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Revolutionizing anti-tumor therapy: unleashing the potential of B cell-derived exosomes

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B cells occupy a vital role in the functioning of the immune system, working in tandem with T cells to either suppress or promote tumor growth within the tumor microenvironment(TME). In addition to direct cell-to-cell communication, B cells and other cells release exosomes, small membrane vesicles ranging in size from 30-150 nm, that facilitate intercellular signaling. Exosome research is an important development in cancer research, as they have been shown to carry various molecules such as major histocompatibility complex(MHC) molecules and integrins, which regulate the TME. Given the close association between TME and cancer development, targeting substances within the TME has emerged as a promising strategy for cancer therapy. This review aims to present a comprehensive overview of the contributions made by B cells and exosomes to the tumor microenvironment (TME). Additionally, we delve into the potential role of B cell-derived exosomes in the progression of cancer.

KEYWORDS

B cell, B cell-derived exosome, therapy, TME, anti-tumor

1 Introduction

Cancer remains a significant global cause of mortality (1). Historically, cancer research solely emphasized studying cancer cells. However, with the introduction of the "seed and soil" concept (2), researchers have redirected their focus towards investigating the development of cancer cells within TME. The TME fosters cancer cell growth and progression through its complex composition of ECM, neuroendocrine cells, immune cells, stromal cells, fibroblasts, and lymphatic networks (3, 4). Immune cells play a significant role in the survival of tumors, as cancer cell metabolites and secretions from

specific TME cells can influence the activation, proliferation, differentiation, and function of immune cells (5).

Reports suggest that extracellular vesicles (EVs), particularly exosomes, hold significant potential as a cancer treatment (6). Standard chemotherapy methods may cause harm to normal cells, resulting in detrimental side effects (7, 8). In contrast, Targeted therapy has become a more appealing approach to combatting tumors as it offers greater specificity and can spare adjacent healthy tissues (9). The idea of utilizing exosomes for targeted therapy is intriguing, given that almost all cells produce exosomes (10). Bioengineered exosomes have garnered considerable attention due to their exceptional stability, extensive tissue penetrability, potent targeting capability, and precise drug modulatory properties (11). Although there are no standardized protocols for exosome isolation and purification (12), their potential role in cancer therapy warrants further investigation into their biological functions.

B cells are present in both secondary lymphoid organs (SLOs) and tertiary lymphoid structures(TLSs). TLSs, which represent lymphoid neogenesis sites that occur in most solid tumors (13), primarily consist of B cell follicles and T cell zones, along with mature dendritic cells (DCs) (14, 15). Within these lymphoid structures, there is a rich signaling crosstalk between B cell-derived exosomes and other cells.

2 B cells and the tumor microenvironment

In the past decade, immune cells have gained significant attention in TME research due to their capacity to regulate tumor growth (16). Despite incomplete comprehension of the role of B cells in cancer research, their heterogeneity has been demonstrated as indispensable in the TME (17). B cells are also involved in the formation of TLSs, which has been instrumental in advancing cancer research (18).

2.1 Immunomodulatory functions of B cells

B cells are a component of the adaptive immune system that can differentiate into various subsets when subjected to diverse stimuli and stress conditions (19). The multifaceted nature of B cell subsets, which is primarily due to the absence of a precise definition of their transcription factors, makes comprehending their functions a difficult and complicated process (17).

B cells assume a pivotal role in antibody production and antigen presentation to facilitate effective immune responses among other immune cells (20, 21). After antigen recognition, B cell activation occurs through activation of B cell receptors (BCRs) and Toll-like receptors present on the surface of them. Subsequently, activated B cells differentiate into plasma cells through two distinct pathways. In the first pathway, plasma cells differentiate outside the lymphoid follicle, exhibit lower affinity for antigens, and have shorter lifespans. In the second pathway, B cells migrate into the follicle and establish a germinal center (GC) that differentiates into long-lived plasma cells and memory B cells (22–24). Plasma cells produce IgM antibodies that contribute to humoral immune responses. Moreover, B-cell-associated immunoglobulins, including IgG, IgE, and IgA, have been extensively reviewed in the literature with respect to their subclasses (21). IL-10 promotes plasma cell production through CD40 activation and is superior to IL-4 (25). Recent studies have found that tumour-associated neutrophils in TME rely on TNF-α to recruit B cells and regulate B cell differentiation into plasma cells *via* the BAFF pathway (26).

