Review

Cancer Research

The Emerging Role of B Cells in Tumor Immunity

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Abstract

There is increasing evidence supporting a role for B cells in tumor immunology. Paraneoplastic syndromes occurring before a cancer diagnosis have pointed to the potential for harnessing the humoral immune response for early cancer detection. The presence of tumor-infiltrating B lymphocytes has been linked to a favorable clinical outcome in many types of cancers. However, B cells represent a heterogeneous population with functionally distinct subsets, and the balance among subtypes impacts tumor development. Here, we review recent findings related to B cells and to the humoral immune response in cancer and their translational significance. *Cancer Res; 76(19); 5597–601. ©2016 AACR.*

Introduction

The importance of T cells in antitumor responses has become well established and extensively studied. In contrast, the potential contributions of B cells to the immune response to tumor development are less well investigated. Apart from the immune-regulatory function of antibody and antibody–antigen complexes, B cells can shape the functions of other immune cells by presenting antigens, providing costimulation, and secreting cytokines (1). B-cell gene signatures uncovered through tumor global gene expression profiles have been associated with a favorable prognosis for several cancer types, including breast and ovarian (2, 3). However, B cells represent a heterogeneous population with functionally distinct subsets, contributing to both pro- as well as antitumor immune responses, and the balance among the subtypes may affect tumor development and behavior (4, 5). In this review, we highlight recent findings pertaining to the contributions of B cells to the cellular and humoral immune responses to cancer and their potential relevance to cancer detection and treatment.

Autoimmunity in Cancer

B cell–associated autoimmune responses are frequently found in many tumor types. A broad spectrum of autoantibodies is found to be associated with certain manifestations of paraneoplastic syndromes, either as only markers or as direct mediators (6). Whether autoimmune diseases are associated with increased or reduced risk of cancer is unclear. Compared with the general population, patients with systemic lupus erythematosus (SLE) have an increased risk of non-Hodgkin lymphoma, lung, liver, and thyroid malignancies and a reduced risk of breast and prostate cancers (7). Remarkably, one recent report (8) supported that cancer can trigger acquired humoral immunity, showing that the appearance of certain autoantibodies is part of a defensive (although eventually unsuccessful in some cases) immune response against a developing tumor. This is in line with the concept of cancer immunoediting, that emphasizes the dual host-protective versus tumor-sculpting processes of the immune system in cancer (9).

Tumor-associated autoantibodies as diagnostic markers

Autoantibodies have attracted interest as potential biomarkers for early diagnosis or for their potential as prognostic indicators for many types of cancer. Importantly, the occurrence of autoantibodies has been found to precede clinical manifestations by several months to years (6). The mechanism through which an autoantibody response is triggered, particularly against proteins that are ubiquitously expressed, such as glycolytic enzymes, is not clear. The fundamental function of the immune system is to discriminate self from non-self. As immune tolerance against self-antigens is a highly regulated process, the presence of autoantibodies may signal either breakdown of immune tolerance or that some self-antigens are not encountered by immune cells in nonpathologic states because of their intracellular turnover and limited accessibility in nonmalignant cells.

Autoantibodies have the potential to provide unique fingerprints that reflect the nature of the malignant process in the affected organ. For example, by comparing patient sera from breast cancer versus an autoimmune disease, Madrid and colleagues (10) demonstrated characteristic serologic findings (antimitochondria antibodies, multiple nuclear dots, centrosome, and nucleolar staining) in breast cancer sera reflecting a distinct autoantibody repertoire. This suggests that autoimmunity to tumor-associated antigens residing in breast tissue is a prominent feature in breast cancer. Moreover, subtype-specific autoantibody signatures, as exemplified by the spliceosome and glycolysis panels for estrogen receptor–positive, luminal breast cancer (11), and the networks of BRCA1, TP53, and cytokeratin proteins of mesenchymal/basal phenotype were distinct for triple-negative breast cancer (TNBC; ref. 12). Cytokeratins have utility for fingerprinting carcinomas. In breast tissue, the luminal epithelial cells express cytokeratin 8/18, 7, and 19, whereas basal/myoepithelical cells express cytokeratins 5/6, 14, and 17 predominantly. Autoantibodies directed at cytokeratin 5/6 and 14 were elevated in prediagnostic plasmas of a basal type mouse model of breast cancer and in human TNBC but not in luminal type of

