Title

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Journal

The Journal of cancer research, 83(23)

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Publication Date

2023-12-01

DOI

10.1158/0008-5472.CAN-23-0620

Peer reviewed

Published in final edited form as:

Cancer Res. 2023 December 01; 83(23): 3835–3845. doi:10.1158/0008-5472.CAN-23-0620.

The Evolving Landscape of B Cells in Cancer Metastasis

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Abstract

Metastasis is the leading cause of cancer mortality. Functional and clinical studies have documented diverse B cell and antibody responses in cancer metastasis. The presence of B cells in tumor microenvironments and metastatic sites has been associated with diverse effects that can promote or inhibit metastasis. Specifically, B cells can contribute to the spread of cancer cells by enhancing tumor cell motility, invasion, angiogenesis, lymphangiogenesis, and extracellular matrix remodeling. Moreover, they can promote metastatic colonization by triggering pathogenic immunoglobulin responses and recruiting immune suppressive cells. Contrastingly, B cells can also exhibit anti-metastatic effects. For example, they aid in enhanced antigen presentation, which helps activate immune responses against cancer cells. Additionally, B cells play a crucial role in preventing the dissemination of metastatic cells from the primary tumor and secrete antibodies that can aid in tumor recognition. Here, we review the complex roles of B cells in metastasis, delineating the heterogeneity of B cell activity and subtypes by metastatic site, antibody class, antigen (if known), and molecular phenotype. These important attributes of B cells emphasize the need for a deeper understanding and characterization of B cell phenotypes to define their effects in metastasis.

Keywords

B lymphocyte; B cell; cancer; metastasis; humoral immunity; autoimmunity

Introduction

Cancer metastasis is the leading cause of mortality for patients despite major efforts towards its prevention(1). Metastasis is a complex bottleneck process that involves a multitude of variables that encompass changes in cancer cells, the tumor microenvironment (TME),

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Author Contributions:

MR designed the study, drafted the manuscript, edited the summary table, and created the figure. AL designed the study, edited the manuscript, and created the summary table. DH designed the study and edited the manuscript. All authors approved of the final version before submission.

The authors declare no potential conflicts of interest.

and the prospective metastatic niche(2–5). The hallmarks of cancer cell metastasis can include: 1) motility and invasion, 2) ability to modulate the secondary site or local microenvironments, 3) plasticity and 4) ability to colonize secondary tissues(5). Despite major advancements, the heterogeneity of each primary cancer type and secondary site has hindered development of efficacious anti-metastatic therapeutics.

B cells can contribute to innate immunity and adaptive immune responses, underscoring the importance of understanding how various B cell subsets function in metastasis, and how B cell biology can be leveraged for treatment. The immune system can influence the hallmarks and factors that contribute to the metastatic process(6,7). Intriguingly, immune responses can make tumors more aggressive while also protecting against metastasis(8–10). This phenomenon raises the need for the field to discern these seemingly opposing roles of immune cell associations in metastasis. In this review, we focus on studies that investigated B cell heterogeneity and function in metastasis. With continued delineation of B cell involvement in metastasis, the field can translate this knowledge for therapeutic development to prevent and treat metastasis (Figure 1, Table 1).

B cell Development, Biology, and Function

B cells develop in the bone marrow where they undergo positive and negative selection. Here, a successfully assembled B cell receptor (BCR) is tested for self-reactivity(11). Distinct secretory factors in the bone marrow further inform B cell differentiation. B cells then migrate to the spleen and lymph nodes (LN) to undergo functional maturation. Upon cognate antigen encounter, the unique BCR can further diversify and optimize binding affinity through the processes of somatic hypermutation and immunoglobulin class-switching (e.g., IgM to either IgG (types 1–4 human), IgA, IgD, or IgE), which primarily occur in germinal center (GC) reactions. GC B cells then clonally expand and mature to become plasmablasts (PB), plasma cells (PC), or long-lived memory B cells (MBC). PBs rapidly proliferate and produce short-lived antibody responses whereas PCs can be long-lived, thereby providing long-term protection(12). MBCs can provide rapid immune responses upon re-encounter of their cognate antigen. Antibody secretion by PBs and PCs can confer antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), or antibody-dependent cellular phagocytosis (ADCP) with cells of both the innate and adaptive immune system. Among the subtypes of B cells, regulatory B cells (Breg) can manifest to dampen immune responses(13). After maturation, B cells can reside in the bone marrow, secondary lymphoid organs such as LNs and spleen, or acquire tissue-resident status(14).

B cell functions in primary tumors

The immune composition of a tumor has been linked to prognosis(15). More specifically, immune “hot” tumors that are highly immune infiltrated are prognostically favorable, whereas immune “cold” tumors are poorly immune infiltrated and are associated with a poor outcome(15). Given this prognostic significance, many immunotherapies leverage T cell-based anticancer activity(16). Unfortunately, there persists a large portion of patients which fail to respond(16). Recently, B cells have gained appreciation for their ability to

enhance the favorable prognostic value of T cells and ignite T cell effector function, thereby highlighting the therapeutic potential of B cells for cancer treatment (17–19).

Immune responses to cancer feature dynamic interplay between local and systemic signaling. Among the immune cells that infiltrate tumors, B cells are capable of both anti- and pro-tumoral effects depending on the cancer type, cell and molecular composition of the tumor, and B cell phenotype(7). Notable anti-cancer B cell functions include antigen presentation which activates CD4+ and CD8+ T cells, and the secretion of antibodies which can elicit tumor cell death(20).

