,73] GEP [60,63,65,70,71] FC [71]	Favorable [60,61,65] Poor [70,71]	Favorable [73]	Favorable	NA	NA	Favorable [62]	[60-68,70,71,73]
Liver	7856	IHC [74-77,81-84,86-89,91,92,95,96] GEP [101] FC [77,84]	Favorable in most studies Poor only in 5 studies [89-92,95]	Favorable in 2 studies [75,84] Poor in 3 studies [92-95]	Favorable	Favorable [79,80]	NA	NA	[74-96]

TLS, tertiary lymphoid structures; FC, flow cytometry; GEP, gene expression profiling; IHC, immunohistochemistry; NA, not applicable; OS, overall survival; PFS, progression-free survival

Gastric carcinoma (GC) and B cells

GC is the second most common malignant tumor of the digestive tract and is related with high mortality, making it urgent to take further steps towards improved treatment [1]. It is evident that adaptive immune responses are important factors in the clinical outcomes of this carcinoma. Accumulating evidence suggests that tumor-associated CD20+ B cells and PCs in gastric adenocarcinoma restrain tumor growth and are correlated with prolonged survival [9,23-26]. These antitumoral responses become more efficient when a functional interplay takes place in the TME between B cells, PCs and T cells [27]. According to previous data, B cells organized in TLS, mainly in the invasive margin area, were associated with significantly better prognosis in GC [28-30]. Lastly, Zhang *et al* showed that Bregs can also protect *Helicobacter pylori*-infected individuals from the development of GC through the production of immunosuppressive cytokines, and mainly IL-10, which inhibit the local inflammatory processes promoting carcinogenesis [31].

In contrast, other studies demonstrated the negative role of B cells in GC progression, possibly as a result of their action at different time points. Consequently, when the gastric tumors have developed, Bregs induce immune escape in the TME by downregulating T helper cells and promoting differentiation of Tregs and their density, which is correlated with a greater risk of tumor progression [32-34]. Miyatani *et al* showed that IgG4+ PCs in GC are closely related to more aggressive behavior and a worse prognosis [35]. Taken together, the role of B cells and PCs in GC is debatable, and additional studies are necessary to reveal the status of B cell immunity in this tumor type.

Colorectal carcinoma (CRC) and B cells

CRC is the third most common malignancy globally, and the long-term survival of patients depends not only on the conventional staging, but also on the TME immune response, which plays a vital role in different aspects of disease evolution [1]. Increasing evidence has indicated that high B cell and PC density in the central region and the invasive margin of tumor is associated with favorable pathological characteristics, and successful tumor regression following chemoradiotherapy and is an independent predictor of better outcomes [36-45]. Interestingly, Berntsson *et al* observed that CRC is a heterogeneous disease, and the prognostic impact of TILs differs between proximal and distal CRCs. Thus, CD20+ B cells are correlated with a better prognosis in right-sided tumors, while PCs are associated with a better prognosis in left-sided but not rectal tumors [46]. Similarly, the TLS quantity seems to be greater in right-sided tumors than those in left-sided CRC, which may lead to an individualized treatment strategy [47]. This can probably be attributed to the different fetal origin of colon segments, as well as to diverse genetic and molecular features of tumors depending on their location [46]. Moreover, some studies have reported that B cell infiltration in CRC is diverse and is related to stage progression. Thus, primary tumors are enriched by terminally differentiated memory B cells and PCs that inhibit development, whereas advanced tumors and metastases contain a lower B cell density, or are infiltrated by Bregs with protumor immune responses [48,49]. Additionally, B cells are in close proximity to T cells, and particularly organized in TLS, mostly in the invasive margin, leading to a lower risk of disease relapse and prolonged survival [50-54]. Recently, Xia *et al* reported that patients with enrichment of B cells, PCs and TLS in the CRC TME presented significant therapeutic advantages after anti-PD1 immunotherapy, demonstrating the role of these cells as potential predictive biomarkers for treatment response [55].