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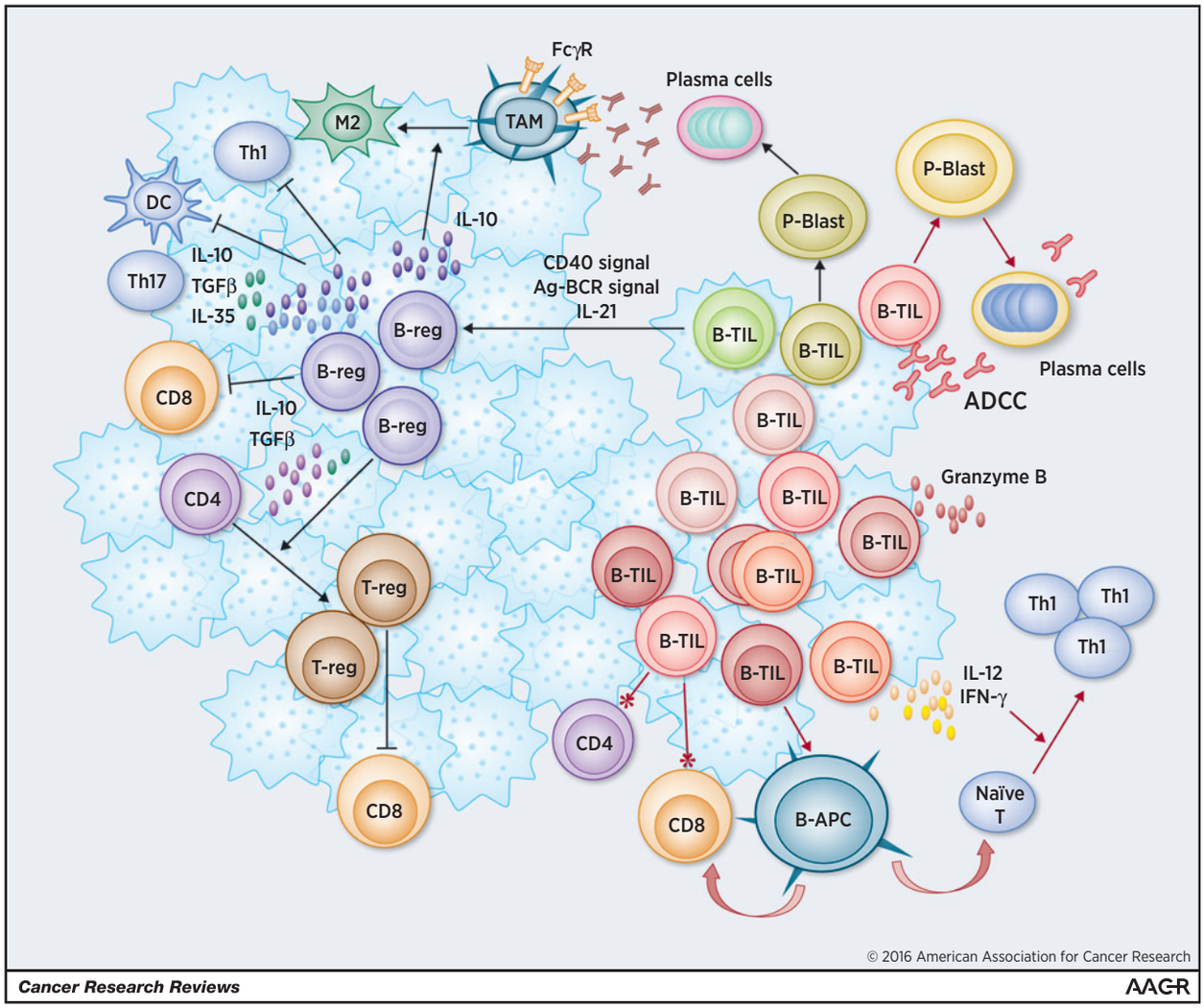

Figure 1.
Distinct subsets of B cells dynamically help shape the tumor microenvironment in both a pro- (black) and antitumorigenic manner (red). ADCC, antibody-dependent cellular cytotoxicity; Ag-BCR signal, antigen B-cell receptor signal; B-APC, B antigen-presenting cells; FcγR, Fcγ receptor; M2, M2 macrophages; P-blast, plasmablast; TAM, tumor-associated macrophage; T-reg, regulatory T cells.

breast cancer (13). Autoantibody reactivity was not only a predominant feature observed both in tumor-bearing mice and in prediagnostic human samples, but also interestingly, autoantibody reactivity was more pronounced further away than closer to diagnosis (11). The temporal evolution in autoantibody reactivity during tumor development and progression further illustrates the dynamics of the autoantibody response.

