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REVIEW ARTICLE

The B7 Homologues and their Receptors in Hematologic Malignancies

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Abstract

The B7 homologues and their receptors regulate both peripheral tolerance and adaptive immunity. This field is rapidly evolving as new ligands and receptors are being identified. Much of the work supporting their role in the regulation of host anti-tumor immunity has been derived from experimental models and clinical trials in solid malignancies. However, a growing body of evidence demonstrates that the B7-H family has important immunologic and non-immunologic functions in a variety of hematologic malignancies. Herein, we will review recent evidence that supports the therapeutic targeting of the B7 homologues in hematologic malignancies.

Key words leukemia; lymphoma; B7-H1; PD-1; T cell; costimulation

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The 'classical' B7 family members, B7-1 (CD80) and B7-2 (CD86), provide T-cell costimulatory or coinhibitory signals upon binding their receptors CD28 or CTLA-4, respectively [reviewed in (1)]. Over the past decade, a number of ligands/counter-receptors with homology to B7-1/B7-2 have been identified. These B7 homologues ('B7-H'), including B7-H1 (CD274 or PD-L1), B7-H2 (CD275 or ICOS-L), B7-H3 (CD276), B7-H4 (B7S1 or B7x), B7-H6, B7-DC (CD273 or PD-L2), and BTLN2, play a critically important role in the maintenance of self-tolerance and the regulation of innate and adaptive immunity in the tumor-bearing host (Fig. 1). Many of these B7-H family members are exploited by tumor cells to escape and suppress host immunity and are being actively investigated as therapeutic targets in solid tumors. While a comprehensive discussion of the B7-H family is beyond the scope of this review, recently published reviews provide an excellent overview of the B7-H family, emphasizing their role in solid tumor immunity (2–6). Instead, we hope to highlight areas that are of particular relevance in hematologic malignancies.

The B7-H family: a primer

The rapid expansion of the B7-H family coupled with improved understanding of their immunologic functions has changed the view of T-cell co-stimulation within the context of the 'two-signal hypothesis' (7, 8). Simply stated, the 'two-signal hypothesis' postulates that combined antigen-dependent signaling via the T-cell receptor and a second 'costimulatory' signal are required for optimal T-cell activation. In this view, costimulatory ligands function as molecular 'toggle' switches. It is now apparent that B7-H family members not only influence the activation of naïve T cells following antigen presentation, but also have broad roles in the control of T-cell differentiation, effector functions, deactivation, and survival. Therefore, members of the B7-H family are molecular 'dimmer' switches that fine-tune adaptive (and innate) immunity.

B7-H family members with either stimulatory or inhibitory functions are widely expressed by both tumor cells and constituents of the tumor microenvironment in hematologic malignancies (Table 1)(9–24). B7-H2 provides a T-cell costimulatory signal (25–29) upon engaging

