B cells present a double-sided effect in digestive system tumors: a review for tumor microenvironment

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Abstract: Over the past few years, there has been an increasing interest in investigating tumor-infiltrating lymphocytes. B lymphocytes (B cells) are extensively distributed within tertiary lymphoid structure (TLS) as multifaceted subgroups and are intimately linked to the anti-tumor properties of TLS, as well as the survival and prognostication of individuals. While the investigation of T lymphocytes in the TLS has advanced to the level of clinical practice, the study of B cells remains limited. The principal impediment to the utilization of B cells in immunotherapy is their notable dual impact on tumors. Compared with tumors in other parts and systems, the function of B cells in the microenvironment of digestive system tumors to promote tumors proliferation, differentiation and migration cannot be ignored. Therefore, this review collects the studies of B cell subsets in tumor microenvironments, particularly related single cell sequencing research. The multifaceted role and function of B cells are investigated in esophageal, liver, colorectal, gastric and pancreatic cancers. And through the identification of B cell subsets and specific markers, this review attempts to explain the reasons why B cells produce different tumor-promoting effects in those tumors. The insights gleaned from this review may provide potential help and support the development of B cell-based immunotherapies.

Keywords: Tumor microenvironment; cancer; B cells; immunotherapy

Introduction

Recently, the immune mechanism and changes of tumors is deeply exploring. The function of T lymphocytes (T cells) has been studied in depth and applied in clinical practice, such as immune checkpoint inhibitors. Although some immunotherapy strategies targeting B lymphocytes (B cells) have shown therapeutic effects in some studies, there are still many problems and deficiencies to be solved.

For example, the identification of regulatory sites of B cell immune function, the prevention of up-regulation of cancer-promoting functions such as immune escape, the way of combining with other treatments to improve the therapeutic effect, etc. Therefore, it is of great significance to further study the mechanism of B cells in cancer and explore new immunotherapy strategies to improve the therapeutic effect of cancer.

In this review, the differentiation and types of B cells, the classification and function of antibodies, and some immune structures were described first. Next, according to the anatomy, B cells' roles and functions in esophageal, liver, colorectal, gastric and pancreatic cancer were shown. Through the B cells' dual function in tumors and the function changes in B cell associated with different organs, some relevant influencing factors were inferred. This review is expected to promote the understanding of the mechanism of B cells in cancer and help to realize the practice of B cells in immunotherapy.

The differentiation process of B cells

B cells, which primarily develop in the bone marrow, are humoral immunity cells that secrete antibodies for immune effects. Specifically, B cells arise from progenitor B cells (Pro-B cells) located in the fetal liver hematopoietic cells' island before migrating to the bone marrow (1). Upon the initiation of heavy chain expression by Pro-B cells, precursor B cells (Pre-B cells) differentiate and lack the capacity to react to antigens or perform immune functions (2). At this stage, differentiation antigens specific to B cells, such as major histocompatibility complex (MHC), CD19, and CD20, manifest (3). Following light chain gene rearrangement, immature B cells (Bµ cells) differentiate from Pre-B, possessing intact IgM molecules capable of binding to antigens. When Bµ cells are bound to antigens, they undergo inhibition, which prevents their maturation. This mechanism is recognized as a contributing factor to the formation of B cell self-tolerance (4). After undergoing negative selection in the bone marrow, immature B cells migrate into the circulatory system and undergo maturation into transitional B cells within the spleen (5). In the initial stages, transitional B cells are designated as T1 B cells and could be found in the spleen, bone marrow, and the peripheral arterial lymphatic sleeves (PALS) outside of hair follicles (6). Through signal stimulation mediated by the B-cell activating factor (BAFF) family, T1 B cells differentiate into T2 B cells. Following their maturation, T2 B cells undergo differentiation into two distinct subtypes, namely naive B cells (NBC) and marginal zone B cells (MZB) (7). Following stimulation, NBC undergoes further differentiation into follicular B cells (FOB) as well as germinal center B cells (GCB) (*Figure 1*).

