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FOCUSSED RESEARCH REVIEW

The expression, function, and clinical relevance of B7 family members in cancer

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Abstract The modulation and suppression of anti-tumor immune responses is a characteristic feature of tumor cells to escape immune surveillance. Members of the B7 family are involved in this process, since the level of activation of the anti-tumor immune response depends on the balance between co-stimulatory and co-inhibitory signals. Some molecules are often overexpressed in tumors, which has been associated with the pathogenesis and progression of malignancies as well as their immunological and non-immunological functions. The B7 homologs play a key role in the maintenance of self-tolerance and the regulation of both innate and adaptive immunity in tumor-bearing hosts. Furthermore, the blockade of negative signals mediated by the interaction of co-inhibitory ligands and counter-receptors of the B7 family is currently being studied as a potential immunotherapeutic strategy for the treatment of cancer in humans.

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Abbreviations

ALL	Acute lymphoblastic leukemia
BTLA	B and T lymphocyte attenuator
CTL	Cytotoxic T lymphocyte
CTLA4	Cytotoxic T lymphocyte-associated antigen 4
CR	Complete remission/response
CTL	Cytotoxic T lymphocyte
HLA	Human leukocyte antigen
ICOS	Inducible co-stimulatory molecule
IFN	Interferon
JAK	Janus kinase
mAb	Monoclonal antibody
MAPK	Mitogen-activated protein kinase
MDS	Myelodysplastic syndrome
MDSC	Myeloid-derived suppressor cell
MHC	Major histocompatibility complex
MZL	Marginal zone lymphoma
NK	Natural killer cell
NSCLC	Non-small cell lung cancer
OR	Objective response
PR	Partial response
PTEN	Phosphatase and tensin homolog
RCC	Renal cell carcinoma
STAT	Signal transducer and activator of transcription
T-ALL	T cell lymphoblastic leukemia
TAM	Tumor-associated macrophage
TCR	T cell receptor
TLR	Toll-like receptor
TNF	Tumor necrosis factor
Treg	Regulatory T cell
SD	Stable disease

Co-stimulatory signaling plays an important role in the initiation and termination of immune cell responses by regulating the T cell priming, growth, maturation, and tolerance. Effective activation of naïve T cells requires two signals: The first is mediated by the recognition of an antigen presented via the major histocompatibility complex (MHC) on antigen-presenting cells (APC) by a corresponding antigen-specific T cell receptor (TCR) and the second is provided by the delivery of a co-stimulatory signal by binding of co-stimulatory molecules to their receptors.

The co-stimulatory pathways have recently gained interest and have been extensively investigated, since they represent elegant strategies to modulate T cell responses in autoimmune diseases, viral infections, and cancers, which are currently therapeutically exploited. In the absence of co-stimulation, the contact between the T cell receptor (TCR) and the human leukocyte antigen (HLA)-presented antigen will result in dysfunction or anergy of T cells, creating an immunological antigen-specific tolerance. In addition, some classical co-inhibitory molecules are also expressed on immune cell populations and may contribute to the escape of tumors to T cell response.

Therefore, it is of interest to understand the balance of co-stimulatory and co-inhibitory molecules, which provide attractive targets to modulate T cell-dependent immune responses in various diseases. In addition, beyond mere co-stimulation/co-inhibition, several components of these pathways can provoke cellular responses without the requirement of antigen presentation and even on a variety of immune cells that may modulate the course of the disease. Augmenting specific anti-tumor T cell responses by blocking the co-inhibitory signals might release the brakes on immune responsiveness leading to tumor elimination.

The following review will therefore focus on the T cell-dependent and -independent involvement of the major co-stimulatory/co-inhibitory components of the increasing group of B7 family members and their important downstream signaling pathways in the pathogenesis of tumors as well as highlights their potential for the treatment of cancer.

The characteristics of the B7 family

The best characterized co-stimulatory pathway includes members of the growing B7-CD28 superfamily, which are involved in both co-stimulatory and co-inhibitory processes. The B7 superfamily comprises the receptor ligand pairs CD28/CTLA4:B7-1 (CD80)/B7-2 (CD86), ICOS:ICOS-L; PD1:PD-L1/PD-L2; B7-H6:NKp30 [1–6].

For the B7-H3 and B7-H4 (also known as B7x or B7S1) molecules, no human receptors have been so far identified (Fig. 1) [7, 8]. The processes that are initiated upon interaction of the specific receptors with their respective ligands play important roles in the regulation of T cell activation or in the induction of tolerance. These different pathways not only provide critical positive secondary signals that produce and sustain T cell responses, but also contribute to negative signals. It has been suggested that