B cells are intertwined with other immune cells in the tumor and tumor draining lymph nodes (TDLNs). Here, antigen transfer and cooperation between B cells, T follicular helper cells, dendritic cells, and macrophages are important for antigen interpretation. Depending on the context and nature of the antigen, the result can be a GC or extrafollicular response in either TDLNs or tertiary lymphoid structures (TLS) of tumors(21,22). T cell-dependency on B cells for effective antitumor responses has been observed in multiple cancer models(18,22). Presumably, these powerful anti-tumor functions of B cells can limit regional and distant metastasis through systemic immune responses(18,23,24).

Pro-tumor effects of B cells are often associated with B regulatory cells (Bregs), which are commonly distinguished by expression of PD-L1, IL-10, IL-35, and TGFβ(25,26). Like T regulatory cells (Tregs), Bregs are vital for protection against self-reactivity. Their presence in primary solid tumors is associated with T cell exhaustion and poor clinical outcomes due to immune suppression(27–30). Accordingly, studies demonstrate that Bregs enable tumor cell metastasis(31–34).

B cell Influence on tumor cell metastatic potential

At the molecular level, B cells can pave the way for invasion, dissemination, and colonization of distant sites. Firstly, B cells can alter the TME by producing proangiogenic factors(35–37), which facilitate the survival and dissemination of cancer cells. Secondly, B cell antibody-antigen complexes can invoke a cytokine milieu that enhances tumor cell invasion, angiogenesis, lymphangiogenesis and metastasis(38–42). Yet, evidence demonstrates that human IgG1 antibody responses via FcγRI can inhibit angiogenesis(43). Thirdly, B cells can perturb the extracellular matrix (ECM) and facilitate cancer cell invasion by directly expressing or inducing expression of matrix metalloproteinases (MMPs), and inducing fibroblast collagen production in the TME, thereby remodeling the ECM(44–48). Thus, B cells can support tumor invasion and indirectly provide collagen substrates for migratory and metastasizing cancer cells. Finally, tumor cell-derived chemokines that signal to B cells can affect processes that contribute to metastatic progression such as promoting angiogenesis(49,50), epithelial-to-mesenchymal transition (51), invasion, and cancer cell motility(46).

One of the molecules implicated in enhancing cancer cell invasion is B cell-secreted B cell survival factor (BAFF), which induces EMT(52). It has been demonstrated that BAFF signaling acts on cancer cells in a manner distinct from the established BAFF-APRIL signaling pathway, suggesting cancer cells utilize expression of BAFF receptors to enhance

their migration and invasion. This BAFF-EMT association correlated with poor clinical outcomes and metastatic incidence in PDAC patients(52). Other studies have demonstrated that cancer cells undergoing EMT induce Breg phenotypes while inhibiting the proliferation of activated B cells, inferring possible ways that mesenchymal-state cancer cells influence their TME and premetastatic niche(53). Notably, metastatic sites can be directly modulated by Bregs through immunosuppressive cues that direct Treg differentiation and prime regulatory function in myeloid-derived suppressive cell (MDSC) populations(54). This favors metastatic colonization of new sites by fostering permissive and supportive immune microenvironments.

Evidence of B Cell Involvement in Regional and Distant Metastasis

B cells exhibit multifaceted roles in regional and distant metastases, where the B cell phenotype and metastatic site may delineate the impact of B cells on patient outcome (Figure 1, Table 1). B cell target antigens also play a key role in eliciting distinct B cell responses, as observed with self-antigens, glycosylated proteins, and neoantigens (Table 1). How these antigens drive distinct B cell responses remains an area of active research as antigen induced responses have revealed opposing effects on metastasis(55–63). Known effects of B cell and immunoglobulin subtypes on the metastatic process, including known tumor antigens, are summarized in Table 1.

Here, we explore the evidence supporting both pro- and anti-metastatic roles for B cells in various documented metastatic sites, including lymph nodes, lungs, liver, bones, brain, and other locations.

Lymph Node Metastasis—TDLNs are sites of tumor antigen transfer and interactions between B cells, T follicular helper cells, dendritic cells, and macrophages. The TME makeup, lymphatic vasculature and afferent pressures from the primary tumor can facilitate tumor cell migration through the lymphatics to sentinel lymph nodes(64). Majority of cancers preferentially metastasize through lymphatics rather than hematogenous routes(65); a phenomenon interestingly associated with TDLN B-cell accumulation and lymphangiogenesis(65,66).

Metastatic tumor cells often invade TDLNs before spreading to more distant organs(67,68), thus LN involvement has long been discussed as either protecting against or facilitating further metastatic spread. Cancer reduces T cell responsiveness in these immunosurveillance intensive sites using immunosuppressive mechanisms such as programmed death-ligand 1 (PD-L1)(69). Consequently, lymph node metastasis (LNM) may inadvertently induce immune tolerance to tumor cells(69). The presence and activity of B cells in LNM has exhibited both a positive and negative association with metastatic incidence (Table 1). This emphasizes the need for advanced phenotyping and expanded functional testing of B cell involvement in LNM.