The final stage prior to the commencement of immune function by B cells is activation. Based on the reliance of their activation on T cells, B cells can be classified into two categories (8). T-cell-independent cells, including MZB, FOB, B1 cells, and regulatory B cells (Breg), constitute one such group (9). B1 cells, which are classified as innate lymphoid cells, are capable of recognizing nonprotein antigens (10). B1 cells are present in low quantities, which is not addressed in this review. Rather, conventional B cells undergo T-cell-dependent activation and differentiate into plasma cells (PC) and memory B cells (MBC) (11). The activation of B cells is facilitated by mature T follicular helper cells (TFH), which provide CD40 ligands and interleukin-21 (IL-21). Upon activation, B cells undergo proliferation and differentiation, with a significant proportion differentiating into PCs (12). This differentiation is marked by the appearance of surface markers such as plasma cell antigen-1 (PCA-1), which replace the original B cell surface markers (13). During class conversion, the immunoglobulin (Ig) produced by B cells transformed from IgM into IgG, IgA, or IgE. Meanwhile, a small subset of activated B cells undergoes differentiation into MBC, which exhibits limited proliferation and differentiation capabilities and can persist for several months to years (14). Upon encountering the same antigen, MBC rapidly activates and differentiates, exhibiting a short incubation period, high antibody (Ab) levels, and prolonged maintenance.

Immunoglobulin

The glycoprotein known as antibody is generated by B cells upon stimulation by antigens and is present in bodily fluids (15). It serves as a crucial effector molecule that facilitates humoral immunity by selectively binding to corresponding antigens. The heavy chains of antibody are classified into five categories, namely µ, δ, γ, α, and ε chain, which correspond to the five types of antibodies, namely IgM, IgG, IgD, IgA, and IgE (16). As a result, the identification of various B cell subsets can be achieved by discerning the different types of antibodies they produce.

The human body produces IgM as the initial antibody to combat new infections, comprising approximately 10% of normal serum Ig content (17). IgM serves as a receptor on the B cell membrane, receiving antigen stimulation. While a single molecule of IgM exhibits higher bactericidal and conditioning effects than other antibodies, its protective efficacy is limited due to its low blood concentration, short half-life, rapid clearance, and weak tissue penetration (18).

IgG is the most prevalent antibody type present in all bodily fluids and contributes significantly to humoral immunity (19). IgG serves as the primary antibody in re-
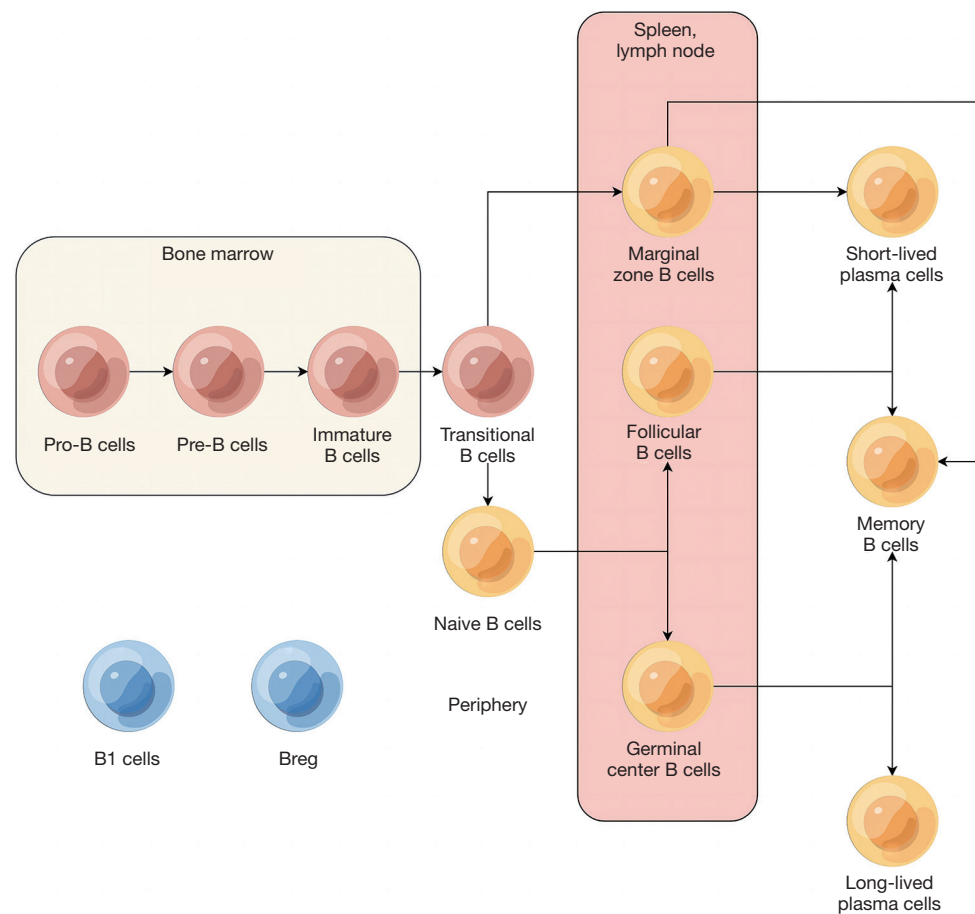
Figure 1 The differentiation of B cells is shown in the schematic diagram. B cells, B lymphocytes; Pro-B cells, progenitor B cells; Pre-B cells, precursor B cells; Breg, regulatory B cells.