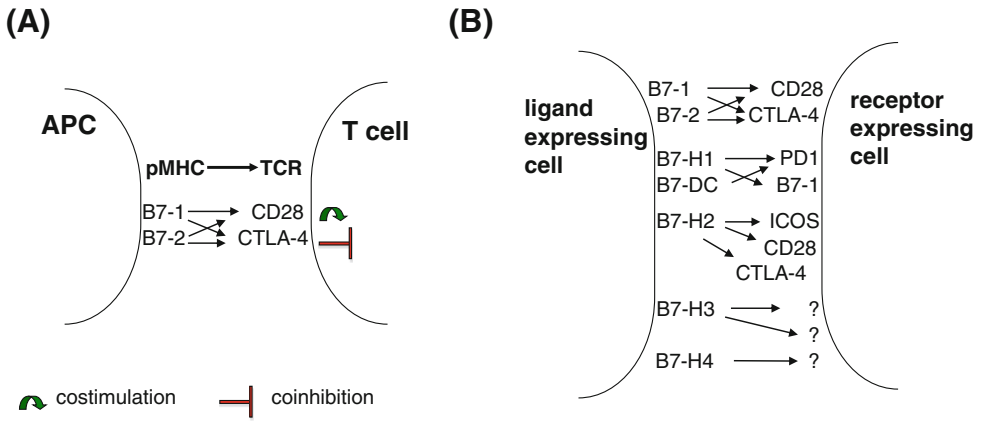

Fig. 1 Co-stimulatory and co-inhibitory molecules of the B7 family and their receptors. **a** The classical view of co-stimulation: the first signal originates from pMHC–TCR binding of APC and T cells, and the second signal is provided by co-stimulatory molecules of the B7 family that tune the immune response by generating either co-stimulatory (B7-1/2-CD28 interaction) or co-inhibitory signals (B7-1/2-CTLA-4 interaction) to T cells. **b** Extension of the classical view: the recently identified, novel B7 family members are widely expressed on different immune cells and/or on cells of non-hematopoietic origin. Within immune cell populations, the B7 family member = ligand expressing cells are not only professional APC (like DC, monocytes, and macrophages), but also B cells, T cells, NK cells, and mast cells. In addition, also mesenchymal stem cells and cells of non-hematopoietic origin do constitutively express some of these molecules. B7 family members are membrane-bound molecules (soluble forms of B7-H1, -H-2, -H-3, and -H-4 exist) that exert their biological function by binding their respective receptors. Receptor-expressing cells are mainly $CD4^+$ and $CD8^+$ T cells, but also B cells, NK cells as well as cells of myeloid origin.

the negative regulation is critical for immune homeostasis and that the interaction of co-inhibitory receptors with their respective ligands induces a negative feedback regulation after the activation of T cells. Thus, they can modulate immune responses by limiting, terminating, and/or attenuating T cell responses and induce either anti-tumor responses or tumor immune escape mechanisms. In general, B7-H molecules primarily execute their functions in peripheral tissues to attenuate immune responses in target organs/tissues [9].

The prototype of co-stimulatory molecules is represented as the B7-1 and B7-2 molecules, which have been described more than two decades ago [10, 11]. Upon binding to their receptor CD28, T cell activation and survival is promoted, while in the absence of the co-stimulatory signal, the ligation of the TCR with the HLA/peptide antigen results in T cell dysfunction and anergy. In addition to the positive co-stimulatory signal augmenting and sustaining T cell responses, co-inhibitory signals could be delivered, which down-regulate T cell activity. Binding of B7-1 or B7-2 molecules to their inhibitory receptor, the cytotoxic T lymphocyte-associated antigen 4 (CTLA4) inhibits T cell responses by blocking IL-2 synthesis and cell cycle progression thereby inducing peripheral tolerance. Thus, CTLA4 constitutes a T cell-intrinsic control mechanism as it competes with CD28 for B7-1 and B7-2 without activating T cells.

In contrast to the defined roles of B7-1 and B7-2 in T cell activation, the function of the novel members of the B7 family has not yet been well characterized. The inducible co-stimulatory receptor (ICOS, CD278) and its respective ligand (ICOS-L, CD275, B7-H2) represent another member of the B7 co-stimulatory molecules [2, 12]. While ICOS is not constitutively expressed on naïve T cells, it could be induced on effector T cells upon activation. Like CD28/B7-1/B7-2, the ICOS/B7-H2 interaction induces cell proliferation, differentiation, and secretion of Th1 and Th2 cytokines. When analysed in highly polarized T cell lines, ICOS blockade reduced the production of Th2, but not of Th1 cytokines [13]. Thus, the ICOS/B7-H2 signal may favor Th2-type responses. Since ICOS has also been found to be constitutively expressed on regulatory T cells (Treg), it exerts a dual role on immune modulatory processes. Recently, B7-H2 has been identified as a ligand of CTLA4 and CD28 on human cells [14].