Anti-metastatic evidence: Several studies have demonstrated that elevated presence of B cells is inversely associated with LNM (Table 1). Firstly, higher frequencies of B cells (CD20+, Marginal Zone-like, CD69+) in LNM of prostate cancer had a favorable outcome(70). Secondly, LTA+ memory-like B cells, activated B cells, and active memory

class-switched B cells provided protection against LNMs(71,72). Thirdly, the investigations of TLSs have yielded prognostic implications in which TLSs have been associated with favorable outcomes due to enhanced cytotoxic lymphocytes in TDLNs and lower instances of LNMs(73). Interestingly, PBs and CD86+ B cells were found to be higher in LNMs in comparison to node negative patients; though it is undocumented whether their presence was protective(74). Worse outcomes with lower B cell frequencies could be explained by a lack of immunoreactivity and increased immunosuppression in colonized LNs.

Pro-metastatic evidence: Firstly, it's been shown that tumor infiltrating B cells (TIL-Bs) have the capacity to enhance bladder cancer (BCa) cell invasion and subsequent LNM through an IL-8/Androgen Receptor (AR)/MMP signaling axis(75). Importantly, AR signaling, which is known to be involved in BCa progression, increases when BCa cells are co-cultured with B cells. This modulation results in increased levels of MMPs on tumor cells thereby enhancing invasive capacity. It was mechanistically deciphered that IL-8 produced by both B and BCa cells was responsible for the increased AR and MMP levels driving the invasive phenotype(75). Upon implantation, tumor cells that were cultured in the presence of B cells significantly increased metastases exclusively in TDLNs. Given that IL-8 is a cytokine elevated in many cancer types, this signaling axis may be a prominent pro-metastatic B cell function(76) These results may be extended to B cells contributing to IL-8-mediated upregulation of PD-1 on cytotoxic T cells in gastric cancer, which also correlated with LNM(77). IL-8 perturbations caused by the presence of B cells may therefore drive cancer cell invasion, cytotoxic immunosuppression, and LN colonization.

Secondly, pro-metastatic activity of TIL-Bs has been demonstrated in TLSs of hepatocellular carcinoma. Specifically, TIL-B produced lymphotoxin B protected tumor progenitor cells and supported their metastatic outgrowth to TDLNs(78). Pan-cancer analyses found that TLSs influence tumor differentiation, node status, and lymphovascular invasion thereby suggesting TLSs are tightly related to cancer evolution(79,80).

Thirdly, general B cell depletion via CD20 or B cell knockout in the MMTV-PyMT mouse model reduced and/or prevented LNMs, respectively(57). Bregs, defined by CD27(hi) CD25(+) and CD1d(hi) CD5(+) were found to be increased in distant nonmetastatic LNs of node-positive breast cancer (BC) patients in comparison to node-negative patients(72). This could suggest reprogramming of distant LNs to optimize premetastatic niches for future tumor cell colonization. This evidence is supported by the positive correlation between B cells with elevated interferon (IFN) stimulating gene signatures and Treg presence in LNMs(69).

Liver Metastasis—The liver is a very common metastatic site in the pan-cancer context(81–83). Patients with liver metastasis (LVM) have poor clinical outcome and low response rates to immune therapy(84). The immunosuppressive and tolerogenic environment of the liver may adversely provide a well-suited niche for disseminated cancer cells(85). Currently, besides surgical resection, there are no effective anti-metastatic therapies to cure LVM(86).

Pro-metastatic evidence: In cancer, B cells have been reported to lack therapeutic responsiveness in patient LVM as compared to the primary tumor(87,88). Beyond reduced activation states, B cells are consistently found in fewer numbers in LVM than in both the primary tumor and healthy liver tissue(87,88). In PDAC, the B cells in LVM that mediated resistance to therapy were characterized as CD24+CD44-CD40- B cells(89). These tumor cell-recruited immunosuppressive B cells cause macrophage-mediated adaptive immune tolerance through CD200 and BTLA, thereby thwarting macrophage and T cell immunogenicity. Lower activated B cell frequency in LVM can also be attributed to recruitment of myeloid-derived suppressor cells (MDSCs) from the bone marrow which support premetastatic niche formation and metastatic colonization of the liver(90). One mechanism identified in colorectal cancer (CRC) is S1PR1-STAT3 signaling between cancer cells and MDSCs in LVM(91). It's important to note that STAT3-expressing B cells also have pro-metastatic effects in melanoma and B cell-like diffuse large B-cell lymphoma(36). Additionally, these pro-angiogenic signals from STAT3-expressing B cells may increase the success of liver colonization. Therefore, it is possible that B cells in the liver or from the primary tumor can contribute to this immunosuppressive signaling axis to recruit MDSCs and promote metastasis.

Anti-metastatic evidence: Activated B cell populations in the primary tumor site of CRC patients and mouse models is associated with lower incidence of LVM(88). Moreover, B cell activity (specifically, activation-induced cytidine deaminase (AID)-positive and highly proliferative) within ectopic lymphoid structures of LVM in CRC patients is associated with reduced disease recurrence and increased overall survival(92,93). A mechanism governing anti-metastatic B cell activity and tumor infiltration was discovered in a CRC-LVM mouse model and further validated in colorectal, breast, lung, and uterine cancer clinical datasets(88). It was found that the SDF1-CXCR4 signaling axis promoted migration of activated B cells; an effect which is negatively regulated by Wnt and TGFβ(88).