Some cancer-associated autoantibodies are triggered by cellular proteins that are mutated, modified, or aberrantly expressed in tumor cells and hence are regarded as specific "immunological reporters." This is exemplified by calreticulin, a target for autoantibodies in several cancer types (14). Full-length calreticulin has been identified as an autoantigen in rheumatoid arthritis, SLE, Sjögren syndrome, celiac disease, congenital heart block, and connective tissue disease, whereas a C-terminal truncated form of calreticulin but not intact calreticulin has been associated with a humoral response in patients with hepatocellular carcinoma, indicating that a specific cleavage of the protein may induce this autoimmune response (14). Further evidence for cleavage of calreticulin in hepatocellular carcinoma was obtained by finding the remainder of the molecule in the form of a cleaved N-terminal fragment released in serum in hepatocellular carcinoma (14). The concept that new antigenic epitopes may arise from protein processing has both diagnostic and therapeutic relevance.

Critical questions in considering autoantibodies as biomarkers for cancer detection are sensitivity and specificity. It is not clear why only a subset of patients exhibit humoral immune response to certain antigens. The extent of immunogenicity could be determined by multiple factors: the antigen processing and MHC molecules variability among individuals, the heterogeneity of tumors with different levels of protein expression and diverse

posttranslational modifications, and other factors yet to be elucidated. Limited performance of autoantibody markers may stem from the occurrence of similar autoantibodies in autoimmune diseases. In addition, autoantibody reactivity interpreted as a manifestation of autoimmune disease may in fact represent a paraneoplastic manifestation. As illustrated by the calreticulin example, detailed epitope mapping may help elucidate the cancer- versus autoimmune disease-specificity of an autoantibody biomarker.

Tumor-associated autoantibodies as prognostic markers

So far, few autoantibodies have been assessed as cancer prognostic biomarkers. For example, one of the most extensively studied tumor-associated autoantibodies, P53, has been variably linked to prognosis in different reports. One possible explanation is that the association with prognosis is cancer type specific. However, more recently, several cancer type-specific meta-analyses, for example, lung cancer (15), have found substantial discordance between studies. The frequency and intensity of serologic responses to antigens may vary significantly due to both intrinsic tumor features (e.g., molecular subtype, histologic grade, stage, etc.), as well as host immune and general health conditions. Therefore, detailed characterization of subject characteristics and tumor molecular profiles, and autoantibody subtypes together with other immune response factors, may yield a clearer picture for predicting clinical outcome.

B Cells and the Tumor Microenvironment

Emerging evidence suggests that the role of B cells in the tumor microenvironment extends beyond eliciting humoral immune responses. In addition to secretion of antibodies and inflammatory cytokines, B cells have the capacity to recognize antigens, regulate antigen processing and presentation, and mount and modulate T-cell and innate immune responses. Moreover, through antibody production, and the formation of antigen–antibody complexes, B cells could potentially influence all immune cell types expressing Fc receptors (e.g., granulocytes, dendritic cells (DC), nature killer cells, and myeloid-derived suppressor cells).

The tumor microenvironment contains a heterogeneous population of B cells with functionally distinct subsets, contributing to both pro- as well as anti-immune responses. The balance of these responses may determine whether B cells serve a pro- or an antitumorigenic function.

Protumorigenic B-cell responses

B cells may promote tumorigenesis and tumor progression by contributing to an angiogenic and proinflammatory microenvironment, and by directly or indirectly suppressing T-cell activation. Evidence from mice that develop cancers spontaneously suggests a protumoral role of B cells (16) due to the production of cytokines, for example, IL10, and IgG, which can form antigen–IgG antibody complexes. These can either recruit immunosuppressive myeloid cells or facilitate tumor progression through degradation of the extracellular matrix and enhancement of angiogenesis in a granulocyte- and macrophage-dependent manner. Tumor-infiltrating B lymphocyte (B-TIL)–derived lymphotoxin has been reported to promote androgen-independent prostate cancer progression by activating the NF-κB and STAT3 pathways (17). Moreover, it has been shown that a robust *in vivo* antitumor cytotoxic T response occurred in B cell–deficient but not in wild-type mice, and that adoptive transfer of B cells to B cell–deficient mice restored tumor growth (18), indicating an inhibitory effect of B cells on cytotoxic T cells.