immune response and possesses various functions, including phagocytosis, neutralization of toxins and viruses, mediation of antibody-dependent cell-mediated cytotoxicity (ADCC), and activation of the classical pathway of complement (20). Additionally, IgG is the sole antibody capable of crossing the placenta, thereby safeguarding newborns during the initial months of life. IgG comprises four subgroups, with IgG4 exhibiting a close association with the digestive system.

The molecular structure of IgD is remarkably similar to that of IgG, and it functions as a surface antigen receptor on B cells (21). However, due to its low concentration in normal human serum, research on IgD remains limited.

IgA is present in mucous membranes, including the respiratory and digestive tracts, as well as in bodily fluids such as saliva, tears, and breast milk (22). As a monomer, IgA functions to eliminate antigens in a noninflammatory manner and maintain internal stability. Secretory IgA, synthesized

locally in gut-associated lymphoid tissue (GALT), exists as a dimer and serves a crucial role in immune defense (23).

IgE is present in its monomeric form and exhibits the lowest serum concentration among the five classes of Ig (24). It is predominantly localized in the respiratory tract and intestinal mucosa. However, IgE is essential in allergic responses and provides protection against parasitic infestations.

Immune structure

Immune composition of the digestive system

The immune system, which encompasses immune cells, tissues, and organs, serves as a protective barrier to the human body (25). Within the digestive system, the spleen and intestine play crucial roles as components of the immune system. The spleen functions not only as an immune

site and storage location for immune cells but also as a synthesizer of immune molecules, including complement (26). The intestinal immune response is comprised of inherent immunity, adaptive immunity, and mucosal immunity.

GALT plays a pivotal role in intestinal immunity, acting as the principal mediator. It encompasses a diverse array of components, including Peyer's patches (PP), independent lymphoid follicles, mesenteric lymph nodes, and lymphocytes located in the mucosal lamina propria (27). PP, a collection of lymphatic follicles within the small intestine's mucosa, is comprised of B and T cells and is enveloped by a stratum of microfold cells referred to as M cells (28). These M cells possess the ability to recognize antigens within the gastrointestinal tract, phagocytose viruses and pathogens, and present ingested intestinal antigens to immune cells (29). Activated immune cells undergo homing to the lamina propria of the intestinal mucosa, where they differentiate into IgA-secreting PCs or effector T cells, thereby contributing to the local immune response of the intestinal tract.