Anti-metastatic B cell activity in LVM can also be attributed to antibody-mediated tumor cell destruction via ADCP and/or ADCC(94–96). ADCP studies demonstrate that Kupfer cells, the resident macrophage cells of the liver, are the Fc-responsive cell type that mediate protection against LVM(94,95). Antibody class also determine the mechanism of antibody-mediated protection against LVM. For example, IgM therapy functioned via CDC whereas IgG therapy operated via ADCC in a mouse model of metastatic lymphoma(96). These distinct anti-tumor mechanisms suggest that antigen-specific combinatorial therapies of IgM and IgG may provide synergistic effects in the treatment of LVM.

Lung Metastasis—The lung is also a common site of metastasis and can reduce 5-year survival rates by as much as 80%(97). Lungs are exposed to inhaled antigens and must maintain a highly complex immune response to foreign stimuli. B cells play an integral role in the mucosal homeostasis of the lung and are commonly found in the bronchus-associated lymphoid tissue alongside T cells and dendritic cells(98). Understanding the dynamic evolution of the lung's immune status and composition during the progression of metastasis and colonization is critical.

Anti-metastatic evidence: B cells can protect against lung metastasis (LM) as demonstrated in several cancer mouse models(99–104). For instance, B cell aggregates in lymphoid-like tissue in melanoma abrogated LM(105). Additionally, CD20+ B cells were found to protect against LM and were critical for effector-memory and IFNγ or TNFα-secreting CD4+ and CD8+ T cells(104). Moreover, these CD20+ B cells enhanced tumor-antigen specific CD8+ T cell proliferation, emphasizing the importance of B and T cell collaboration for optimal anti-tumor activity(104). In a model of breast cancer lung metastasis, B cells rapidly infiltrated lung tumors shortly after tumor implantation and were the most prevalent lymphocyte in lung tissue(102). In accordance with an anti-metastatic role, neutralization of these B cells enhanced LM, thereby suggesting that B cells engaged in crucial tumor surveillance during the early response to the metastatic cells' attempt to colonize the lung. The anti-metastatic nature of activated B cells is further supported by studies using 4T1 breast cancer cells, which demonstrated that adoptive transfer of B cells isolated from TDLN and activated *in vitro* with LPS and anti-CD40 (CD40 agonist), protected against LM(101). Likewise, adoptive transfer of CpG-activated B cells to mice bearing B16-F10 lung metastatic melanoma demonstrated anti-tumor and anti-metastatic effects attributed to a reduction in immunosuppressive cells and cytokines as well as increased CD8+ T cell activity as measured by IFNγ(99).

Epitope spreading, a process by which BCR antigen specificity can recognize and be activated by other epitopes of the initial antigen or other antigens entirely, has been implicated in enhanced tumor cell reactivity(106,107). Models of metastatic melanoma demonstrated that epitope spreading abrogates LM by breaking tolerance to cancer antigens that normally fail to evoke antibody or cytotoxic T cell responses(107). Immunoglobulin class can also influence an anti- or pro-metastatic effect on LM in melanoma (B16) as observed by IgM promoting cancer cell dissemination whereas IgG had an anti-metastatic effect(108). Moreover, human IgG immune responses have been shown to prevent LM in an Fc-R1 dependent manner(103).

Pro-metastatic evidence: Tumor cells can influence B cell differentiation and effector function in LM. For example, tumor-produced metabolite, 5-lipoxygenase, drove tumor-transformed regulatory B (tBreg) cell differentiation from CD19+ B cells in cancer models of LM(109,110). This suggests that tumor-induced metabolic rewiring can alter immune cell differentiation thereby promoting an immune evasive environment and LM. Another mechanism by which Bregs and/or tBregs exert pro-metastatic effects is through TGFβ-dependent FoxP3+ Treg conversion of naïve T cells(33,109). When this process is blocked through STAT3 inhibition and consequent reduction of TGFβ produced by tBregs, LM is prevented due to thwarted immune suppression(109).

Another mechanism by which tBregs exacerbate LM has been shown through TGFβR1/TGFβR2 signaling where tBregs educate MDSCs to subsequently suppress CD4+ and CD8+ T cells(54). This tBreg-dependent priming of MDSCs increases reactive oxygen species and nitric oxide production and T cell suppression. An interesting connection to TGFβ-producing B cells involves Erbin-expressing B cells. CD19+ B cells in LM had differential expression of Erbin, a gene related to the cell adhesion molecule family and an adaptor for the receptor Erbb2/Her2(111). Using a B-cell conditional Erbin deletion mouse

model, IgA+ CD138+ plasma cells were higher in LM than wild-type mice and suppressed LM. Intriguingly, Erbin knockout abolished TGFβ-mediated suppression of IgA+ CXCR5+ cell recruitment to LM, inhibited PD1 expression on IgA+ B cells via a STAT3-STAT6 mechanism, and enhanced CD8+ T cell tumor cell killing. Regulatory B cell activities in LM are not exclusive to mice as supported by evidence in human ovarian, breast, and colon cancers(54,112).

An innate-like B cell, B1 lymphocytes, are known for high production of IgM and IgG(113,114). In the B16 mouse melanoma model, B1 lymphocytes invoked tumor growth and LM(115). Notably, depletion of B1 lymphocytes significantly reduced LM. This effect was attributed to direct cell-cell communication between B1 lymphocytes and melanoma cells via MUC18, an established melanoma adhesion molecule associated with tumor growth and metastasis. The association of B1 lymphocytes with MUC18 expression was confirmed in clinical melanoma samples(115). These findings suggest a new mechanism by which B1 lymphocytes may facilitate melanoma LM.