Memory B cells exhibit signaling molecules, such as MHC and co-stimulatory molecules, along with cytokines (IL-6, TNF, GM-CSF) on their surface, which stimulate T cells, thereby amplifying the immune response (24). Upon a second exposure to antigens, memory B cells produce high-quality antibodies (27).

B regulatory (Breg) cells are distinct in that their primary function is to suppress the immune system (28). Breg subsets containing IL-10 and IL-35 have the ability to suppress effector T cells (both CD4 and CD8), NK cells, and neutrophils (29). Additionally, Bregs regulate levels of extracellular metabolites such as ATP, ADP, AMP, and adenosine in TME, resulting in the suppression of T and B cell proliferation, forming a complex network (30, 31).

Tumor-infiltrating B cells (TIBs) participate in the development of TLSs, which stimulate an active anti-tumor response *via* antigen presentation (32, 33). Activated TIBs release enzymes or receptors to kill cancerous cells, leading to their lysis (34). B cells secrete angiogenic factors to stimulate the activation of STAT3 and facilitate angiogenesis (35). In prostate cancer, TIBs may produce lymphotoxin (LT), and high levels of LT can lead to CR-CAP and adversely affect treatment outcomes (36).

2.2 B cells in cancer therapy

Surface markers CD19, CD20, and CD37 are expressed at varying levels by B cells during development. Although studies indicate that targeting these molecules therapeutically holds promise for B-cell cancers (37), their potential efficacy against other cancer types remains largely unexplored. Mediation by CD19 increases antigen presentation by B cells, consequently improving the T cell response (38). Attracting B cells, CXCL13 functions as a chemokine (36, 39). Tumor-induced Bregs (tBregs) serve as a marker of tumor persistence (40). CD20 is expressed on both anti-tumor B cells and tBregs, and targeting CD20 B cells with CXCL13-coupled CpG-ODN can enrich and inactivate tBregs, thereby controlling tumor immune escape (41). This approach minimizes the potential side effects of B-cell depletion methods. In bladder cancer, CXCL13 expression can be used as a surrogate marker for tumor TLSs and correlates with the response to immune checkpoint inhibitors (ICIs) in patients (42). Additionally, in a subset of patients with soft tissue sarcoma, B-cell-enriched TLSs was associated with a better response to anti-PD-1 blockade therapy and increased survival rates (43).

However, the inhibitory mechanisms of tumors mediated by TLSs and B cells in ICI therapy remain poorly understood (44). It is noteworthy that within GCs, B cells are activated to produce antibodies, while Bregs and Tregs produce cytokines such as IL-10, IL-35, and TGF-β to suppress T cell function (18). Furthermore, chemotherapy (45) and vaccination (46) have also demonstrated associations with TLSs.

B cell-enriched TLSs have been found to exhibit tumor-suppressing properties (47). Infiltration of CD19/CD20 B cells has now emerged as a promising target for immunotherapy of hepatocellular carcinoma (48). Thus, combining immunotherapies such as cancer vaccines, cytokine therapies, and immune checkpoint inhibitors (ICIs) with strategies targeting B cells and TLSs may represent promising new anti-tumor approaches.

3 Exosomes and tumor microenvironment

Exosomes facilitate substance transfer between cells, activating signaling pathways (49). The secretion of exosomes by B cells is among the most important ways in which they influence the TME. Additionally, exosomes secreted by other cells and cancer cells also play pivotal roles (50, 51). Therefore, it can be speculated that exosomes hold great potential for advancing the exploration of new therapeutic pathways in cancer (Figure 1A).

3.1 The biological characteristics and functions of exosomes

Exosomes, a type of extracellular vesicles, have been extensively studied (52–55). Exosomes are generated through the intracellular process of inward budding of multivesicular bodies, followed by their subsequent release into the extracellular space through fusion events with the plasma membrane (56). The secretion of exosomes is regulated by the RAB family (57, 58). Secretion of exosomes can be divided into an ESCRT mechanism and a RAB31-mediated mechanism independent of ESCRT (59). Despite being previously viewed as waste materials, exosomes are now acknowledged as vital components of the intercellular communication network (60). Exosomes, containing biologically active substances can be found in bodily fluids and are discharged by originating cells (54, 61). Exosomes are structurally more stable than parent cells due to their higher concentration of lipid components (62). CD81 and CD63 are common exosome markers, and along with CD82 and CD37, are highly abundant transmembrane proteins in exosomes. Exosomes also carry a diverse range of membrane signaling proteins (63). These signaling molecules can be delivered to target cells by exosomes (64), making them an integral component of TME communication.