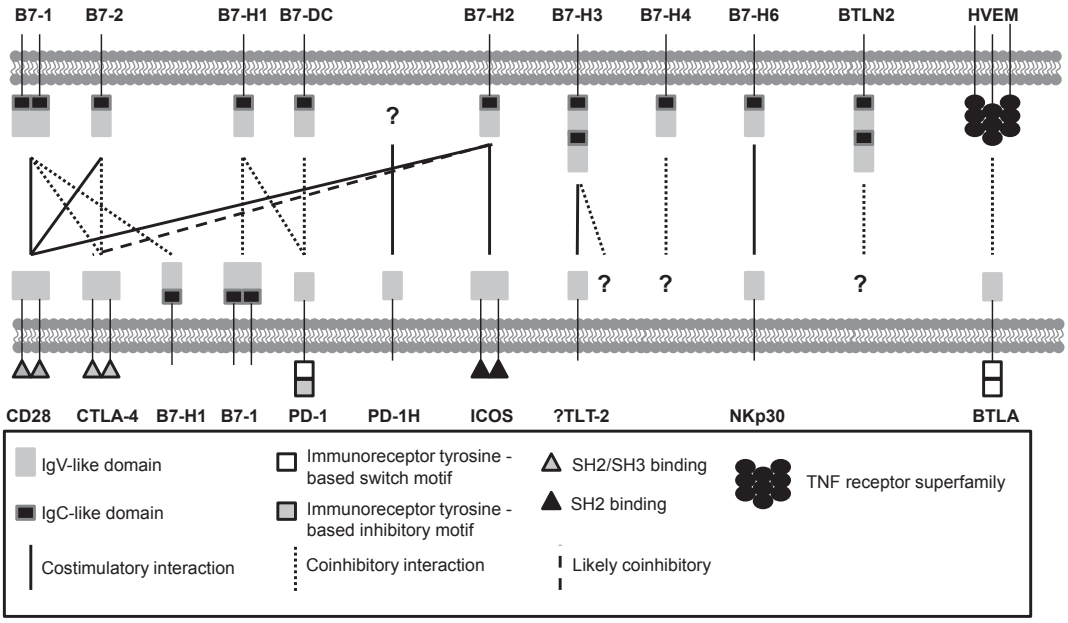

Figure 1. The B7-H family and their receptors.

either of its receptors, CD28 and ICOS (25, 30). In contrast, B7-H1 (2) and B7-H4 (31–33) both inhibit T-cell immunity. The available evidence suggests both inhibitory and stimulatory functions for B7-H3 (6). Whether the triggering receptor expressed on myeloid cells family member TLT-2 is a bona fide costimulatory receptor for B7-H3 is also controversial (34–36). The identification of B7-H3 receptors using novel techniques should help clarify its role in immunity (30). Ultimately, the B7 ligands exert disparate effects on T-cell immunity depending upon the particular receptor/counter-receptor engaged (Fig. 1; B7-1/CD28 cf. B7-1/CTLA-4/B7-H1).

With the exception of CTLA-4, the B7-H1/PD-1/B7-1 axis is best understood among the inhibitory B7-H family members. In contrast to CTLA-4-deficient mice that develop a profound lymphoproliferative disorder, PD-1-deficient mice, depending upon their genetic background, develop a variety of more subtle autoimmune manifestations (37–39). This work clearly supports the role of PD-1 as an important inhibitory receptor. The striking difference in phenotypes between CTLA-4- and PD-1-deficient mice suggests that targeting PD-1 may be associated with fewer immune-related adverse events compared with CTLA-4 blockade. While it may be premature to draw any definitive conclusions, the available evidence supports this conclusion (40–42). Recruitment of SH2-domain containing protein tyrosine phosphatases (SHP-1 and/or SHP-2) to the immunoreceptor tyrosine–based switch motif (ITSM) within the PD-1 cytoplasmic tail inhibits signaling events, particularly PI3K/AKT activation, downstream of the T-cell receptor (43). PD-1 also promotes tumor cell evasion of host immunity as a major counter-receptor for B7-H1. Recent studies also demonstrate that B7-1 engagement by B7-H1 downregulates T-cell immunity (44). Engagement of B7-H1 on tumor cells confers resistance to cytotoxic T-cell (CTL)-mediated killing, thus functioning as a 'molecular shield' (43). In the setting of persistent antigenic exposure, PD-1 engagement contributes to the maintenance of functionally incompetent antigen-specific T cells (45). This has been nicely demonstrated in chronic viral infections, like HIV. In most patients with HIV, viral-specific CTL highly express PD-1 and are functionally suppressed or 'exhausted' (46, 47). However, T-cell effector functions and proliferation are restored upon B7-H1 blockade. In contrast, a low viral load and maintenance of peripheral blood $CD4^+$ T-cells are observed in the absence of antiviral therapies in a subset of HIV patients. These long-term non-progressors have a pool of functional HIV-specific T cells that express little PD-1. These observations have significant implications for virally associated lymphoproliferative disorders. Adult T-cell leukemia/lymphoma (ATLL) is associated with human T-cell leukemia virus-1 (HTLV-1) infection, but only develops in a minority of infected patients after a long latency period. In contrast to HTLV-1 carriers, antigen-specific T cells in ATLL patients highly expressed PD-1 and are suppressed by B7-H1-expressing lymphoma cells (20). The contribution of the B7-H1/PD-1 axis in the maintenance of T-cell anergy or exhaustion is unlikely to be limited to virally associated lymphoproliferative disorders (48).