Bone and Other Metastatic Sites—Relative incidence of bone metastasis can range from 14–75% depending on the primary tumor type(116). B cells with abnormally high PD-L1 expression suppress T cell-mediated IFNγ expression by promoting T cell exhaustion in bone metastases(117). Importantly, these B cells failed to align with canonical Breg markers, indicating further heterogeneity in Bregs. B cell localization within bone metastases remains poorly studied though some evidence suggests association with osteoclasts may limit their ability to infiltrate bone metastatic lesions(118); a surprising finding considering B cells primarily interact with osteoblasts during B cell development in the bone marrow(119).

Currently, there is a need for expanded research on the roles of B cells in other metastatic sites. In brain metastases, 6-fold reduction in B cells in comparison to the primary tumor is observed and paralleled with the overall poor B cell infiltration in glioblastoma (as low as 0.66%)(120,121). In omental metastases of ovarian cancer, B cells and proliferative plasmablasts support T cell-dependent antitumor responses(122,123). Protection against peritoneal metastases of triple negative breast cancer (TNBC) and therapeutic response has been attributed to IgM secreted by distinct innate-like B1 B cell populations(124). Interestingly, it has been demonstrated that perturbations in the glycomics profile of IgG can be predictive of peritoneal metastases; presumably associated with the large numbers of tumor-specific antibodies being directed against glycans that are known to be involved in multiple pathophysiological steps of tumor progression(125). Like their prognostic power in LNM, LVM and LM, autoantibody levels can also predict ascites and brain metastases(126,127).

Conclusions and Future Directions

It is critical for researchers to identify changes of the immune composition in the metastatic site. To date, most progress in understanding how B cell activity influences metastatic incidence and behavior has been in the context of primary tumors. The field can have a synergized understanding if B cell activity and phenotypes within the regional and distant metastases are also characterized. Capturing the immune reactive state of the metastasis

in addition to the primary tumor can grant a stronger understanding of prognosis and therapeutic options. For instance, a patient could have an immune “hot” primary tumor and an immune “cold” metastasis.

Across all metastatic sites covered here, there are consistently fewer frequencies of B cells in the distant site in comparison to the primary tumor. The field has yet to establish the mechanisms that underpin reduced B cell surveillance in the metastatic site. The evidenced roles of B cells in metastasis covered here are multifaceted. Pro-metastatic functions of B cells include enhancing tumor cell motility and invasion, angiogenesis, lymphangiogenesis, ECM remodeling, pathogenic immunoglobulin responses, recruitment of MDSCs, promoting Treg differentiation, and suppressing anti-tumor T cell activity (Figure 1). Many pro-metastatic functions of B cells in the distant site are characteristic of Bregs; however, Bregs appear to have substantial heterogeneity, as indicated by the diverse features reviewed here. In contrast, anti-metastatic B cell functions include anti-cancer B cell activity in the primary tumor preventing metastatic cell dissemination, enhanced antigen presentation, augmented anti-tumor T cell activity, and amplified tumor cell recognition via increased antibody pools (Figure 1). Further investigation into the mechanisms and contexts of specific antibody responses is needed to clarify conflicting evidence for the role(s) of antibodies in cancer metastasis (Table 1).

Lessons from this review suggest that understanding how B cells’ dual roles in metastasis directly impact the metastatic cascade may aid advanced cancer therapy development. The field has much to uncover considering the ever-growing evidence of the heterogeneity and plasticity(128) of B cells and B cell responses. The nature of the antigen, B cell and antibody subtype, co-stimulatory signals, and microenvironmental cues may influence whether the resultant immune response is either anti- or pro-metastatic (Table 1, Figure 1)(129). Fortunately, major efforts are underway to document the B cell recognized antigens in cancer.

The importance of B cell signatures and antibody responses when predicting patient response to therapy in the metastatic setting, suggests a future role for the evaluation of a patient’s functional B cell activity(123,127,130–132). Novel B cell biomarkers and high-sensitivity methods for measuring and characterizing serum antibodies are in development and have the potential to advance early detection and treatment of metastases(41,55,133,134). Several promising early-stage clinical trials are investigating the therapeutic potential of B cell directed immunotherapies in cancer and have been reviewed elsewhere(135,136).

General strategies for harnessing the anti-tumor functions of B cells are consistent with those for driving anti-metastatic responses. Current studies generally take one of three strategies: 1) augment B-cell antigen-presentation by stimulating CD40-CD40L signaling(137–139), 2) drive tumor-antigen specific B cell activity through vaccination, direct antigen delivery(140,141) or targeted monoclonal antibody(142,143) and, 3) activated B cell adoptive transfer(144). Conversely, the clinical trials currently inhibiting B cell numbers (i.e. anti-CD20) or function are those directed at B cell hematological malignancies(145,146). Due to the pro-tumorigenic and -metastatic functions of B cells

summarized here, there is currently a need to develop more anti- B cell-based therapies in solid tumors. For example, anti-B cell-based therapies may include leveraging existing knowledge on Bregs in primary tumors to enable specific depletion of Bregs to alleviate immune suppression within metastatic sites. The technical requirements and knowledge needed to develop anti-metastatic activated B-cell transfers, pro-metastatic B-cell depletion therapies and new targeted antibody infusions are areas of active study which hold immense promise for patients with metastatic cancer(89,147–149).