The programmed death ligands 1 (B7-H1, PD-L1, CD274) and 2 (B7-DC, PD-L2, CD273) belong to the group of co-inhibitory molecules of the B7 family. B7-H1 and B7-DC exert a 41 % amino acid homology [1] and interact with the PD-1 receptor on activated T cells, B cells, and myeloid cells. While B7-H1 is constitutively or upon activation expressed in different cell types including hematopoietic cells, such as B cells, T cells, dendritic cells (DC), and macrophages, but also in non-lymphoid cells, like heart, lung, placenta, kidney, and liver [3], B7-DC expression is more restricted and mainly found in lymphoid tissues and DC. Recently, the importance for B7-H1 expression on activated $CD8^+$ T cells for their survival and anti-tumor immunity has been demonstrated in mice [15]. B7-H1 induces apoptosis of activated T cells and hinders tumor-specific killing of $CD8^+$ cytotoxic T lymphocytes when expressed on tumor cells [16], while Latchman et al. [4] reported that B7-H1 and B7-DC interaction with PD1 inhibited T cell proliferation by blocking cell cycle progression, but not by increasing cell death.

B7-H3, a B7 homolog sharing approximately 31 % sequence homology with B7-H1, is a type I trans-membrane protein. Despite B7-H3 is broadly transcribed in lymphoid and non-lymphoid organs, its protein expression is more limited. However, the broad expression pattern of B7-H3 suggests not only a more diverse immunological, but also non-immunological function of this molecule. Two possible receptors have been postulated for B7-H3 on T cells, one that gives rise to activating signals, whereas the other exerts inhibitory signals (2). Furthermore, the function of B7-H3 is controversially discussed since both co-stimulatory and co-inhibitory properties have been described for this molecule [7, 17]. B7-H3 could enhance the proliferation of $CD4^+$ and $CD8^+$ T cells, induce cytotoxic T lymphocytes (CTL), and stimulate interferon (IFN)-γ secretion [7], while it has also been shown to inhibit $CD4^+$ and $CD8^+$ T cell proliferation and IFN-γ production in mice and man [17, 18].

Like B7-H3, B7-H4 is a type I trans-membrane molecule, which exerts a 20 % amino acid homology in the extracellular region with other B7 molecules. It is broadly transcribed in human tissues and cells including lung, testis, pancreas, placenta, intestine, stomach, kidney, liver, brain, and ovary, while protein expression is limited [19]. Furthermore, B7-H4 is not constitutively expressed on naïve T and B cells, but it can be modulated by various cytokines or during the differentiation process of APC. While IL-6 and IL-10 induce B7-H4 expression, GM-CSF and IL-4 decrease and TNFα counteracts the IL-10-induced expression [20, 21]. Until now, the receptor of B7-H4 has not yet been identified, although the B and T lymphocyte attenuator (BTLA4) had been postulated as its receptor [22], which could not be confirmed by binding studies [23]. Analogous to B7-H1, B7-H4 negatively interferes with immune responses and blocks T cell proliferation and IL-2 production [8].

The B7-H6 represents the newest member of the B7 family and exerts a sequence homology comparable to that of other B7 members. B7-H6 binds to the NK cell receptor NKp30 and could trigger NK cell mediated to toxicity and cytokine secretion. B7-H6 expression is absent in normal untransformed tissues [6].

In addition to the membrane-bound ligands, soluble B7-H (sB7-H) molecules have been detected, which are mainly involved in pathophysiologic processes and are released by different cell types. sB7-H1 is secreted by mature DC, but not by immature DC, T cells, monocytes, or macrophages, and induces apoptosis when incubated with $CD4^+$ or $CD8^+$ T cells [24]. sB7-H2 is detectable at elevated levels in patients with lupus erythematosus [25], whereas elevated sB7-H3 levels were found in the sera of patients with chronic hepatitis B virus infections and higher levels were associated with increased risk of liver cirrhosis [26]. Additionally, sB7-H3 has been detected in the supernatant of monocytes, DC, and activated T cells and binds the unknown B7-H3 receptor, which opens novel interesting immune regulation pathways [27]. sB7-H4 is described in disease settings, such as autoimmune disease and tumor. In rheumatoid arthritis (RA), serum levels of sB7-H4 are high and correlate with DAS activity, and in a mouse model of RA, a function for sB7-H4 as decoy could be demonstrated as it blocks the membrane-bound B7-H4 binding and thereby exacerbating autoimmunity [28].

B7-H molecule expression on tumors

Although initially discovered as membrane-bound ligands in myeloid lineage cells and activated T and B cells, tumors could aberrantly express several types of B7-H molecules (Table 1). The best studied B7-H family member in tumors is B7-H1. B7-H1 is expressed on a variety of solid and hematopoietic malignancies including breast, bladder, lung, colon, pancreatic, gastric, skin, esophagus, liver, ovary, brain, and kidney cancers, Hodgkin lymphoma; acute myeloid leukemia; and myelodysplastic syndromes [16, 29–44]. In contrast, B7-DC has not yet been analyzed in a large series of tumor samples, but the frequency of B7-DC expression in human tumors appears to be low and not associated with clinical outcome. In contrast to the high frequency of B7-H1 expression in human tumors, B7-H2 expression has been mainly detected in cells of hematologic malignancies [45].

B7-H3 expression has also been found on a variety of human tumors including prostate, non-small lung, pancreatic, gastric, endometrial, skin, colorectal, and urothelial cancer as well as RCC [46]. The frequency of B7-H3 expression in human tumor strongly varied between the tumor entities analyzed, ranging between 17 and 100 % [47, 48].