As researchers continue to investigate exosomes, their overall functions have become increasingly evident. In a normal physiological context, exosomes contribute to the maintenance of immune response, cell proliferation, maturation, and homeostasis (65). Exosomes have been identified to play crucial roles in various processes within TME, including but not limited to immune regulation, promotion of cancer cell proliferation, metastasis, drug resistance, and angiogenesis (66, 67).

Exosomes can facilitate crosstalk between B cells and other cells, making them a potent target for cancer treatment (Table 1).

3.2 application of exosomes in cancer therapy

Exosomes are widely recognized as significant biomarkers for cancer diagnosis, prediction, and monitoring (78). Due to their stability and prevalence in circulation, they serve as valuable indicators for liquid biopsy techniques (79), enabling more accurate and less invasive treatments (80). Considering the active cross-talk of exosomes between immune and cancer cells, they can be utilized for immunotherapy to promote (81, 82) or suppress (83, 84) tumor proliferation. Additionally, cancer vaccines based on exosomes have also been developed (85).

Compared to other types of extracellular vesicles (microvesicles, membrane particles, apoptotic bodies), the majority of the biological components, lipids, and proteins of exosomes are relatively clear (86). In comparison to synthetic nanovesicles (polymeric nanoparticles, liposomes, and solid lipid nanoparticles), exosomes possess more membrane proteins, stronger biocompatibility, and a longer circulation half-life naturally (87). They can easily pass through the plasma membrane, blood, and blood-brain barrier (88) to infiltrate tumor tissues (89), which allows for precise and targeted therapeutic interventions (90). Consequently, emerging research is focused on the development and design of bioengineered exosomes.

Bioengineered exosomes can be designed to target specific cells, provide therapeutic cargo, and regulate the immune system (11).

Certain surface-adhesive proteins and carrier ligands allow exosomes to attach to target cell surfaces and efficiently deliver them into the cells (91). Exosomes can efficiently deliver drugs like paclitaxel (92), transport siRNA (93, 94). But the presence of the blood-brain barrier (BBB) limits the access of small molecule drugs to glioma tissue (95). Exosomes derived from brain endothelial cells can transport drugs to BBB, which may become a breakthrough for the treatment of brain cancer (96).

Immune suppressive factors can inhibit the function of immune cells (97–100). By transporting cargo that neutralizes these immune suppressive factors, exosomes can enhance the body's anti-tumor immune response and improve the efficacy of cancer immunotherapy. An investigation has demonstrated that the T-cell suppressive effects of exosomes can be mitigated by the administration of anti-TGF-β (101). Franz L and colleagues conducted a PD-1 blockade experiment using EV secreted by glioblastoma, which almost reactivated T cells and suppressed tumor progression (102). In the HNSCC microenvironment, the T-cell inhibitory effect of circulating PD-L1 exosomes can be blocked by PD-1 antibodies (103). However, the interference of molecules carried by exosomes in immunotherapy may be related to mechanisms of drug resistance (104, 105).

4 B-cell-derived exosomes and the tumor microenvironment

The investigation of B cell-derived exosomes initiated with the initial characterization of these vesicles in 1996 (106). Through their surface effector molecules, these exosomes can signal to various cells to regulate the TME (Figure 1B).