Acknowledgments:

This work was supported by several funding sources. MR, Mary K Chapman Foundation at the Salk Institute for Biological Sciences, UC San Diego Pathways in Biological Sciences Training Program T32GM133351. AL, Grillo-Marxuach Family Fellowship at Moores Cancer Center. DH, National Institutes of Health (NIH P30 CA014195), METAvivor Early Career Investigator Award, Susan G. Komen Career Catalyst Grant.

Abbreviations

ACVR2B	Activin A Receptor Type 2B
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
AHSG	Alpha 2-HS Glycoprotein
AID	activation-induced cytidine deaminase
ANA	anti-nuclear antigen
APRIL	A proliferation-inducing ligand
ASAH1	N-Acylsphingosine Amidohydrolase 1
BAFF	B cell activating factor
BCOR	B cell lymphoma 6 Corepressor
BCR	B cell receptor
Breg	regulatory B cell
C1GALT1	Core 1 Synthase, Glycoprotein-N-Acetylgalactosamine 3-Beta-Galactosyltransferase 1
CAR-T	chimeric antigen receptor T cell
CCL	chemokine ligand
CCNY	cyclin Y
CD	cluster of differentiation
CDC	complement-dependent cytotoxicity
CpG	cytosines followed by guanine residues

CRC	colorectal cancer
CREB3	CAMP Responsive Element Binding Protein 3
CTSD	Cathepsin D
CXCL	CXC chemokine ligand
CXCR	CXC chemokine receptor
dsDNA	double stranded deoxyribonucleic acid (DNA)
Dsg1	desmoglein 1
ECM	Extracellular matrix
EMT	epithelial-mesenchymal transition
ENA	extractable nuclear antigen
ERP44	endoplasmic reticulum protein 44
FoxP3	forkhead box protein 3
Gp75	tyrosine related protein 1
GRP	Glucose regulated protein
HADH	hydroxysteroid (17-β) dehydrogenase variant
HSP	heat shock protein
ICI	immune checkpoint inhibitors
IFNγ	interferon gamma
IgA	immunoglobulin A
IgD	immunoglobulin D
IgE	immunoglobulin E
IGFBP2	Insulin Like Growth Factor Binding Protein 2
IgG	immunoglobulin G
IgM	immunoglobulin M
IL	interleukin
LDHB	lactate dehydrogenase B
LM	lung metastasis
LN	lymph node
LNM	lymph node metastasis

LPS	lipopolysaccharide
LVM	liver metastasis
MAPKAPK3	mitogen-activated protein kinase activated protein kinase 3
MBC	memory B cell
MDSC	myeloid-derived suppressor cell
MMP	matrix metalloproteinase
MMTV-PyMT	mammary specific polyomavirus middle T antigen
MRLP46	large-subunit mitochondrial riboprotein 46
MUC	mucin
MZ	marginal zone
NSCLC	non-small cell lung cancer
NY-ESO-1	New York esophageal squamous cell carcinoma-1
p53	tumor suppressor protein 53
PB	plasmablast
PC	plasma cell
PD-1	programmed cell death protein 1
PD-L1	programmed cell death-ligand 1
PDAC	pancreatic ductal adenocarcinoma
S100B	S100 calcium-binding protein B
S1PR1	sphingosine-1-phosphate receptor 1
SC-1	immunoglobulin-superfamily cell adhesion molecule 1
SCC	squamous cell carcinoma
SDF1	stromal cell-derived factor 1
SMA	smooth muscle actin
STAT	signal transducer and activator of transcription
STGP1	six thioguanine permease 1
TA90	tumor-associated antigen 90
tBreg	tumor transformed regulatory B cell
TDLN	tumor draining lymph node

TF	Thomsen-Friedenreich antigen
TGFβ	transforming growth factor beta
TGFβR	transforming growth factor beta receptor
TIL-B	tumor infiltrating B cell
TIL	tumor infiltrating lymphocytes
TLS	tertiary lymphoid structure
TNBC	triple negative breast cancer
TNFα	tumor necrosis factor alpha
TPI	triosephosphate isomerase
TPO	thyroid peroxidase
WTp53	wild-type tumor suppressor protein 53