Tertiary lymphoid structure (TLS)

TLS, which are anomalous lymphoid organs that emerge in non-lymphoid tissues, are commonly detected in a diverse range of persistent inflammatory ailments such as inflammatory diseases, autoimmune and infectious diseases, transplanted organs, and tumors (30). TLS is comprised of B cells, enveloped by T cells, and additionally encompasses TFH, dendritic cells, fibroblasts, blood vessels, and other cellular and structural components (31). TLS has been detected in the matrix, invasive margin, and core of various tumor types, particularly in proximity to tumors. Researches have demonstrated that TLS plays a pivotal role in the immune microenvironment by conferring distinct T cell phenotypes and that T cells exhibit dysfunctional molecular phenotypes in tumors lacking TLS (32).

Currently, TLS is widely regarded as a reliable indicator of tumor therapeutic immune response in numerous studies, thereby facilitating the promotion of antitumor immune response and positively impacting the overall survival (OS) and disease-free survival (DFS) of patients (33). Additionally, TLS can exert an influence on tumor invasion and metastasis.

B cells in cancers

Consistent with most studies, high B cell infiltration is positively correlated with tumor prognosis. However, some studies have shown that high B cell infiltration is unfavorable, especially in digestive system tumors. Therefore, the following takes digestive system cancers as the main direction, and discuss in detail the function and role of B cells in various cancers (*Figure 2*, *Table 1*).

Esophageal cancers

Esophageal cancer represents a prevalent and lethal form of cancer, histologically classified into two subtypes: esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC) (52).

ESCC, which constitutes approximately 90% of global esophageal cancer cases, has been studied through single-cell sequencing of tumor samples to obtain its transcription map. The tumors exhibit a presence of common immune cells, such as T cells, natural killer (NK) cells, monocytes/macrophages, dendritic cells (DC), B cells, and mast cells. Mature TLS, which is rich in various immune cells, significantly enhances the anti-tumor immunity of ESCC (53). However, ESCC displays a higher infiltration of T cells and monocytes/macrophages and a lower presence of B cells compared to normal tissues and other cancers (54). Despite the low quantity of B cells, they exhibit a diverse range. B cells in ESCC exhibit a diverse range of subgroups, totaling at least 20, which can be further classified into ten distinct subtypes based on their respective functions. These subtypes include NBC, GC1, GC2, PC, MBC, interferon (IFN)-induced, Innate, double negative (DN), mature, and activated B cells (35). Furthermore, data revealed the identification of novel and unique B cell subtypes, such as NBC-NF-κB, MBC-ITGAX, and other four plasmablast subtypes (34). Notably, the gene-phenotype of NBC-NF-κBx has been shown to have an enhanced effect on T cells. The MBC-ITGAX subtype has demonstrated significant antitumor benefits.

The MBC-ITGAX subtype is characterized by an enrichment of tumor necrosis factor-α (TNF-α) signaling through the nuclear factor κB (NF-κB) pathway and the IL-2-STAT5 signaling pathway (55). The NF-κB pathway plays a role in B cell maturation and adaptive immunity, positively regulating B cell activation and cytokine production through TNF-α signal transduction (56). The presence of NF-κB related genes is indicative of a favorable prognosis in esophageal cancer.