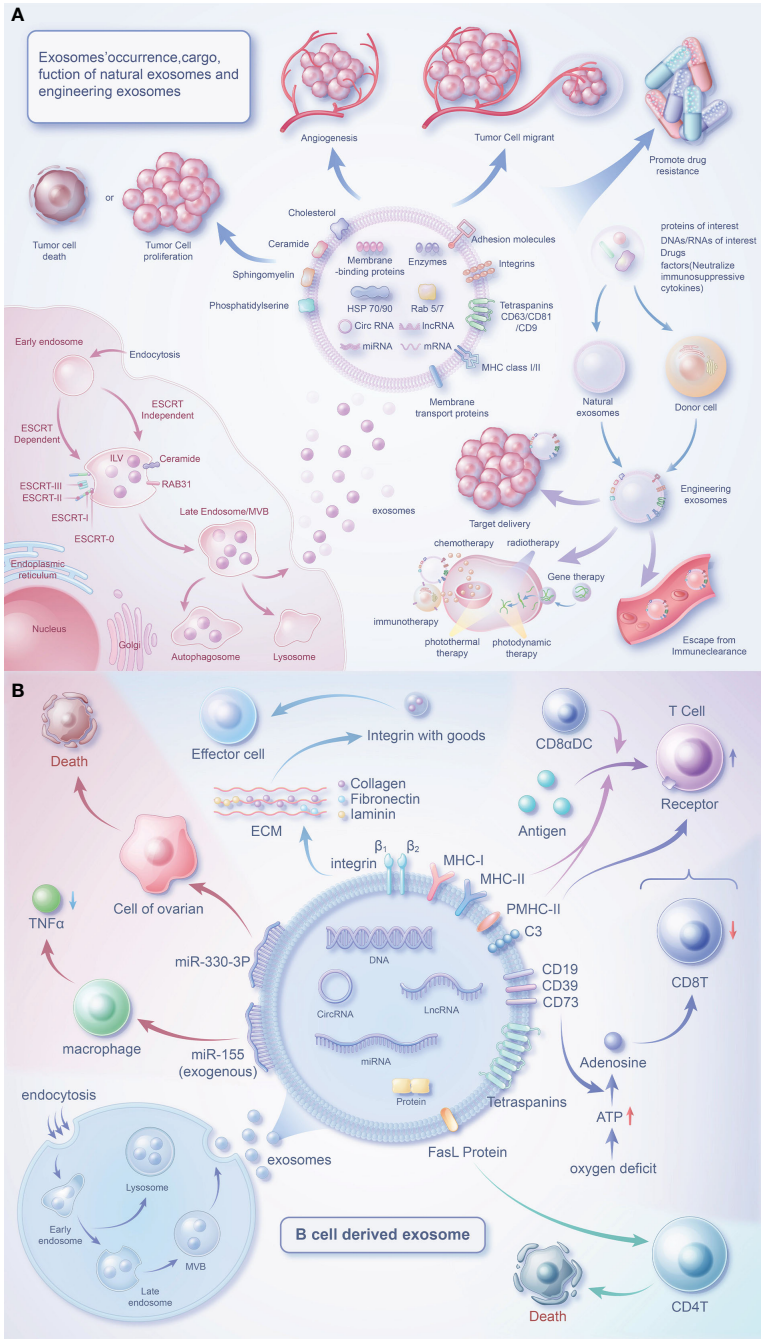

FIGURE 1
Biology of exosomes and the role of their cargo in the tumor microenvironment. **(A)** Exosomes are produced in dependence on the ESCRT mechanism or a RAB31-mediated pathway independent of the ESCRT mechanism. Exosomes carry a variety of proteins and effector molecules that can determine the direction of tumour development and tumour metastasis, promote tumour angiogenesis and participate in tumour drug resistance.Engineered exosomes carry cargoes of interest that also have multiple roles closely related to tumours. **(B)** B cells release exosomes through endocytosis of the plasma membrane, the formation of early endosomes and late endosomes, and fusion of polyvesicular bodies with the plasma membrane. In addition to MHC protein and quadruple transmembrane protein, the surface of B cell-derived exosomes contains special FasL proteins, integrins, C3, CD19, CD39, CD73, etc., which can regulate immune cells (T cells) or affect the survival of tumor cells through special factors.

4.1 The biological components of exosomes released by B cells

Mass spectrometry analysis has uncovered a wealth of constituents in exosomes originating from B cells, including MHC-I, MHC-II, CD20, CD45, and BCR complexes (comprising surface Ig, CD19, and Tetraspanins), as well as chaperones such as heat shock protein 70 and 90, integrins and other proteins (107–109). Furthermore, these exosomes also express cholesterol, sphingomyelin, and ganglioside GM3 (107). Addition of macrophage-derived exosomes to naive monocytes induces cell differentiation (110), however this mechanism is unclear in B cells and B cell exosomes. When B cells

TABLE 1 Exosome crosstalk between B cells and other cells.