B7-H4 expression was detected in a large variety of tumors of distinct origin, including melanoma, non-small cell lung, prostate, ovary, stomach, pancreas, breast, esophagus, and kidney cancer [48–56]. Immunohistochemical analysis of B7-H4 revealed a heterogeneous expression in tumor types of distinct origin with a frequency ranging between 15 and 100 % [50, 51]. Interestingly, B7-H4 was preferentially expressed in non-dividing tumor cells and in a subset of $CD133^+$ stem cells [57]. The discordant mRNA and protein levels suggest a post-transcriptional control of B7-H4 expression in human tumors.

B7-H6 expression was detected with a relative abundance in tumor cells of distinct origin, but not in normal tissues. B7-H6 was found on different hematologic and solid tumor cells lines and interacts with NKp30 on NK cells, thereby activating NK cells to control tumor cells (Fig. 2 and [6]).

In addition, soluble B7-H (sB7-H) ligands have been detected in sera of tumor patients (Table 2). For example, sB7-H1 and sB7-H4 have been found in the sera of RCC patients [58, 59], while sB7-H3 and sB7-H4 are discussed as prognostic biomarkers for NSCLC (sB7-H3), ovarian, and renal cell cancer (sB7-H4) [59–61].

Of note, as described in the previous chapter, not only tumor cells, but also immune cells could release sB7-H molecules during immune responses including anti-tumor immune reactions. Therefore, the source of sB7-H molecules in the sera of tumor patients is not necessarily exclusively derived from tumor cells.

In this context, it is noteworthy that the function and clinical significance of the sB7-H expression still remain to be determined. Although, it has been suggested that sB7-H molecules independent of their source deliver inhibitory signals that adversely affect anti-tumor responses.

Indeed, expression of B7 family members in non-tumor cells of the tumor microenvironment has been found [62].

Clinical relevance of B7 homolog expression

In order to determine the clinical relevance of the expression of B7 homologs in cancer, their expression levels in tumors, in cells of the tumor microenvironment or the concentration of sB7-H in patients' serum should be correlated with clinical parameters. Due to the higher expression levels of B7-H1 and B7-H4 in cancer tissues when compared to corresponding normal tissues and their close correlation with tumor stage, grade, pathologic types, and the biologic behavior of tumors, recurrence and survival rate of patients, these molecules might be used as potential diagnostic, prognostic, and predictive markers, for monitoring of treatment efficacy as well as for therapeutic targets. However, the expression pattern of the various B7-H family members has still to be investigated on a larger number of well-defined samples from different tumor types in different centers using the same protocols and antibodies.

The prognostic relevance of B7-H1 expression is in many different tumor entities high, but in some tumor

Table 1 B7 family member expression on tumor cells (lesions) of different tumor entities and functional consequences

B7 family member	Number pos. cases/ total sample number	Tumor entity	Immunological and pathophysiologic consequences
B7-H1	14/78	AML (acute myeloid leukemia)	Protected from CTL-mediated lysis upon TLR trigger, stronger expression upon relapse [43]
	65/65	Bladder urothelial carcinoma	Strong expression correlates with relapse and poor survival [31]
	77/280		High-grade tumors with increased cell infiltration [67]
	41/69	Breast cancer	High-risk grading, Ki-67 expression [30]
	13/31	Esophageal cancer	Associated with poor prognosis [36]
	43/102	Gastric carcinoma	Correlated to tumor size, invasion, LN metastasis, and survival [34]
	36/48	Glioma	Associated with tumor malignancy [40]
	60/60	Hepatocellular carcinoma	High expression associated with tumor IL-10 [37]
	8/61	Myelodysplastic syndrome	Associated with high-risk patients [44]
	5/43 prim.	Melanoma	No difference in overall survival and immune infiltrates [66]
	8/20 t meta.		
	59/59		Strong expression 34/59 correlates with Breslow and overall survival [35]
	24/56		Longer overall survival in strong B7-H1-expressing melanoma, more TILs in B7-H1 + cases [114]
	52/52	NSCLC	Focal expression, no clinical association, but less TILs in B7-H1 + regions [32]
	58/109		Associates with histological types and with reduced overall survival [63]
	62/70	Ovarian cancer	High expression correlates with poor prognosis [38]
	22/40	Pancreatic cancer	Correlates with poor tumor differentiation and advanced tumor stage [33]
	40/81		Strong expression correlates with TNM status and poor survival [64]
	130/196 prim.	RCC	Associates with likelihood of death [65]
	17/26 meta.		
	73/306		Correlates with increased risk of death [41]
B7-H2	9/59	AML	Poor survival [45]
B7-H3	55/102	Colorectal cancer	Correlates with more advanced tumor grade [115]
	60/102	Gastric carcinoma	Associated with longer survival and penetration depth [68]
	ns/107	Endometrial cancer	High expression associates with shorter survival [71]
	29/29 prim.	Melanoma	No impact on clinical parameter [48]
	28/29 meta.		
	26/70	NSCLC	Associated with reduced numbers of TILs and enhanced LN metastasis [49]
	60/68	Pancreatic cancer	Correlates with prolonged survival [69]
	212/823	Prostate cancer	Associated with cancer recurrence and death [50]
	67/338		Fourfold increased risk of cancer progression after surgery [70]
	126/743	RCC	Associated with increased risk of death [47]