Table 1 Expression of selected B7 homologues in hematologic malignancies

	Tumor Cell B7-H Expression (%)			
	B7-H1	B7-H2	B7-H3	B7-H4
MDS	Present (<25%) (9)			
AML	≈25% (10–13)	≈15%† (21)		
ALL			Absent (23)	
DLBCL	≈25% (14)		≈5% (24)	
PMBCL	>50% (16)			
BL			Rare (23, 24)	
FL	Absent (14)		Rare (24)	
CLL/SLL			Rare (24)	
MCL			Absent (24)	
CBCL				Present (131)
cHL	≈90% (14, 15)		≈5% (24)	
NLPHL			Absent (24)	
MM	>50% (17, 49)	Rare (22)		
PTCL-U	≈20% (18)			
AITL	Rare (18)			
ALCL, ALK+	33% (18)		≈20% (ALK status unknown) (24)	
ALCL, ALK-	15% (18)			
ATLL	≈20% (20)			
CTCL	≈25% (18, 19)			

MDS, myelodysplastic syndrome; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; PMBCL, primary mediastinal large B-cell lymphoma; BL, Burkitt lymphoma; FL, follicular lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; MCL, mantle cell lymphoma; CBCL, cutaneous B-cell lymphoma; cHL, classical Hodgkin lymphoma; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; MM, multiple myeloma; PTCL-U, peripheral T-cell lymphoma, unspecified; AITL, angioimmunoblastic lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ATLL, adult T-cell leukemia/lymphoma; CTCL, cutaneous T-cell lymphoma.
†Associated with survival.

In addition to regulating T-cell immunity, B7-H family members have recently been shown to influence NK-cell activation. This observation is particularly relevant in hematologic malignancies given the widespread use of monoclonal antibodies that mediate antibody-dependent, NK-cell-mediated cytotoxicity (ADCC). NK cells derived from multiple myeloma patients, in contrast to healthy donors, highly express PD-1. As myeloma cells highly expressed B7-H1, PD-1 blockade enhanced conjugate formation between NK cells and myeloma cells, increasing NK-cell-mediated cytotoxicity (49). Interestingly, lenalidomide decreased myeloma cell B7-H1 expression. Therefore, lenalidomide may increase ADCC when used in conjunction with monoclonal antibody-based therapies by directly stimulating NK-cell cytotoxicity and by impairing B7-H1 expression on target cells (50, 51). Analogous to its role in maintaining a state of T-cell exhaustion, PD-1 was found to mediate NK-cell 'exhaustion' in EBV-associated post-transplant lymphoproliferative disorders (52). In contrast to B7-H1, B7-H2 and B7-H6 promote NK-cell cytotoxicity (53–56).