Other cell-derived exosomes act on B cells						
Tumor type	Source	In vivo/ in vitro	Action type/specific axis	Effect	Effects on tumors	Ref.
——	DC	*In vivo*	Stimulate B cell proliferation	CD8 + T cell response was induced	Kill cancer cells	(68)
——	Mature DC	*In vivo*	Binds to B cell receptors	Induces T cell proliferation	——	(69)
——	T cells	*In vivo*	——	Promote B cell proliferation and differentiation	——	(70)
——	Mesenchymal cells	——	TGF-β1 is produced	Regulates B cell proliferation and survival	——	(71)
HCC	Tumor cells	*In vitro*	HMGB1-TLR2/4-MAPK	Induction of B cells to become TIM-1Breg, impairing CD 8T cell function	Promote HCC progression	(72)
HNSCC	plasma	*In vitro*	——	Inhibits the proliferation, viability and function of B cells	Helps immune escape	(73)
B-cell-derived exosomes act on other cells						
Tumor type	Target cells	*In vivo/in vitro*	Action type/specific axis	Effect	Effects on tumors	Ref.
Ovarian cancer	cancer cell	*In vitro*	miR-330-3p/JAM2 axis	Inducing mesenchymal procedures	Promote the growth of cancer cells	(74)
——	T cell	*In vivo*	Rab27a expression is up-regulated	Impaired CD8T cell response	Promote tumor survival	(75)
——	T cell	*In vivo*	C3 fragments are deposited on the surface of the cell membrane	Enhance T cell response, conducive to the development of immune response	Inhibits tumors	(76)
——	Macrophages	*In vivo*	Enhances lipopolysaccharide stimulation	Reduces the release of TNFα	Promote tumor survival	(77)

are activated, they release a greater amount of exosomes (111, 112), which carry more effector molecules (77, 108, 109). CD45 is a key positive regulator of the BCR-mediated signalling pathway (113, 114) and, interestingly, is absent from T-cell-derived exosomes (115, 116). Triggering the classical NF-κB pathway *via* downstream of BCR is able to increase HLA expression in B-cell exosomes (111). However, these two regulatory pathways may be linked and need to be explored in further experimental studies.

4.2 Mechanism of involvement of components of B cell-derived exosomes in the tumour process

4.2.1 Proteins

MHC-II molecules in exosomes are predominantly located in SLOs and are expressed exclusively by professional APCs, including B cells (117). The presence of CD20, CD81, and HSC70 is associated with MHC-II on the plasma membrane, which promotes antigen presentation and T cell activation (118). CD20 can form complexes with both MHC-II and CD40 (119), while the R21 monoclonal antibody selectively recognizes CD20 on B cells. Additionally, R21 mAb can induce lfa-1-dependent cell adhesion but inhibits MHC-II-mediated lfa-1-dependent cell adhesion. It's worth noting that CD40 may interfere with mAb binding to CD20 by competitively binding with it (119).

It is not surprising that exosomes are present in TLSs, as B cells are abundant in these structures (120). CD20 can form complexes with BCR to participate in signal transduction (121), ultimately initiating immune responses. Additionally, CD20 can activate B cells through calcium channels (122), and the resulting stimulated calcium channels may induce the release of a large number of exosomes (108). Some of the mechanisms of CD20 are not yet clear (37). The augmented abundance of CD20-positive B lymphocytes in sentinel lymph nodes is indicative of a favorable prognosis in cases of breast cancer (123). CD20 accumulates at the tumour-liver border in patients with colorectal cancer (124), where it may act as a prognostic marker for the tumour.

These indications suggest that these complexes may be crucial factors in MHC-II or antigen-mediated B cell responses.

B cell-derived exosomes express MHC-II and form a complex (PMHC-II) with peptide antigens. The notion that B-cell exosomal exosomes may transport PMHC-II, proposed more than 20 years ago (106), is confirmed. Exosomes released by most primary B cells express PMHC-II. When antigen-loaded B cells meet specific T cells, B cell activation stimulates exosome release, while stimulating pMHC-II to escape intracellular degradation. pMHC-II interacts with the TCR and activates naive CD4 T cells to initiate an immune response (125). However, exosomes from mature DCs only activate naïve T cells as inefficient APCs (126).

4.2.2 ncRNAs

B-cell exosomes have emerged as viable candidates for the delivery of miRNA-155. When miRNA-155 inhibitor-loaded

exosomes were administered to miRNA-155 knockout mice, a notable reduction in TNF-α production was observed in mouse RAW macrophages (77). After treatment with rituximab, a downregulation of miR-155 levels in exosomes was observed (127). This study highlights the potential of B cell-derived exosomes as therapeutic vehicles.