Table 1 continued

B7 family member	Number pos. cases/ total sample number	Tumor entity	Immunological and pathophysiologic consequences
B7-H4	165/173 prim.	Breast cancer	Associated with negative hormone receptor status, independent of tumor stage and grade [54]
	240/246 meta.		
	107/112	Esophageal cancer	Strong expression associated with shorter survival [55]
	70/156	Gastric cancer	Correlates with shorter overall survival [52]
	28/29 prim.	Melanoma	Strong expression correlates with shorter overall survival [48]
	26/29 meta.		
	30/70	NSCLC	Associated with reduced numbers of TILs and LN metastasis [49]
	59/59 prim	Ovarian cancer	ND [51]
	30/30 meta		
	ns/70		Tumor cell expression is not associated with clinics [98]
	33/36	Pancreatic cancer	ND [53]
	120/823	Prostate cancer	Associated with cancer recurrence and death [50]
	153/259	RCC	Associated with tumor size, stage, grade, positive patients are 3 times more likely to die [56]
B7-H6	5/43	Acute lymphoblastic leukemia, T cell lymphoblastic leukemia, marginal zone lymphoma	ND [6]

ALL acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *MDS* myelodysplastic syndrome, *MZL* marginal zone lymphoma, *ND* not determined, *prim* primary tumor, *t meta* in transit metastasis, *LN* lymph node, *ns* not specified, *RCC* renal cell carcinoma, *T-ALL* T cell lymphoblastic leukemia

entities controversial results were reported. For example, a significant prognostic value of B7-H1 was found in melanoma, bladder, esophageal, gastric, non-small cell lung cancer (NSCLC), ovarian, pancreatic, and kidney carcinoma [34–36, 38, 43, 63–65]. Discrepant results concerning the number of B7-H1-expressing tumor cases and clinical relevance were found in melanoma [66] and NSCLC [32], which might be at least partially explained by the samples investigated (frozen vs. paraffin embedded) or the antibodies used for the studies. The B7-H1 overexpression in tumor cells was associated with tumor grading and staging in glioma, bladder, breast, and pancreatic cancer [30, 33, 40, 67]. Furthermore, sB7-H1 has been detected in blood samples from tumor patients. In RCC patients, high sB7-H1 levels were associated with an increased risk of death and thus correlate with a poor clinical outcome [58].

Furthermore, for B7-H2, a prognostic relevance has been shown for acute myeloid leukemia [45]. B7-H2 expression is associated with a poor survival of patients, which may be due to stimulation of Tregs or even due to binding of the newly identified partner CTLA-4 [14], thereby dampening anti-tumor responses.

The impact of B7-H3 expression on clinical outcome highly depends on the tumor entity analyzed. Retrospective analyses demonstrated that high levels of B7-H3 expression on the tumor were associated with a prolonged patients' survival in, for example, gastric and pancreatic cancer [68, 69]. In contrast in RCC, prostate, endometrial, and non-small cell lung carcinoma (NSCLC), an opposite effect was observed, since tumor B7-H3 correlated with an increased risk of death, a higher frequency of recurrence, poor survival of patients, and/or with lymph node metastasis [47, 49, 50, 70, 71]. sB7-H3 in patients with NSCL was also associated with a higher tumor stage, tumor size, and metastasis formation [60].

Most of the studies revealed a correlation between B7-H4 expression on the tumor or in the blood of patients and the TNM stage, pathologic types, patients' prognosis, and survival [72]. These data suggest that B7-H4 represent a potential prognostic and predictive marker for some tumor entities, such as melanoma, esophageal, gastric, prostate, and renal cancer [48, 50, 52, 55, 56]. In addition to membrane-bound B7-H4, sB7-H4 appears to be also of prognostic relevance at least in ovarian and renal cancer and might serve as prognostic marker in both diseases [59, 73].

So far, there exist no data on the clinical significance of B7-H6, but its tumor-specific expression indicates an up-regulation due to a neoplastic transformation [6].

In addition to the correlation of aberrant expression of B7-H molecules with the clinical outcome of patients,