When considered in conjunction with other clinical studies, B cell infiltration is positively associated with a favorable prognosis (57). While some B cells that are associated with lymph node metastasis and poor prognosis
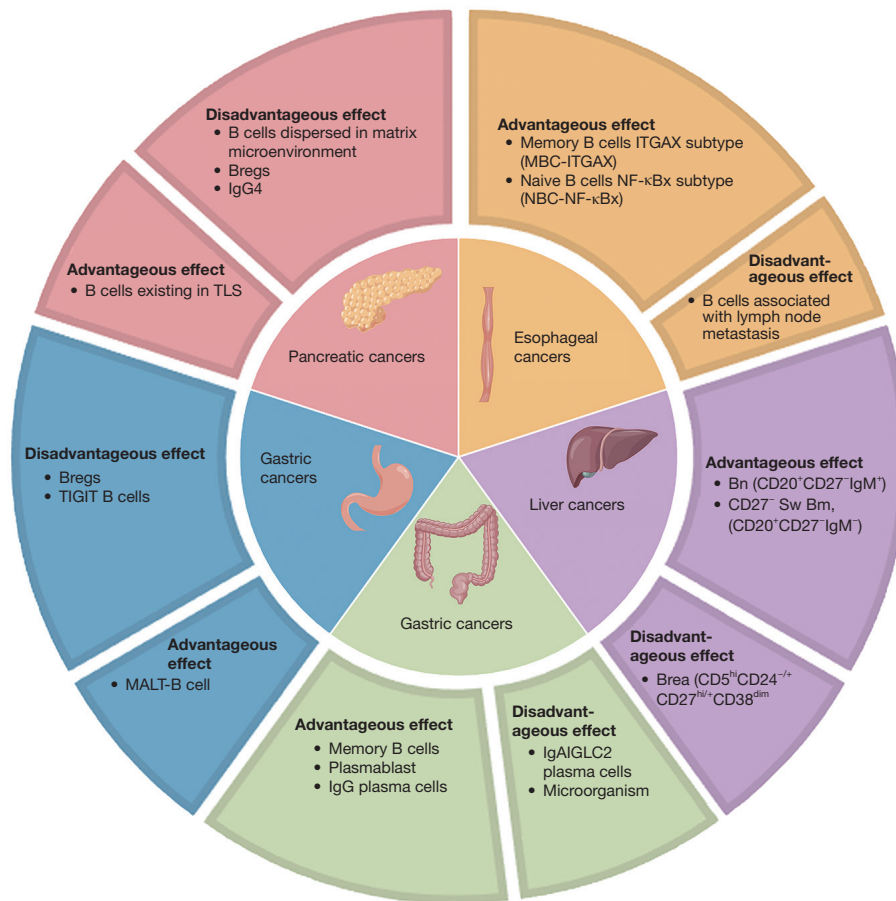
Figure 2 The advantages and disadvantages effects of B cells in different cancers. +: positive expression; –: negative expression; hi: high expression; dim: dim expression. NBC, naive B cell; MBC, memory B cell; GCB, germinal center B cell; MALT, mucosa-associated lymphoid tissue; TLS, tertiary lymphoid structures; TIGIT, T-cell immune receptor with immunoglobulin and ITIM domain.

have been identified, their presence is insufficient to diminish the tumor-killing effect of high B cell infiltration (35).

Liver cancers

Numerous risk factors have been identified as contributing to the development of liver fibrosis or sclerosis, which is often accompanied by substantial immune infiltration and ultimately culminates in the emergence of liver cancer (58).

Throughout the progression of hepatocellular carcinoma (HCC), the concentration of B cells in liver tissue varies, with B cells being abundant in normal liver tissue. Upon the transformation of tissue to cirrhosis, the proportion of immune cells, namely T cells (1.40%), B cells (5.49%), and macrophages (0.41%), decreases (37). Then the proportion of B cells in HCC increases by 18.85%. B cells predominantly infiltrate the tumor margin and are comprised of five

subgroups: NBCs (Bn, $CD20^+CD27^-IgM^+$), IgM^+ MBCs (IgM^+ Bm, $CD20^+CD27^+IgM^+$), $CD27^-$ isotype-switched MBCs ($CD27^-$ Sw Bm, $CD20^+CD27^-IgM^-$) and $CD27^+$ isotype-switched MBCs ($CD27^+$ Sw Bm, $CD20^+CD27^+IgM^-$) and PCs ($CD20^-CD24^-CD27^{hi}CD38^{hi}$) (36). Researches have established that a high density of B cell infiltration is positively correlated with small tumor size, absence of vascular invasion, and increased density of $CD8^+$ T cells (59). Bn and $CD27^-$ Sw Bm, in particular, showed better survival correlation. Simultaneously, a substantial correlation exists between elevated B cell infiltration and prolonged survival time, with patients exhibiting high B cell density presenting with better clinicopathological features, providing compelling evidence for the antitumor effect of B cells (60).