MiR-330-3p has been identified as a key factor in tumor progression. It targets TPX2, which negatively regulates TPX2 expression to inhibit melanoma cell proliferation (128). In addition, miR-330-3p from plasma cell-derived exosomes is a critical regulator of ovarian cancer stroma and promotes tumor metastasis through the JAM2 pathway (74). TPX2 (129) and JAM2 (130, 131) have been described as associated with cancer progression. However, the ability of miR-330-3p to target these proteins may suggest a potentially important role for our B-cell exosome miR-330-3p.

4.3 B cell-derived exosomes are taken up by other cells

4.3.1 Follicular dendritic cells

In vitro isolated B cell-derived exosomes specifically bind follicular dendritic cells (FDC) (132). The fate of B cells in GC depends on the adhesion of the VCAM-1 pathway and is associated with FDC (133). More importantly, FDC themselves do not express MHC-II, but rather pick up peptide-loaded MHC-II on the surface of B cells (134). Exosome binding to FDC may be through interaction with VCAM-1, which then stimulates T helper cells. Additionally, tumor-associated FDCs express CXCL13, which effectively recruits lymphocytes (135). We postulate that in tumor tissues, FDCs may attract B cells, which then bind to the released exosomes, leading to antigen presentation. Therefore, FDCs may represent a physiological target for B cell-derived exosomes (132).

4.3.2 Fibroblasts

Compared to FDCs, fibroblasts exhibit a limited expression of leukocyte adhesion molecules on their surface (132). Treatment of fibroblasts with TNF-α induces the upregulation of ICAM-1 expression on their surface, thereby enhancing the adhesion of B cell-derived exosomes to fibroblast surfaces (136). TNF-α may be a key factor in inducing exosomes to be adsorbed.

4.3.3 Macrophages

In the subcapsular sinus of the lymph node, B-cell-derived exosomes are captured by CD169 macrophages, which then penetrate deep into the paracortex (137). CD169+ cells are present within B-cell follicles (138) and the T-B cell zone boundary of the GC (139). The presentation of antigens by CD169+ cells to CD8 T cells and/or B cells causes them to being activated (140). Activated B cells may release more exosomes. Exosome-induced CTL responses (141) are enhanced in CD169+ mice in cooperation with T and B cells, suggesting that exosomes enter lymphoid organs possibly to reduce the immune response to autoantigens (137).

5 Discussion

In recent years, exosomes have gained increasing attention as important mediators of intercellular communication. While many studies have focused on cancer cell-derived exosomes for diagnosis, prognostic testing, and drug delivery, less is known about exosomes derived from B cells. Fortunately, there are still some relevant studies targeting B-cell-derived exosomes, as outlined in our earlier discussion.

As previously outlined, the effective delivery of miRNA-155 by B cell-derived exosomes has been established. For the delivery of miR-330-3p, researchers may consider the design of a B cell (142) transfected with the V600E mutation. Subsequently, lipid transfection or electroporation can be employed to introduce the miR-330-3p construct into B cells. In addition, the design of a short hairpin RNA (shRNA) or small interfering RNA (siRNA) targeting TPX2 is essential. These molecules should be transfected into B cells along with miR-330-3p for culture, followed by the isolation of exosomes. To enhance the yield of exosomes, researchers can employ additional stimuli, such as TLR3, TLR7, TLR9, and other motifs discussed earlier.It is crucial to emphasize that researchers must continually optimize and thoroughly validate the experimental design at each stage to ensure the exosomes effectively downregulate TPX2 and inhibit melanoma growth. It should be noted that miR-330-3p and TPX2 are merely two components of a complex regulatory network, and their specific roles and effects on tumor growth are contingent upon various factors in the experimental context. Furthermore, although the production of exosomes with multiple engineered cargoes is theoretically feasible, it may induce cellular stress or potentially cytotoxic effects, thereby posing challenges for manipulation.

The study of B-cell-derived exosomes for cancer therapy presents a number of challenges, including inadequate comprehension of their interactions within the complex milieu of TME and insufficient clinical investigations to verify their functionality and potential side effects. We anticipate that with increasing research into B-cell-derived exosomes, their functions and the mechanisms underlying their biological components will soon become clearer.

Author contributions

JX, FY and GT conceived the study. JX, HC and GY drafted the manuscript. JX, SZ, JZ, LT and ZX performed the literature search and collected the data. ZX, FY and GT helped with the final revision of this manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2023.1188760/full#supplementary-material

SUPPLEMENTARY FIGURE 1
There can be many types of B cells (plasma cells, memory B cells, breg, TIL-B). In their respective ways, they regulate the tumor microenvironment and affect tumor growth.

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