The role of the B7-H family is not limited to direct interactions between malignant cells and effector cells of the adaptive immune response. B7-H family members expressed on non-malignant cells within the tumor microenvironment play a critically important role in providing a niche favorable for tumor growth and survival in hematologic malignancies. For example, in various T-cell lymphoproliferative disorders B7-H1 expression was far more common within the tumor microenvironment and was less commonly expressed by clonal T cells (18). A considerable body of work now supports the important role of both myeloid-derived cells and regulatory T cells (Treg) in many hematologic malignancies. Monocytes and their progeny within the tumor microenvironment (e.g., lymphoma-associated macrophages) provide trophic factors that support the growth of malignant lymphocytes, promote angiogenesis, and regulate host immunity (57). Not surprisingly then, increased frequencies of peripheral blood monocytes and lymphoma-associated macrophages are associated with inferior outcomes in both Hodgkin and non-Hodgkin lymphomas (58–61). Dendritic cells (DC) and other myeloid cells, including subsets of monocytic cells (18, 62, 63), determine the fate of activated T cells, at least in part, by the provision of costimulatory/coinhibitory ligands. For example, T-cell lymphoma cells were found to stimulate B7-H1 expression on both monocytes and DC (18). *In vitro* co-culture experiments demonstrated that DC promote Treg generation in a B7-H1-dependent

manner (18, 64). This was further supported by immunohistochemical analyses demonstrating the co-localization of B7-H1$^+$ DC and Treg in T-cell lymphoma specimens (18). While these studies support the role of B7-H1 in Treg induction, B7-H1 may also promote the expansion of Treg (65). Regulatory T cells have also been implicated in the pathogenesis of MDS/AML (66, 67) and B-cell malignancies (68, 69). B7-H1, expressed by either malignant cells or tumor-infiltrating DC, appears to similarly regulate the induction and suppressive functions of Treg in these diverse hematologic malignancies (69–72).

Given their inhibitory role, expression of many B7-H family members by tumor cells is an adverse prognostic factor in most solid tumors that have been examined (4–6). This is usually attributed to their immunologic affects. However, recent evidence demonstrates that 'reverse signaling' mediated by B7-H1, B7-H3, and B7-H4 may regulate tumor cell survival. Using tumor cells transfected with B7-H1 constructs lacking the cytoplasmic domain, Azuma et al. demonstrated that B7-H1 signaling following engagement by T-cell PD-1 led to resistance to CTL-mediated killing (73). A more generalized role for B7-H1 in regulating tumor cell survival is demonstrated by the observation that these cells were similarly resistant to Fas- or chemotherapy-mediated apoptosis. In a murine model, B7-H1 increased the survival of CD8$^+$ T cells during the contraction phase of the immune response by upregulating Bcl-x_L expression (74). Silencing of B7-H3 or B7-H4 expression have similarly been shown to increase tumor cell apoptosis (75, 76). Therefore, these ligands promote tumorigenesis by both immunologic and non-immunologic affects. Not surprisingly then, malignant cells inducibly express members of the B7-H family by a variety of different mechanisms.

B7-H expression in hematologic malignancies

Given their important immunoregulatory roles, B7-H expression is strictly regulated. For example, B7-H1 is post-transcriptionally regulated by type I and II interferons and by MyD88, JAK/STAT, TRAF6, MEK, and PI3K/AKT signaling in solid tumors (2). While B7-H1 may be similarly regulated in hematologic malignancies (9, 10, 17), both anaplastic large cell lymphoma (ALCL) and primary mediastinal large B-cell lymphoma (PMBCL) regulate the expression of B7-H family members by novel mechanisms, including chromosomal translocations and gene amplification.

A subset of ALCL harbor a novel nucleophosmin (NPM) – anaplastic lymphoma kinase (ALK) fusion protein resulting from a chromosomal translocation [most commonly t(2;5)(p23;q35)]. Constitutively active NPM-ALK is oncogenic and culminates in the activation of multiple signaling pathways, including STAT3. In ALK$^+$ ALCL, B7-H1 expression was strictly dependent upon NPM-ALK expression and activity and was attributed to NPM-ALK-dependent activation of STAT3 and its subsequent binding to the B7-H1 promoter (77). In similarly performed experiments, STAT3 was shown to bind the ICOS promoter and inhibit the expression of miR-219, culminating in ICOS expression (78). Whether NPM-ALK further regulates B7-H1 expression in a miRNA-dependent manner is unknown (79). In addition, exposure to a hypomethylating agent further increased ICOS expression owing to its effects on the putative ICOS enhancer, which is methylated in ALK$^+$ ALCL cell lines (78).