Nevertheless, reports acknowledging the acceleration of tumor progression by B cells cannot be disregarded, with Breg playing a pivotal role in this regard (61). In

Table 1 Functional organization of various B cells in different tumors

Tumors	B cells	Functions	Ref.
Esophageal cancers	NBC-NF-κB	Enhance T cell function	(34)
	MBC-ITGAX	Promote B cell maturation, activation, production of cytokines	(34)
	GC1 B	Prompt bad prognosis	(35)
	GC2 B	Prompt good prognosis	
Liver cancers	Bn	Contribute to T cell activation	(36)
	CD27 Sw Bm	Produces antibodies (IgG or IgA) to promote humoral immunity	
	PC	Negative regulatory T cells	(37)
	Breg	Effectively inhibits tumor-specific T cell immunity, and promote tumor growth through IL-10	(38)
		Increased production of IL-40 and TGF-β promotes tumors progression, thereby reducing TNF-α levels and reducing anti-tumor immune responses	(39)
Colorectal cancers	MBC	Antigen presentation, chemokine secretion	(40)
	PC	Secrete a lot of IgG	
	Transitional B cells	Suggest loss of immune tolerance	(41)
	Plasmablast	Suppressing harmful Th17 inflammation	(42)
		Inhibition of IFN-γ and TNF-α	(43)
	IgAIGLC2 PCs	Enhance allograft rejection, IFN-α reaction, IFN-γ reaction and inflammatory reaction of tumor-derived cells	(44)
Gastric cancers	TIGIT B cells	Shape immune invasive structures to promote tumor progression	(45)
	MALT-B cells	Activation of complement pathway promotes antitumor immunity	(46)
	Breg	Inhibit the proliferation of autologous CD4 T cells, inhibit the production of IFN-γ by CD4 T cells, and enhance immune escape	(47)
Pancreatic cancers	IgG1 MBC	Complement activation, binding of Fc receptors on the surface of effector cells and involvement of ADCC	(48)
	Breg	Secretion of IL-35 promotes immunosuppression and tumor growth	(49)
		Expresses high levels of PD-L1, resulting in reduced T cells proliferation and IFN-γ secretion	(50)
	IgG4 PCs	Positively correlated with poor histological grade and overall survival	(51)

NBC, naive B cell; NF-κB, nuclear factor κB; IL-10, interleukin 10; TNF-α, tumor necrosis factor α; MBC, memory B cell; GCB, germinal center B cell; PC, plasma cell; MALT, mucosa-associated lymphoid tissue; TIGIT, T-cell immune receptor with immunoglobulin and ITIM domain; ADCC, antibody-dependent cell-mediated cytotoxicity; PD-L1, programmed cell death ligand 1; IFN-γ, interferon γ; TGF-β, transforming growth factor β.

advanced HCC, the percentage of Breg in tumor tissues significantly increased, constituting approximately 10% of all B cells. These Breg exhibited a distinctive phenotype: $CD5^{hi}CD24^{-/+}CD27^{hi/+}CD38^{dim}$ (38). These Breg have been shown to effectively inhibit tumor-specific T cell immunity and promote tumor growth *in vivo* through IL-10 (62). Furthermore, PC is recognized to exhibit an adverse regulatory association with T cells, while the quantity of B cells and FOXP3 Treg cells has been verified to display a

positive correlation (39).

Colorectal cancers

The prevalence and fatality rate of colorectal cancer (CRC) persist in an upward trajectory. Owing to its inconsequential clinical manifestations and absence of specificity, over 80% of patients are diagnosed in the intermediate and advanced stages, with over 40% of patients experiencing liver and

lung metastases (63).

In CRC, macrophages constitute the predominant immune cell type, followed by T cells, B cells, bone marrow cells, and mast cells. In comparison to normal tissues, tumors exhibit enrichment of T cells, while B cells are depleted (44). The identification of B cells in tumor tissues reveals their classification into NBC, MBC, GCB cells, IgA PCs, and IgG PCs (40). Notably, the proportion of effector MBC and plasmablasts is significantly elevated in CRC. MBC exhibits comparable functions to NBC and possesses abundant antigen presentation and chemokine signaling pathways (64). The expression of genes related to antigen presentation is consistently elevated. Tumor tissues exhibit a higher abundance of IgG PCs, with infiltration levels decreasing from the tumor center to the periphery (65). Additionally, the IgG/IgA PC ratio increases.