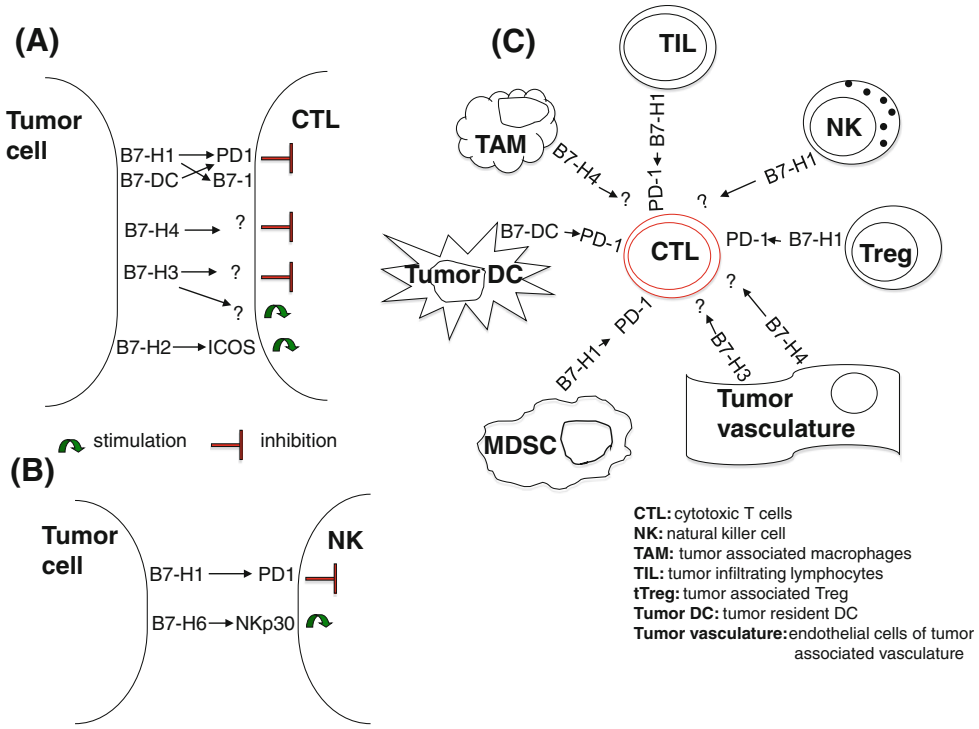

Fig. 2 B7-H expression and function on tumor cells and on cells of the tumor microenvironment. **a** Tumor cells of different origin do express B7 molecules and inhibit (B7-H1, B7-DC, B7-H4, partially B7-H3) or stimulate (B7-H2, partially B7-H3) T cell functions upon cognate receptor binding on cytotoxic T lymphocytes (CTL). **b** Tumor cells also express the more recently identified B7 family member B7-H6. This molecule binds NKp30 on NK cells. NKp30 belongs to the activating NK receptors. B7-H6 binding leads to stimulation of NK cells. NK cells can also express PD-1 and interact with B7-H1 on tumor cells. **c** Many different cell populations belong to the tumor microenvironment and possibly contribute to the control of tumor cells. These cells do also express members of the B7 family, for example, B7-H1 can be found on MDSC, NK cells, Treg, and TILs in the tumor microenvironment. Tumor DC can express B7-DC. TAM and endothelial cells of the tumor vasculature can express B7-H4. B7-H3 can also be found on the tumor vasculature. All of these molecules can interact with the cognate receptor on T cells, thereby mostly inhibiting T cell function with the exception of B7-H1 on NK cells, which stimulates CTL activity

polymorphisms in CD28, ICOS, and CTLA4, which have been shown to influence the protein expression level, were associated with malignancies [74–76].

Molecular mechanisms of aberrant expression of B7 homologs in tumors

So far, little is known about the control of B7 expression in human tumors. It has recently been shown that the regulatory mechanisms of B7-H1 are not uniform, and many signaling pathways are involved in its regulation. Normal human cells contain B7-H1 transcript, but marginally express or lack B7-H1 protein. IFN-γ resulted in an induction of B7-H1, suggesting that the JAK/STAT pathway is involved in the IFN-γ-mediated up-regulation of B7-H1 [77]. Not only IFN-γ, but also TNF-α, could up-regulate B7-H1 expression, which is mediated by the activation of NF-κB [44]). In addition, B7-H1 expression could be post-transcriptionally increased after the loss of the tumor suppressor gene (phosphatase and tensin homolog PTEN) function, which is dependent on the PI3K pathway and S6K1 kinase activation [39]. In PTEN-deficient tumors, IFN-γ treatment resulted in a super-induction of B7-H1 protein [78]. The dependence of B7-H1 on the PI3K pathway and S6K1 kinase could also be confirmed in breast and prostate cancer specimens [79]. Furthermore, the B7-H1 expression could be enhanced via the MyD88-, TNFR6 (tumor necrosis factor receptor-associated factor 6)-, and MEK-dependent pathways after stimulation with IFN-γ and toll-like receptor ligands [80]. In some tumors, the B7-H1 expression is controlled by the MEK/ERK and STAT3 pathway [81], while the MEK/ERK and the p38 mitogen-activated protein kinase (MAPK) pathways participate in the regulation of B7-H1 in other tumor entities [42].