Genomic amplifications involving chromosome 9 (9p24.1) are a characteristic finding observed in over 50% of PMBCL (80). This subtelomeric region of chromosome 9 includes the genes for B7-H1 and B7-DC. Integrative analyses have clearly demonstrated that amplification at these loci results in increased expression of B7-H1 and B7-DC in PMBCL (16). Furthermore, JAK2 is also involved in this amplification and further enhances B7-H1 gene transcription in PMBCL (16). It remains to be determined whether JAK2 amplifications or mutations observed in other malignancies are associated with the induction of B7-H1 expression (81). Alternatively, recurrent translocations involving the major histocompatibility complex class II transactivator (CIITA) and the B7-H1 and B7-H2 loci are associated with overexpression of these ligands in PMBCL and classical Hodgkin lymphoma (82). These observations raise the possibility that the B7-H family may bridge oncogenic events driving tumor proliferation with the suppression of host immunity.

In contrast to ALCL and PMBCL, B7-H expression in other hematologic malignancies may be explained by derivation from a cell subset that normally expresses specific B7-H family members. Therefore, B7-H expression provides important clues about the 'cell of origin' in these hematologic malignancies.

Defining the 'cell of origin': follicular helper T-cell lymphomas

Germinal center formation is regulated by follicular helper T cells (T_{FH}), a subset of differentiated CD4$^+$ T cells regulated by the 'master' transcriptional repressor Bcl-6 [reviewed in (83)]. T_{FH} cells express chemokines (CXCL13), chemokine receptors (CXCR5), and adhesion molecules (SLAM family receptors) that permit co-localization with germinal center B cells and follicular dendritic cells (FDC). Specific cytokines (IL-4, IL-21) and cell-surface ligands (CD40L) expressed by T_{FH} promote somatic hypermutation, class-switch recombination,

and B-cell proliferation/survival leading to memory B cell and plasma cell generation. Angioimmunoblastic T-cell lymphoma (AITL) is an aggressive peripheral T-cell lymphoma (PTCL) that originates from clonally expanded T_{FH} cells [reviewed in (84)]. This is supported by gene expression profiling similarities between AITL and T_{FH} cells (85). The ontogeny of malignant T cells in AITL explains the histologic findings (varying expansion of germinal center B cells and an expanded meshwork of FDC) and clinical manifestations (polyclonal hypergammaglobulinemia, autoimmunity) characteristic of this PTCL. Malignant T cells in AITL share a common immunophenotype with T_{FH} cells, including the expression of B7-H family members PD-1(86–89) and ICOS (90–93).

ICOS and PD-1 play a critical role in T_{FH} regulation. Soon after antigen presentation by dendritic cells, ICOS costimulation induces Bcl-6, leading to T_{FH} differentiation (94). Continued ICOS costimulation, provided by germinal center B cells, is required for T_{FH} maintenance (83). Not surprisingly then, a subset of patients with common variable immunodeficiency owing to the genomic loss of ICOS have a severe loss of memory B cells and IgG (95, 96). Conversely, *Sanroque* mice harbor a missense mutation in Roguin, a negative regulator of ICOS expression, and thus develop T_{FH} hyperplasia, a robust germinal center reaction, and spontaneous autoimmunity (97). PD-1 is highly expressed on T_{FH} and may provide inhibitory signals upon engagement by B7-H1-expressing germinal center B cells. The observation that PD-1- and B7-H1-deficient mice develop increased frequencies of T_{FH} cells following vaccination is consistent with this notion. Perhaps unexpectedly, increased B-cell apoptosis and impaired generation of long-lived plasma cells was observed in PD-1- and B7-H1-deficient mice (98). This phenotype was attributed to decreased cytokine production by PD-1-deficient T_{FH}. However, reverse signaling by B7-H1 was recently demonstrated to promote T-cell survival (74), thus raising the possibility that reverse signaling by B7-H1 may similarly regulate the survival of germinal center B cells. The extent to which malignant T cells in AITL are regulated by ICOS or PD-1 signaling remains to be defined, although it was recently demonstrated that ICOS provides growth and survival signals to malignant T cells in ALK^+ ALCL (78). In addition to classic AITL, both a follicular variant of peripheral T-cell lymphoma, unspecified (PTCL-U) and cutaneous T-cell lymphoma subtypes express ICOS and PD-1 and may be derived from T_{FH} cells (91, 93, 99, 100). Furthermore, non-malignant T_{FH} cells represent an important constituent of the tumor microenvironment in some B-cell lymphomas [e.g., nodular lymphocyte-predominant Hodgkin lymphoma (101, 102) and follicular lymphoma (103–105)]. Therefore, PD-1 and ICOS are rational therapeutic targets in these lymphomas.