The elevated density of infiltrating B cells is associated with the lower stage tumor and the right colon, which is commonly believed to exhibit a more favorable prognosis and lower malignancy degree in tumors (66). Furthermore, patients with heightened B cell infiltration demonstrate a noteworthy increase in survival duration. In CRC, B cells and T cells exhibit a strong positive correlation due to the cooperative nature of immune cells, which is advantageous for tumor eradication (40).

Nevertheless, the role of B cells in tumor elimination becomes intricate due to the abundance of microorganisms and IgA in the intestine (41). The potential etiology of these outcomes may be attributed to the destruction of tumor tissue to the intestinal barrier. The disruption of barrier function may impede the negative selection of autoantigen-specific B cells, leading to the accumulation of immature B cells in tissues, including elevated levels of T1 and T2 B cells (67). These immature B cells are characterized by the expression of IgM and exhibit inadequate immune function when compared to IgG. Furthermore, the impairment of the barrier may result in the loss of intestinal tolerance to microbial antigens (68).

IgA PCs are localized specifically in the mucosa of CRC, and the presence of IgA GLC2 PCs has been linked to a negative prognosis (44). These cells have been found to augment allograft rejection, interferon-α (IFN-α) and IFN-γ reactions, and inflammatory responses, suggesting their involvement in promoting tumor-associated inflammation (43).

Gastric cancers (GC)

GC is a malignancy that arises from the epithelium of the gastric mucosa and is the most common digestive tract malignancy. The immune response plays a significant role in the initiation and progression of GC. The majority of B cells infiltrating tumors in GC are present in the form of TLS surrounding the tumor, as well as in the normal gastric mucosa surrounding the tumor (69).

Upon identification of GC tissues, B cells are classified into various subtypes, including PCs, B cells originating from mucosa-associated lymphoid tissue (MALT), NBC, FOB cells, MBC, inflammatory B cells, and tumor-associated B cells (46). In GC with a high abundance of TLS, the proportion of NBC is low, while GCB cells and PCs are increased. As the predominant subtype, GCB cells exhibit strong activation (69). Furthermore, a significant quantity of MALT-B cells exhibiting specificity were identified within TLS. These MALT-B cells are almost only found in GC tissues that contain TLS, which belong to a terminally differentiated subset of IgA PCs (70). The functions of MALT-B cells may be associated with complement activation, immune response, and B cell activation. Additionally, researches have demonstrated that the infiltration of B cells within GC tissue is positively correlated with the infiltration of T cells, but negatively correlated with TH1 cells, TH2 cells, and Treg cells (71). The elevated degree of B cell infiltration is associated with extended OS and DFS, with particular emphasis on the heightened infiltration of MBC and PCs, signifying a more favorable prognosis (72).

However, some studies indicate that B cells may act in parallel to promote tumorigenesis. Breg in GC tissue was significantly higher than that in normal tissue. Breg in the peripheral blood of GC patients was significantly higher than that of the healthy control group, and Breg decreased significantly after an operation (47). Breg was found to be enriched in CD19CD24CD27 B cell subsets in GC patients. The $CD19^+CD24^{hi}CD27^+$ B cells have been shown to possess the ability to inhibit the proliferation of CD4 T cells and suppress the secretion of IFN-γ by autologous T cells (47,73). Breg has been observed to transform $CD4^+CD25^-$ effector T cells into $CD4^+FoxP3^+$ Tregs through TGF-β1. Additionally, the T-cell immune receptor with immunoglobulin and ITIM domain (TIGIT), which is highly expressed, has been found to be associated with promoting tumor progression by shaping an immune-invasive structure (74). TIGIT-B cells have been observed to infiltrate into and around the tumor in GC, and this has been suggested to be indicative of poor prognosis in GC (45).

Pancreatic cancers

Pancreatic cancer is a highly invasive malignant tumor with a 5-year survival rate of only 5–7%. Current treatment methods have proven little effective in treating this disease, likely due to the ability of pancreatic cancer cells to evade immune surveillance, develop drug resistance, and metastasize early (75).