Conversely, B cells have also been shown to foster CRC progression. It has been suggested that B cells directly inhibit cytotoxic T cells, and after partial B cell depletion with rituximab a reduced tumor burden was described in 50% of patients with advanced CRC [56]. Similarly, in B-cell-deleted mouse models with CRC, B cell reactivation blocked CD8+ T cell responses and enhanced tumor growth [57]. Zhang *et al* demonstrated that, in chemotherapy-treated mouse models, B cell-derived extracellular vesicles in the TME prevent activation of effector T cells and are biomarkers of resistance to chemotherapy [58]. Furthermore, granzyme expressing Bregs suppress CD4+ T cell proliferation and induce Treg differentiation, facilitating tumor escape [4]. Finally, IgA+ PCs express high levels of immune suppressive molecules, such as PD-L1, IL-10 and TGF-β, and prevent activation of CD8+ T cells, while their presence in CRC tumors is correlated with shorter survival [59]. Overall, it is evident that the CRC complex B cell immunity must be well understood before novel therapeutic strategies can be hugely beneficial.

Pancreatic ductal adenocarcinoma (PDAC) and B cells

PDAC is one of the most aggressive GI malignancies, with a devastating prognosis [1]. The TME, which includes scarce cancer cells, excessive desmoplasia and infiltration by an abundant mixture of immune cells, plays a critical role in the biological behavior of this cancer [60]. Accordingly, several studies have highlighted that the presence of CD20+ B cells within PDAC is associated with longer survival, and this correlation is reinforced when these cells are confined in TLS that favor CD8+ T cell recruitment and activation [60-67]. Recently, Zou *et al* demonstrated that the presence of intratumoral TLS was associated with increased immune cell infiltration and improved OS in PDAC patients who underwent upfront surgery [68]. However, this protective role of TLS was not observed in patients who received neoadjuvant chemotherapy, as their samples contained immature TLS with a lower B cell proportion and higher Treg density [68]. Moreover, B cells within germinal centers, proliferate and differentiate to memory B cells or PCs producing tumor specific antibodies, especially IgG, that target KRAS mutant cells [69].

On the other hand, B cells in PDAC may be immunosuppressive, as their presence has been associated with

shorter survival [70]. A series of recent reports demonstrated the tumor-promoting functions of B cells in PDAC mouse models. Firstly, deletion of HIF1, a principal mediator of hypoxic adaptation, accelerates pancreatic tumorigenesis by upregulating the chemokine expression involved in B cell migration [71]. Furthermore, it was shown that the B cell protumor impact is mediated by IL-35 expression that stimulates pancreatic cancer cell proliferation [72]. Finally, it was illustrated that interaction between B cells and tumor-associated macrophages activates Bruton tyrosine kinase, a member of the BCR signaling group, in a PI3Kγ-dependent manner, and favors M2 macrophage polarization and Breg differentiation, leading to immune suppression and tumor growth [3]. Interestingly, although BTK inhibitors, such as ibrutinib or tirabrutinib, reduced PDAC progression in mouse models, the combination of ibrutinib plus nab-paclitaxel and gemcitabine for first-line treatment of patients with metastatic PDAC did not improve survival [3]. Moreover, it has been suggested that IgG4+ PCs infiltration is correlated with negative clinicopathological traits and a poor prognosis in PDAC [73]. In summary, a careful evaluation of all B cell subsets may represent a powerful prognostic tool and open broad perspectives for the development of immunotherapeutic strategies for PDAC.

Liver carcinomas and B cells

The development of hepatocellular carcinoma (HCC), the sixth most common cancer worldwide, representing more than 90% of primary liver cancers, is a well-recognized model of multistep carcinogenesis, with a fine-tuned collaborative action between immune cells [1]. However, B cell distribution, prognostic value and functional status in the TME remain controversial. Several reports showed that TIL-Bs and PCs, especially along the invasive margin, are associated with longer survival, and their proportion can predict immunotherapy response and sorafenib resistance [74-82]. Shi *et al* showed that IgG+ memory B cells organized in the tumor interface execute antitumor effects by producing granzyme B, TRAIL and IFNγ, expressing surface markers characteristic of APCs and cooperating with CD8+ T cells [83]. Indeed, B cells seem to be in close proximity to T cells, forming small clusters or TLS with germinal centers, which result in their bidirectional activation and subsequently tumor control [84-88].