B7-H4 and neutropenia

While their role in the regulation of adaptive immunity is increasingly appreciated, emerging evidence suggests that B7-H family members also regulate the function of the innate immune response (106). This was illustrated by the phenotype observed in B7-H4-deficient mice. Surprisingly, these mice were resistant to infection with Listeria monocytogenes (107). This was observed within a few days of inoculation, suggesting a role for the innate immune response. Therefore, investigators examined the neutrophil response in these mice. B7-H4-deficient mice were found to mount a more robust neutrophil response following infection when compared with their normal littermates. This was explained by the inhibition of neutrophil progenitors by B7-H4. A constellation of hematologic malignancies, most obviously T-cell large granular lymphocytic leukemia (T-LGL), are associated with an expansion of cytotoxic T-lymphocytes and significant neutropenia. The association between severe neutropenia and T-LGL is well described, but its pathogenesis is poorly understood, with increased peripheral destruction as well as impaired neutrophil production being described (108–110). For example, FasL is expressed by T-LGL cells and may be cleaved from the cell surface, thus explaining the elevated levels of soluble FasL observed in the sera of patients (110). Serum from these patients may trigger neutrophil apoptosis in a Fas-dependent manner (110). While reverse signaling via B7-H4 may upregulate FasL in EBV-transformed B cells, we are unaware of any data to suggest that a similar mechanism may exist in T cells (111). T-LGL cells have also been demonstrated to suppress neutrophil colony growth in a manner that is independent of Fas/FasL interactions (109). The observation that T-LGL cells highly express B7-H4 (R.A.W. unpublished observation), in conjunction with the recently described phenotype of B7-H4-deficient mice, implicates B7-H4 in the pathogenesis of disorders associated with immune-mediated neutropenia (112–114).

Targeting B7-H: novel therapeutic approaches in hematologic malignancies

The B7-H family members are important regulators of adaptive and innate immunity in the tumor-bearing host and have non-immunologic effects that promote the survival of malignant cells. Therefore, targeting B7-H ligands with antagonistic monoclonal antibodies is rational and supported by preclinical studies performed in animal models. A phase I study of CT-011, a humanized IgG1 monoclonal antibody (mAb) that