In pancreatic cancer, the function of B cells remains a topic of controversy, with their impact on tumor growth dependent on their localization within tumor tissue. B cells present in TLS have demonstrated a tumor-killing effect, resulting in longer OS and DFS (76). Samples exhibiting high levels of TLS demonstrated upregulation of genes associated with the germinal center reaction, B cell activation, and proliferation. The germinal center reaction is enriched in IgG1 MBC, effector memory CD4+ T cells, and NK cells, indicating the presence of long-lasting immune memory (48).

Conversely, B cells dispersed within the matrix microenvironment exhibited an increase in the expression of immunosuppressive genes. In comparison to healthy individuals, patients with pancreatic cancer exhibited an expansion of Breg, which was associated with tumor stage and low survival rates (77). The expansion of Breg in pancreatic cancer patients is induced by the secretion of IL-18 by pancreatic cancer cells (78). In pancreatic cancers, Breg facilitates the conversion and recombination of pro-inflammatory IgG1 to anti-inflammatory IgG4, which is associated with a significant infiltration of IgG4 PCs and a negative correlation with histological grade and OS rate (79). The production of IgG4 is typically induced by a Th2 immune response driven by IL-10 and IL-4. Thus, the Breg-mediated conversion of IgG classes may serve as an alternative immune evasion mechanism.

Furthermore, in stark contrast to the invasive nature of pancreatic cancer, the majority of tumor volumes consist of cancer-associated fibroblasts (CAFs), extracellular matrix (ECM), and immune cells, collectively referred to as the "tumor matrix" (80). The presence of circulating plasmablasts can stimulate CAFs to produce a significant amount of collagen, thereby promoting tumor progression through increased matrix deposition (81).

Conclusions

In the tumor microenvironment, the function of T cells has been extensively investigated and effectively implemented in clinical practice. However, the functional investigation and clinical application of B cells, which serve as the primary mediator of humoral immunity, remain insufficient, because of the complex regulatory role of B cells. For tumors, B cells' bidirectional regulation is notably pronounced. Undoubtedly, B cells exhibit tumoricidal activity in the majority of tumors. However, in select tumors, particularly those of the digestive system, a high degree of B cell infiltration is associated with a poorer prognosis (82). Notably, in tumors of the esophagus and liver, a high degree of B cell infiltration is generally indicative of a favorable prognosis. In colorectal and gastric tumors, the prognostic implications of high B cell infiltration are equivocal. Finally, in pancreatic cancer, B cells are frequently linked with unfavorable outcomes.

In conjunction with additional research, it is our assertion that the elements contributing to the heightened tumor-promoting properties of B cells in digestive neoplasms encompass IgG4, microorganisms, IgA, and Breg. Although the function of IgG4 immunoglobulin is still being investigated, its association with autoimmune diseases is well-established. IgG4-related diseases are characterized by attacking various tissues and organs, with a predilection for glandular and digestive system involvement, particularly the pancreas (83). This phenomenon may elucidate the atypical elevation of IgG4 and the detrimental consequences of heightened B cell infiltration in pancreatic cancer. Microorganisms are a distinct presence within the digestive tract, whose carcinogenic impact has been established, with particular emphasis on the induction of GC by *Helicobacter pylori* (HP). As previously discussed in the context of CRC, the impairment of the intestinal barrier can have a complex effect on immune function through the alteration of B cell function by beneficial intestinal microorganisms. In contrast to other tissues, the intestinal mucosa is abundant in IgA and exerts a significant influence on the immune milieu of the intestine. As previously stated, certain subsets of IgA PCs have been definitively linked to poorer tumor prognoses. Additionally, IgA PCs in pancreatic cancer secrete a greater quantity of cytokines (e.g., IL-10) that facilitate the development of Breg (84). The functionality and regulation of Breg have been extensively investigated. Breg's role in promoting tumor growth in B cells is a direct responsibility. The remaining three factors, either as inducers of Breg or as parallel influencers, contribute to tumor development. This phenomenon partially accounts for the prevalence of Breg in digestive system tumors. Consequently, immunotherapy for B cells should prioritize

the inhibition of Breg.

Footnote

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