In contrast, the expression of B7-H1 and other B7-H-family members could also be regulated by other mechanisms including structural alterations, for example, polymorphisms and mutations, transcriptional, post-transcriptional, and epigenetic control [82, 83]. In hematopoietic malignancies,

Table 2 B7 family member expression on non-tumor cells and in sera of tumor patients and their functional significance

B7 family member	Specimen	Number pos. cases/total sample number	Tumor entity	Immunological and pathophysiological consequences
B7-H1	TIL	18/44	Breast cancer	Associated with tumor size, grade, and HER-2/neu positivity [116]
	Serum	165/172	RCC	High sB7-H1 levels are correlated to advanced stage and grade and higher risk of death [58]
	TIL	115/196		More aggressive tumors and increased risk of death [117]
B7-H3	Blood	95/95	Gastric cancer	Elevated B7-H3 mRNA level correlates with stage and shorter 5-year survival [118]
	Serum	98/98	NSCLC	Elevated sB7-H3 is associated with tumor stage, size, and metastasis, potential use as biomarker [60]
	Tumor vasculature	37/77	Ovarian cancer	Associated with shorter survival and higher incidence of recurrence [97]
		706/743	RCC	Strong expression associated with increased risk of death [47]
B7-H4	TAM	ns/70	Ovarian cancer	Associated with higher Treg infiltrates and shorter survival [98]
	Tumor lysates	156/251		Associated with poor prognosis [61]
	Serum	268/268		Elevated sB7-H4 levels, potential use as biomarker [73]
	Serum	53/101 pat.	RCC	Elevated sB7-H4, potential use as biomarker,
		18/101 con.		B7-H4 concentration correlates with tumor stage [59]

TAM tumor-associated macrophages, *ns* not specified, *pat.* patients, *con.* control, *TIL* tumor-infiltrating lymphocytes

chromosomal translocations, gene amplifications, hypermethylation, and microRNA control the B7-H expression [84–87].

The immunologic and non-immunologic function of B7 homolog expression in tumors and the tumor microenvironment

Although the functional role of B7-H expression in tumor cells remains unclear, the aberrant expression of B7-H molecules could be associated with both an increased resistance to immune and pharmacological attack. In in vitro assays, B7-H molecules could inhibit T cell proliferation, cytokine secretion, and the induction of CTL [29]. In in vivo assays, the frequency of T cell infiltration and B7-H expression do not always correlate. An association between B7-H4 expression and T cell infiltration has been reported for some tumor types, for example, NSCLC [49], whereas it was not found in melanoma [48].

In addition to the immunological effects, B7-H1, -H3, and -H4 could regulate tumor cell survival. Thus, these ligands are able to promote tumorigenesis and exert not only immunologic, but also non-immunologic activities.

During the past decade, cancer-related inflammation and the avoidance of immune destruction have been recognized as hallmarks of cancer and play an important role in the tumor development. The effect of tumor invasion, recurrence, and metastasis was investigated by the in situ analysis of immune components. A heterogeneous immune cell infiltration was shown between the different tumor types analyzed and is further diverse from patient to patient. All major immune cells might be present in the tumor including macrophages, DC, naïve and memory B cells, and various subsets of effector T cells and regulatory T cells [88]. In the absence of B7-1 co-stimulation and during low antigen stimulation, which is a situation most likely comparable to the tumor microenvironment, repetitively stimulated $CD8^+$ T cells could become susceptible to inhibition by PD1/PD-L1 interaction [89].

Tumor-associated macrophages (TAM) represent a component of cancer-related inflammation and are involved in tumor growth, angiogenesis, invasion, and metastasis [90]. The B7-H1 expression on hepatocellular carcinoma was up-regulated by TAM, which was dependent on the STAT3 and NF-κB signaling [91]. Furthermore, the tumor microenvironment also constitutes of dysfunctional (e.g., $CD4^+$, $CD8^+$ T cells, and DC) and suppressive immune cells like Treg and myeloid-derived suppressor cells (MDSC), which provide a milieu for tumors to evade anti-tumor immunity [92].

B7-H1 expression in tumor cells increased the apoptosis of tumor-reactive T cells [16]. Recent studies showed that the engagement of B7-H1 leads to a down-regulation of T cell immunity, whereas B7-DC could enhance anti-tumor immunity [93]. The B7-DC-related anti-tumor immunity

might depend on a PD-1-independent mechanism [94]. B7-H1 and B7-DC could be expressed on non-transformed cells of the tumor micromilieu, including tumor-infiltrating lymphocytes, NK cells, Treg, MDCS, and tumor-associated DC (Fig. 2). In addition, the number of tumor-infiltrating immune cells, in particular $CD8^+$ T cells, could be increased by using blocking antibodies directed against B7-H1, while antibody-mediated inhibition of B7-DC decreases the number of Tregs. One can speculate that the B7-DC blockade might regulate the suppressive effect of Treg on effector T cells by inhibiting the migration of Treg into tumor cells and thus the direct contact with effector T cells and decrease the intratumoral IL-10. Alternatively, B7-DC might be involved in the expansion of Treg [95]. Furthermore, NK cells also do express PD-1. B7-H1 on multiple myeloma cells interacts with PD-1 on NK cells, thereby restricting the NK cell-mediated anti-tumor response [96]. Thus, tumors could escape anti-tumor immunity by three independent B7-H1/B7-DC controlled mechanisms: decrease in IFN-γ-producing effector T cells by B7-H1, an increase in Treg by B7-DC, and reduced NK cell response.