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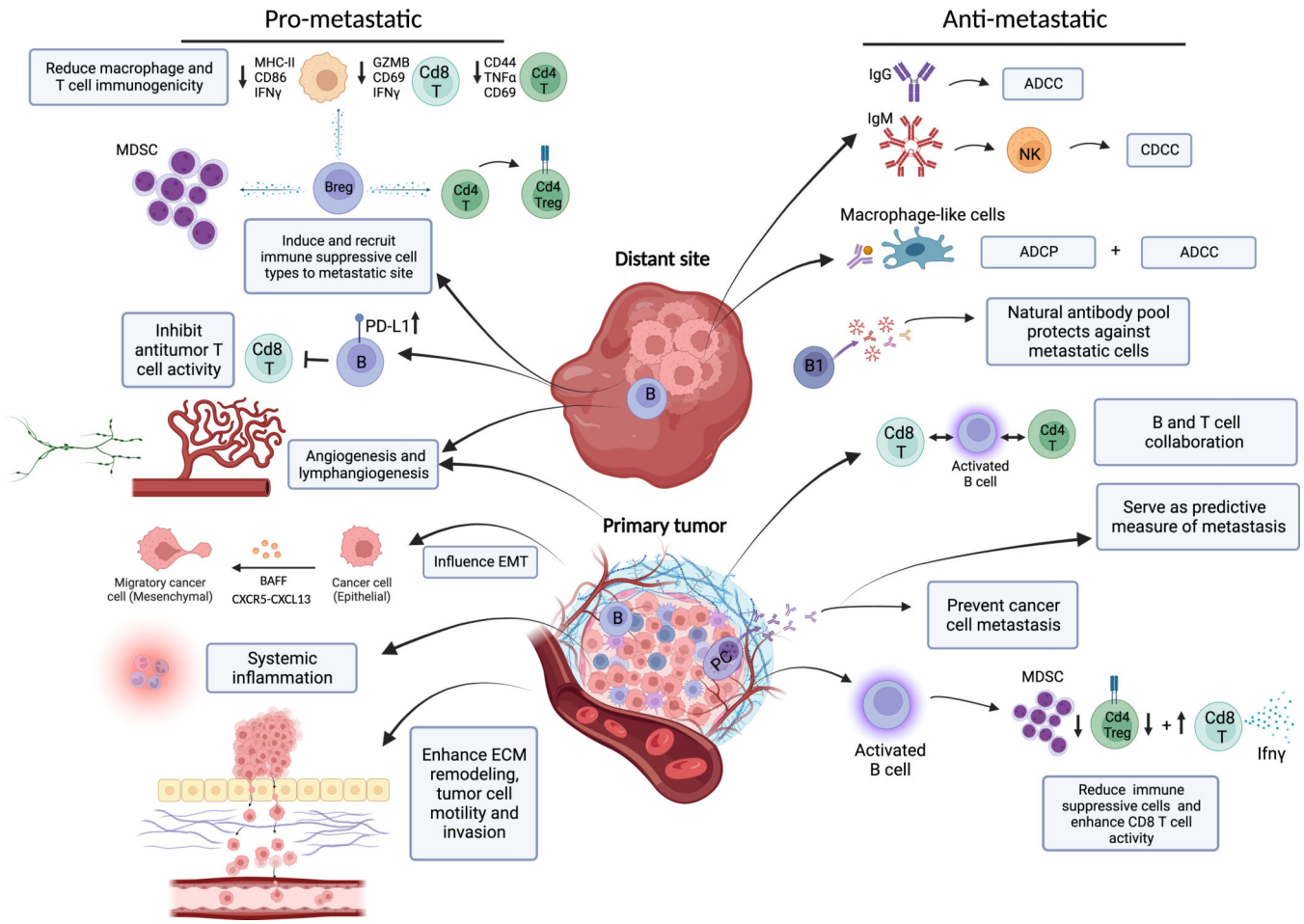

Figure 1.

Schematic diagram highlighting pro- and anti-metastatic functions of B cells reported here. Created with BioRender.

Table 1:

Summary of the literature highlighting known associations for B cells and serum antibodies with metastasis.

B Cell Type	Association with Metastasis	Primary Cancer Type	Metastatic Site	References
General (CD19+ or CD20+)	Associated	Bladder *	LN	PMID: 26305549
		Clear cell renal	*Unspecified distant*	PMID: 34485161
		Clear cell renal	*Unspecified distant*	PMID: 26715281
		Colorectal	Lung	PMID: 33707428
		Colorectal	LN, Liver, Lung	PMID: 10630306
		Head & Neck SCC	LN, *Unspecified distant*	PMID: 35525247
		Hepatocellular	Lung	PMID: 28560063
		Hepatocellular *	LN	PMID: 26502405
		Melanoma	LN, Lung	PMID: 35525247
		Melanoma	*Unspecified*	PMID: 32426497
		Melanoma	Lung	PMID: 23734190
		Melanoma	LN	PMID: 21779876
		Pancreatic	*Unspecified*	PMID: 23940742
		Pancreatic	*Unspecified*	PMID: 32923157
		Pancreatic	Liver	PMID: 35948648
		Prostate	Liver, Lung	PMID: 20220849
	Inversely Associated	Breast	Unspecified distant	PMID: 21846823
		Breast	Skin, Brain	PMID: 29163490
		Breast	Brain	PMID: 23701942
		Breast *	Lung	PMID: 21690573
		Breast *	Lung	PMID: 10070966
		Colorectal	Unspecified	PMID: 35563553
		Colorectal	Liver	PMID: 24905750
		Colorectal	LN	PMID: 30455756
		Head & Neck SCC	LN	PMID: 19698134
		Melanoma	Visceral	PMID: 21779876
		Melanoma *	Lung	PMID: 20194720
		Melanoma *	Lung	PMID: 21278302
		Ovarian	Omentum	PMID: 27354470
		Prostate	LN	PMID: 16955408
		Breast	LN	PMID: 26708831
		Renal cell	*Unspecified*	PMID: 30288343
Memory B cell	Associated	N/A	N/A	N/A
	Inversely Associated	Melanoma	LN, *Unspecified distant*	PMID: 34359321
		Breast	LN	PMID: 26708831