In contrast, B cells are also known to be key components of immunosuppressive responses. Higher levels of Bregs, mainly at the tumor margin, have been correlated with advanced stage and unfavorable prognosis [89]. Shao *et al* reported that Bregs induce HCC development by interaction with liver cancer cells through the CD40/CD154 signaling pathway, resulting in IL-10 and TGF-β1 secretion [89]. IL-10-expressing B cells can suppress cytotoxic CD4+ T cells in HBV-induced HCC, leading to worse survival [90]. Similarly, Xiao *et al* identified a novel PD-1hi Breg subset in HCC that prevents T cell anti-tumor immunity and fosters cancer evolution through IL-10 [91]. Patients with a lower PC proportion had a better prognosis. In particular, when IgA+ B cells concentrate in the liver during chronic inflammation, they inhibit cytotoxic CD8+ T cells and promote tumor progression by producing IL-10 and PD-L1 [92-94]. Finally, it has been observed that CXCR3+ B cells migrate to the HCC invading edge, maturate, produce IgG immunoglobulin and stimulate M2 macrophage polarization, contributing to tumor growth [95]. These studies emphasize the importance of exploring the underlying mechanisms that control the balance between the protumor and antitumor B cell responses in the TME of HCC.

Cholangiocarcinoma, the second most common type of primary liver cancer, is characterized by a rich desmoplastic microenvironment, largely consisting of tumor-associated fibroblasts and a variety of cells of the innate and adaptive immune system. Unfortunately, our knowledge of the role of B cells is limited. A few studies have suggested that a high CD20+ B cell density in cholangiocarcinoma is related to better outcomes, but future investigations are necessary to elucidate their function [96].

Discussion

Digestive tract carcinomas remain an enormous burden on society, representing a major health problem worldwide [1]. Traditional, systemic treatments usually have inadequate therapeutic effect on these tumors, whereas cancer immunotherapy, a current hot topic, may change their dismal prognosis. The importance of T cells in antitumor responses is well established, but the B cell contribution to tumor immunity has been overlooked for decades. In this review, we focused on exploring the distinct role of B cells and PCs in the TME of digestive tract carcinomas and we described their prognostic significance. Existing evidence in the literature about B cell function in digestive tract carcinomas is controversial, possibly because of various clinicopathologic factors, grade and stage of tumors, technical issues and different methods used for calculating immune cells, while diverse cutoff values may also have influenced the results. Moreover, the conflicting B cell effect on cancer depends on activation status, interaction with other immune cells, distribution in the cancer, expression of immunosuppressive signals by cancer cells, and mainly on the presence of different subsets of B cells that have an antitumor or protumor impact. In general, most studies reported a positive prognostic value of TIL-Bs or PCs in digestive tract carcinomas, and their tumorigenic role was associated with the immunosuppressive nature of Bregs (Fig. 3). The favorable prognostic value of B cells is strengthened when they are organized in TLS, which encourages lymphocyte recruitment and differentiation. Additionally, TLS favor the beneficial interplay between immune cells, modulating antitumor activity.

Regarding the multiple functions of B cells in TME, these cells are potential immunotherapeutic targets that may open new avenues in the treatment of digestive tract carcinomas through their activation or their depletion. Several studies highlight the positive association between the presence of B cells and