A distinct subset of B cells, designated B regulatory cells (B-reg), has been described lately. This subset exerts immune-modulatory functions through the production of the immunosuppressive cytokine TGFβ and IL10 (19). B-reg cells may promote metastasis by converting resting $CD4^+$ T cells into T-reg cells.

Another subset of B cells, $CD5^+$ cells, have been recently demonstrated to promote tumor progression. CD5 directly binds to IL6, and the presence of $CD5^+$ B cells was shown to be correlated with phosphorylated STAT3 in human non-small cell lung, prostate, and ovarian cancer tissues (20). Moreover, B cells were linked to pancreatic adenocarcinoma tumorigenesis by several mechanisms. First, B-TILs were shown to secrete IL35 that stimulate tumor growth (21). In addition, increased B-cell chemokine secretion and B-cell infiltration associated with accelerated tumor growth were found in pancreas-specific *HIF1A* deletion (22). Finally, the cross-talk between B cells and tumor-associated macrophages favored TH2-type macrophage reprogramming through BTK activation in a PI3Kγ-dependent manner (23).

A different, deleterious role has emerged for B cells in affecting response to cancer therapy. Immunosuppressive plasma cells in a mouse model have been shown to impede an antitumor T-cell response following chemotherapy (24). Immunosuppressive B cells are a subset of plasma cells that express IgA, IL10, and programmed death ligand 1 (PD-L1). Removing these cells allowed CTL-dependent eradication of oxaliplatin-treated prostate cancer (24). This, again, demonstrates that B-TILs are heterogeneous with context-dependent functions.

Antitumorigenic B-cell responses

B cells also exert multiple antitumor effects. These include production of cytokines coordinating other immune cells, particularly through enhancement of cytotoxic T-cell activity, exertion of a direct tumoricidal effect by secretion of granzyme B, or indirectly through antibody-dependent mechanisms. Interestingly, using multiphoton microscopy *in vivo*, $CD11c^+$ B cells have been shown to form stable interactions with T cells at the B cell–T cell border in the spleen and to function as potent antigen-presenting cells (APC; ref. 25). Under most conditions, DCs, the professional APCs in draining lymph nodes, activate and initiate T-cell expansion. However, during the protracted course of tumor-immune interactions, DCs may decline in number, activity, or even convert to a suppressive phenotype. Theoretically, B cells in the tumor microenvironment may serve as APCs locally and contribute to survival and proliferation of tumor-infiltrating T cells over time when DCs fail to sustain their role presenting antigens effectively. Tumor-infiltrating $CD20^+$ B cells have been found in close proximity to $CD8^+$ T cells, and the presence of both $CD20^+$ and $CD8^+$ lymphocytes has been associated with prolonged survival in ovarian cancer, compared with the occurrence of $CD8^+$ T-cell infiltrates in the absence of B cells (26). In murine models, $CD4^+$ T-cell activation and clonal expansion in response to protein antigens and pathogen challenge has been found to be impaired when an anti-CD20 antibody was used to deplete B cells, supporting a critical role of B cells for optimal antigen-specific $CD4^+$ T-cell priming (27).

The presence of ectopic lymph nodes or tertiary lymphoid structures (TLS) within solid tumors is well documented (28). TLSs are architecturally similar to secondary lymphoid organs, with separated B- and T-cell areas, specialized populations of DCs, well-differentiated stromal cells, and high endothelial venules. The occurrence of TLS in tumors has been associated with better clinical outcome and thus may represent the initiation of a local antitumor B cell–mediated immunity (29).

B-TILs are predictive of clinical outcome in numerous cancers

The characteristics that distinguish tumor promotion and tumor suppression effects of B-TILs are largely unknown. In some cancers, the presence of B-TILs has been linked to a favorable clinical outcome, including breast (3) and non–small cell lung cancer (NSCLC; ref. 30). Although less appreciated, the infiltration of mature plasma cells into tumor tissue has been associated with prolonged survival in NSCLC (30).

A breast cancer gene expression profiling study has identified an independent association of a B-cell metagene signature with better survival in a subgroup of patients having highly proliferative tumors, leading to the suggestion that a protective humoral effect may be of particular importance in fast-proliferating tumors (3). Although global tumor mRNA profiling does not convey spatial features of the tumor microenvironment, several recent studies have corroborated that the presence of B cells, as derived from gene expression signatures, is linked to a favorable prognosis in breast cancer (2, 3). Concordantly, immunohistochemical staining of CD20 as a surrogate marker for B cells was found to have prognostic significance for B-TILs in breast cancer (31).