B Cell Type	Association with Metastasis	Primary Cancer Type	Metastatic Site	References
B1 B cell, Innate-like	Associated	Melanoma	Lung	PMID: 18922915
	Inversely Associated	Breast *	Peritoneal	PMID: 30224373
Plasmablast	Associated	Melanoma	*Unspecified*	PMID: 34095149
	Inversely Associated	Ovarian	Omentum	PMID: 34038734
		Melanoma	Unspecified	PMID: 29031828
		NSCLC	Unspecified	PMID: 29031828
		Renal cell	Unspecified	PMID: 29031828
Plasma cell	Associated	Breast *	Lung, Liver	PMID: 11676396
		Head & Neck SCC	Lung, Liver, Bone	PMID: 32283719
		Melanoma	LN	PMID: 6528940
		Melanoma	LN	PMID: 26867783
	Inversely Associated	Breast *	Lung	PMID: 6345879
Regulatory B Cell, Breg	Associated	Breast	*Unspecified*	PMID: 30244409
		Breast *	Lung	PMID: 24043896
		Breast *	Lung	PMID: 26183924
		Breast *	Lung	PMID: 21444674
		Melanoma	Bone	PMID: 32001420
		Melanoma *	Lung	PMID: 26183924
		Breast	LN	PMID: 26708831
	Inversely Associated	N/A	N/A	N/A
Antibody Type	**Association with Metastasis**	**Primary Cancer Type**	**Antigen**	**References**
Autoreactive Antibody, Unspecified Subtype	Associated	Breast	ANA, SMA	PMID: 1081928
		Breast	*Unspecified*	PMID: 3902126
		Gastric	p53	PMID: 32458231
	Inversely Associated	Breast	*Unspecified*	PMID: 3902126
		Lung	ANA, ENA, SMA	PMID: 31289683
IgM	Associated	Colorectal	*Unspecified*	PMID: 3802011
		Lung	PD-1, PD-L1	PMID: 36127483
		Melanoma *	*Unspecified*	PMID: 12705631
	Inversely Associated	Breast	MUC1	PMID: 10653872
		Colorectal	*Autoreactive*	PMID: 34603722
		Breast	*Unspecified*	PMID: 439898
		Gastric	SC-1	PMID: 16820243
		Melanoma	TA90	PMID: 14698308
		Melanoma	TA90	PMID: 11181684
		Melanoma	*Unspecified*	PMID: 307959
IgD	Associated	N/A	N/A	N/A

B Cell Type	Association with Metastasis	Primary Cancer Type	Metastatic Site	References
	Inversely Associated	Melanoma	*Unspecified*	PMID: 307959
IgA	Associated	Breast	*Unspecified*	PMID: 439898
		Breast	*Unspecified*	PMID: 588419
		Colorectal	*Unspecified*	PMID: 3802011
		Colorectal	*Unspecified*	PMID: 33707428
	Inversely Associated	N/A	N/A	N/A
IgG	Associated	Breast	NY-ESO-1	PMID: 23894724
		Breast	NY-ESO-1	PMID: 17294444
		Breast*	Mucin sialyl-Tn	PMID: 12460925
		Cholangiocarcinoma	NY-ESO-1	PMID: 29262561
		Colorectal	*autoreactive*	PMID: 34603722
		Colorectal	MAPKAPK3, ACVR2B	PMID: 19638618
		Colorectal	ERP44	PMID: 31918032
		Colorectal*	Mucin sialyl-Tn	PMID: 12460925
		Esophageal	NY-ESO-1	PMID: 25906289
		Head & Neck SCC	C1GALT1	PMID: 32427353
		Hepatocellular	GRP78	PMID: 28186997
		Melanoma	NY-ESO-1	PMID: 23894724
		Melanoma	HSP90, GRP94	PMID: 22084687
		NSCLC	PD-1, PD-L1	PMID: 36127483
		NSCLC	Ubiquilin1, HADH, TPI	PMID: 20824709
		NSCLC	S100B	PMID: 27652205
		NSCLC*	GRP78	PMID: 20651985
		Ovarian	BCOR, CREB3, MRLP46	PMID: 31428516
		Ovarian	STGP1	PMID: 11676396
		Pancreatic	WTp53	PMID: 8807362
		Prostate	AHSG	PMID: 25675522
		Rhabdomyosarcoma	IGFBP2	PMID: 32093404
		Thyroid	Thyroglobulin	PMID: 27356742
		Breast*	HSPA4	PMID: 30643287
	Inversely Associated	Breast	MUC1	PMID: 10653872
		Breast	MUC1	PMID: 21385452
		Breast	Endostatin	PMID: 16552441
		Colorectal	TF	PMID: 10213921
		Melanoma	ASAH1, CTSD, LDHB	PMID: 22084687
		Melanoma	dsDNA, Thyroid	PMID: 22145691
		Melanoma*	Gp75	PMID: 8962137
		Thyroid	TPO	PMID: 21837696

Associations or inverse associations with metastatic disease do not equate to causation or function unless the mechanism is reported in the manuscript.

* Indicates studies limited to preclinical models.

Unspecified - specific metastatic organ or tumor antigen not characterized in detail.

Unspecified distant – distant metastases in unspecified organ(s).

Autoreactive – unspecified autoreactive antibody or antigen.

LN- lymph node, NSCLC- non small cell lung cancer, SCC- squamous cell carcinoma, N/A- no studies available in the literature for the specified section.