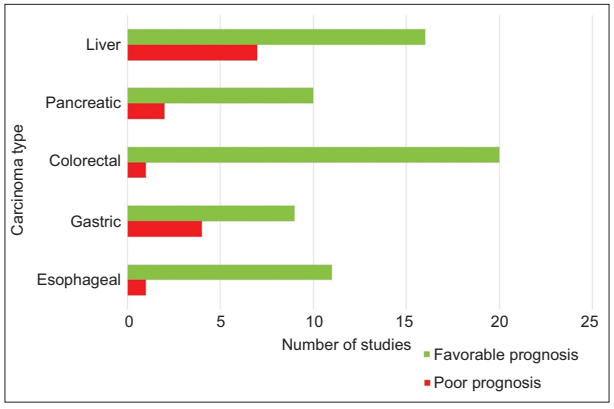

Figure 3 Prognostic value of tumor-infiltrating B cells and plasma cells according to carcinoma type. Bars represent the number of studies with favorable (green) or poor (red) prognosis

TLS, and the clinical response to anti-PD-1 and anti-CTLA-4 checkpoint blockade therapies [19,55,62,80]. Immunotherapy may also increase immune cell infiltration in tumors, including B cells and PCs [5]. Existing evidence in the literature indicates an increase in B and PCs, as well as TLS formation, following neoadjuvant immune checkpoint inhibitor treatment, while patients with a higher TLS and B cell density in pre-treatment tumor tissues had a better response to neoadjuvant and adjuvant immunotherapy [3,4]. Additionally, it has been demonstrated that the B cell density in TME is positively correlated with the response to certain types of chemotherapy [2]. Chemotherapy can also enhance B cell recruitment and induce TLS in TME [2]. Neoadjuvant chemotherapy in ovarian and breast cancer can lead to TLS formation, a higher TIL-B number, and Breg depletion, improving patient outcome [3,4]. Evidence is limited regarding the association between B cell or PC density and the clinical response after neoadjuvant and adjuvant treatment in digestive tract carcinomas. In locally advanced rectal carcinoma, a high pre-treatment B cell density was associated with a better response to neoadjuvant chemoradiotherapy [41,97]. Patients with resectable gastric adenocarcinoma and higher pre-treatment TIL-B numbers had a better response to adjuvant chemotherapy, while TIL-B density increased following neoadjuvant chemotherapy in patients with gastric and esophageal adenocarcinoma [98,99]. On the other hand, neoadjuvant chemotherapy had an immunosuppressive effect in the PDAC microenvironment, resulting in post-treatment TIL-B density reduction [100]. In mouse models, the combination of angiogenesis and immune checkpoint inhibitors promotes HEV formation, which leads to T and B cell recruitment, and may explain the increased efficacy of the combination compared to monotherapy in some cancers [3]. Cytokines such us BAFF and CXCL13 promote recruitment of T cells and B cells, and TLS formation in tumors [3,48]. Thus, cytokine-based therapies can enhance T cell and B cell responses in cancer, improving antitumor immunity. Antibody-mediated effects of B cells in TME may also offer several promising and innovative therapeutic approaches, through inhibition of their target proteins or by inducing ADCP/ADCC [5]. Another possible optimal approach includes cancer vaccines that may promote TLS formation and TIL-Bs responses [2,3]. Finally, given the protumor role of Bregs in TME, the depletion or inhibition of these cells might represent a new and powerful means to improve immune response [4]. This can be achieved by either chemotherapeutic agents and targeted inhibitors, or by antagonism of IL-10, IL-35, and TGF-β [4].

Spatial and quantitative analyses of B cells and PCs can be incorporated into clinical practice as prognostic and predictive tools. These cells might serve as biomarkers that can be used for a better selection of patients who are likely to respond to immunotherapy, chemotherapy and/or targeted therapies. Future work is required for the identification of various B cell subsets in digestive tract carcinomas, and how to take advantage of them, in order to optimize the impact of TIL-B responses and anti-tumor immunity in general.

Concluding remarks

B cells are essential components of the immune response to cancer. The presence and behavior of TIL-Bs have a complex impact on cancer development and progression, and their role in cancer is an active area of investigation. The role of B cells in cancer varies widely among different cancer types and patients and ongoing research may help to elucidate their multifaceted interactions within the TME. A better understanding and careful evaluation of the various B cell and PC subpopulations in the TME is fundamental in order to target them specifically and design individualized and efficient treatments.

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