blocks PD-1, included 17 patients with various hematologic malignancies, including nine with MDS/AML and 7 with non-Hodgkin lymphoma (41). A maximum tolerated dose was not reached in this study. Diarrhea was the most common adverse event, being observed in two patients. Grade 4 graft-versus-host disease (GVHD) developed in one of these patients who had undergone prior allogeneic transplantation for AML. Whether antibody administration may have exacerbated GVHD in this patient is unclear. Otherwise, no serious immune-related adverse events were observed in this study. A single complete remission was observed in a previously untreated patient with bulky stage III follicular lymphoma. A minimal response was observed in a single patient with AML and stable disease reported in four patients (2 CLL, 1 cHL, and 1 MM). Peripheral blood $CD4^+$ and $CD8^+$ T cells were monitored during the course of the study. A statistically significant increase in the $CD4^+$ T-cell count was observed in patients treated at higher dose levels. Lymphopenia is an adverse prognostic factor at diagnosis and is associated with disease relapse in many lymphoproliferative disorders (59, 115–121). For example, in a cohort of 149 consecutive DLBCL patients treated with R-CHOP at a single institution, the cumulative incidence of relapse was 79% for patients with an absolute lymphocyte count (ALC) $< 0.96 \times 10^9$/L at the time of follow-up (121). In contrast, the relapse rate was 6% among those with a higher ALC. In a similarly performed study including DLBCL patients following autologous stem cell transplantation, the development of new-onset lymphopenia during follow-up was associated with a cumulative incidence of relapse of 92%, compared with a cumulative incidence of relapse of only 19% for those with a higher ALC (122). PD-1 blockade may represent a novel therapeutic strategy to reverse lymphopenia and decrease the incidence of disease relapse in lymphopenic, high-risk patients. Two observations may further support this approach. First, elevated serum levels of a soluble form of B7-H1 are associated with lymphopenia in lymphoma patients (123). Finally, soluble B7-H1 was shown to promote T-cell apoptosis (124). In a phase I study conducted in patients with refractory solid tumors, tumor cell expression of B7-H1 appeared to predict the likelihood of response following PD-1 blockade with MDX-1106 (42). Theoretically, antibodies targeting B7-H1 interactions with both B7-1 and PD-1 may be superior to antibodies blocking either receptor/counter-receptor alone. A clinical trial in hematologic malignancies using a B7-H1 targeting antibody (BMS-936559) is planned (http://www.clinicaltrials.gov). The identification of predictive biomarkers will be important in the selection of patients for therapeutic strategies targeting the B7-H1/PD-1/B7-1 axis.

Allogeneic transplantation is frequently considered for patients with various high-risk or relapsed hematologic malignancies. The goal of allogeneic stem cell transplantation is the generation of a robust graft-versus-leukemia (GVL) response. Unfortunately, concomitant graft-versus-host disease (GVHD) is a frequent complication that contributes to significant morbidity and mortality. Recent work demonstrates that therapeutic manipulation of B7-H family members may promote the GVL response (10, 125–127), leading to the eradication of minimal residual disease, and prevent GVHD (128, 129). For example, B7-H1 expression by residual leukemic blasts confers resistance to T-cell mediated eradication and may thus promote immune evasion and disease recurrence following allogeneic stem cell transplantation (126, 127). In a murine model, B7-H1 blockade restored the GVL effect following the adoptive transfer of leukemia-specific T cells without exacerbating GVHD (128). This data should be interpreted cautiously, however, as PD-1 was shown to inhibit GVHD in another model (130). These studies raise the possibility that manipulation of B7-H family members may augment the GVL response without exacerbating GVHD and may thus increase the therapeutic index associated with allogeneic stem cell transplantation.

The significant survival advantage observed in many lymphoproliferative disorders following the introduction of rituximab highlights the important role of mAb-mediated targeting in these malignancies. These antibodies mediate ADCC, complement-dependent cytotoxicity, or have direct apoptotic affects. As B7-H1 impairs NK-cell-mediated ADCC, therapeutic strategies targeting B7-H1 may be rationally combined with targeting mAb, like rituximab (49–51).

Conclusions

Members of the B7-H family are widely expressed by malignant cells, and within the tumor microenvironment, in many hematologic malignancies. Inhibitory B7-H ligands promote the suppression of host anti-tumor immunity while those with stimulatory functions may directly stimulate the growth and survival of malignant cells. It is anticipated that further clarification of their pathogenic role in hematologic malignancies will have significant implications for the classification and risk stratification of these disorders. The development of novel therapeutic strategies targeting the B7-H family in hematologic malignancies is warranted.

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