Therapeutic Use of Tumor-Associated Autoantibodies

Apart from their potential utility as biomarkers, in principle, autoantibodies may have a therapeutic benefit. They not only possess the capability of implementing antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, but can also facilitate antigen cross-presentation and activation of T cells. Moreover, autoantibodies against surface receptors can hamper ligand/receptor interactions and signaling cascades. A case in point is endogenous anti-HER2 antibodies, which can effectively suppress HER2 kinase activity and downstream signaling to inhibit the transformed phenotype of HER2-expressing tumor cells (32). Recently, Hansen and colleagues (33) found that a lupus autoantibody 3E10 preferentially binds DNA single-strand tails, inhibits key steps in DNA single-strand and double-strand break repair, and sensitizes cultured tumor cells and human tumor xenografts to DNA-damaging therapy, including doxorubicin and radiation. Adoptively transferred B cells have been demonstrated, using a mouse model, to promote tumor rejection by producing complement-fixing, tumor-reactive antibodies (34). Moreover, through vaccination, the induction of autoantibody responses in mice was shown to boost $CD8^+$ T-cell responses against tumors (35).

Still, so far, there has been no definitive and direct evidence that autoantibodies have therapeutic benefit. One potential reason may be that the local concentration of endogenous autoantibodies in the tumor microenvironment may be far below the optimal dose for effective tumor killing. There are also numerous mechanisms of immune evasion as, for example, the presence of coinhibitory molecules in the tumor microenvironment. Patients that are seropositive for NY-ESO-1 have NY-ESO-1–specific T cells accumulating at the tumor site in ovarian cancer patients. However, the antitumor activity of these autoantibodies was found to be dampened by expression of coinhibitory molecules CTLA-4, PD-1, and LAG-3 (36). Nevertheless, the therapeutic potential of tumor-specific autoantibodies holds promise and is under active investigation. It has been shown that in transgenic mouse models of breast cancer (TgMMTV-neu), vaccination against breast-specific antigenic repertoire (HER2, IGFBP2, and IGFIR) increased both disease-free and overall survival (37). Importantly, initial human clinical trials have demonstrated these approaches to be safe and feasible (38). An emerging, innovative therapeutic approach, initially applied to develop antibodies against infectious diseases, is to isolate memory B cells taken from a human donor with a favorable response to a cancer. These memory B cells are grown and activated to propagate and differentiate into antibody-producing cells and their antibodies screened for biological activity. The genes for selected antibodies can then be inserted into immortalized mammalian cells to enable production of unlimited quantities of that antibody clone for further therapeutic assessment (http://www.theraclone-sciences.com). Moreover, these autoantibodies can be further exploited for broader applications, including antibody–drug conjugation or chimeric antigen receptor-T therapy.

A challenge for cancer immunotherapy is to identify immunogenic neoantigens. It is not clear why only a small fraction of mutations is immunogenic, leading to the formation of neoantigens presented on MHC class I molecules. Traditionally, the identification of mutated and aberrantly expressed self-tumor antigens has been notoriously labor intensive. With the advent of next-generation sequencing and epitope prediction, rapid identification of mutant tumor neoantigens has become possible. However, the efficiency of neoantigen identification and selection is far from ideal for clinical applications. Most identified neoepitopes were considered as "cryptic antigens," as they either failed to stimulate T cells or were not processed or presented by the tumors.

One option for enhancing the process of neoantigen identification would take advantage of sero-reactive autoantibodies and identification of corresponding antigens, including epitopes that may result from post-translational modifications (PTM). For example, aberrant mucin-type o-glycosylation is one of the most frequently detected PTM in various types of adenocarcinoma, and the cancer-specific glycan structures serve as epitopes that can be targeted by the immune system. Recently, high anti-MUC1 IgG levels were shown to positively associate with improved overall survival in breast cancer patients (39). Identification of such cancer-specific PTM peptides may be accomplished through the use of mass spectrometry. Thus, antigenic targets of autoantibodies merit further investigation for T cell–related immunotherapy.

Conclusion

Understanding the diverse roles of B cells and the humoral immune response in cancer has the potential to yield novel

avenues for cancer screening and the development of predictive and prognostic markers and to impact therapeutic approaches. In addition, there is a substantial opportunity to mine the autoantibody repertoire to develop antibody and vaccine strategies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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