B7-H3 and B7-H4 expression was found on endothelial cells of the tumor-associated vasculature in ovary cancer and RCC [56, 97], but the underlying molecular mechanisms leading to the aberrant expression of both B7-H molecules have still to be defined. B7-H3-positive tumor vasculature in ovarian carcinoma was associated with a shorter survival of patients and higher incidence of recurrence [97]. These data suggest that one had to destruct or block the tumor vasculature-associated B7-H3 and B7-H4 expression, which might provide a benefit for T cell-based anti-tumor immunity. It is noteworthy that tumor-derived Treg could trigger macrophages to produce IL-6 and IL-10, which are able to stimulate APC to express B7-H4 in an autocrine or paracrine manner [98]. Even more important, B7-H4 expression on TAM is associated with higher frequency of Treg infiltrates and shorter survival of patients [98].

Potential role of B7 molecules regarding their clinical application

Based on the frequency of the expression of co-stimulatory and co-inhibitory molecules on tumors cells and their role in disease development and progression, it could be hypothesized that the expression of a respective B7 co-inhibitory molecule represents an immune escape mechanism by down-regulating the anti-tumor immunity, in particular the T cell response at the level of effector cells. Thus, these molecules might serve as attractive targets for tumor immunotherapy. Since B7-H1 and B7-H4 molecules block T cell function, their inhibition may offer an opportunity to enhance anti-tumor immunity. Targeting co-inhibitory molecules of the B7 family with antagonistic antibodies is a rational approach and has been confirmed by animal experiments. The profound importance of CD28, CTLA4, and PD-1 for the induction of immune tolerance has further led to the development of several human drugs that target the co-stimulatory/co-inhibitory pathways.

Recently, the blockade of the most extensively studied co-inhibitory molecule, CTLA4, has been studied in tumor patients with advanced disease (Table 3). The approval and implementation of fully human anti-CTLA4 monoclonal antibody (mAb) (ipilimumab) that binds to CTLA4 and thus inhibits the binding to B7 for the treatment of patients with metastatic melanoma is an example of a targeted immune-modulatory agent [62, 99, 100]. This treatment resulted in an enhanced recruitment of memory $CD4^+$ and $CD8^+$ T cells, objective tumor regressions, and durable responses both in murine model systems as well as in humans with an extension of the life span of stage 3–4 melanoma from a median of 6.4–10 months [101]. Additionally to melanoma patients, prostate and renal cancer patients also responded to anti-CTLA-4 Ab therapy [102, 103]. As expected from the CTLA4 knock-out mice, which exert an uncontrolled lymphoproliferation, the anti-CTLA4 mAb therapy in humans was associated with severe immunologic side effects. Therefore, additionally, alternative checkpoints with a more favorable profile should be envisaged.

Blocking of the B7-H1 signaling pathway might also represent a promising approach to improve the efficacy of anti-tumor immune responses. Indeed, two fully human-blocking anti-PD1 antibodies (MDX-1106, CT-011) have been developed and are currently tested in clinical trials [104–107]. The antibody administration is well tolerated, and there exists evidence of anti-tumor activity [104]. In experimental models, systemic disruption of PD1 caused autoimmune diseases, while short-term administration exerts no side effects. A more targeted strategy was developed by selective disruption of the PD1 signaling using PD1-specific siRNA, which prevents PD1 expression on the cell surface [108]. The reduced PD1 expression led to improved T cell functions and thus might achieve a long-lasting enhancement of tumor-specific T cell responses.

Antibodies targeting B7-H1 and B7-H3 for use in humans have been developed. There is an initiated clinical trial as phase I multicenter study, still in the patient recruitment phase, with anti-B7-H1 antibody (MDX-1105) for therapy of multiple cancers (web: National Cancer Institute: Clinical trials). Additionally, there is a recruiting phase I study with anti-B7-H3 antibody (MGA271) for therapy of multiple refractory cancers that express B7-H3 (web: National Cancer Institute: Clinical trials).

Table 3 Therapeutic approaches targeting B7 family members or their receptors in anti-tumor therapy

Therapeutic strategies	Therapeutic agents	Tumor patients	Clinical outcome
Antibodies	Anti-CTLA-4 (Ipilimumab, MDX-010, BMS-734016)	Melanoma	2/137 complete response (CR), 13/137 partial response (PR), 24/137 stable disease (SD) [101]
		Prostate Cancer	2/14 PR [102]
		RCC	6/41 OR [103]
	Anti-CTLA-4 (Tremelimumab, CP-675206)	Melanoma	4/29, 2x PR, 2x CR [119]
	Anti-PD-1 antibody (MDX-1106)	Mixed tumor entities	5/39 Mixed, PR or CR [104]
		Melanoma	15/46 PR [105]
		RCC	7/19 PR or CR [106]
	Anti-PD-1 antibody (CT-011)	Mixed advanced hematological malignancies	Clinical benefit in 6/17 patients, 1 CR [107]
Combination	Anti-CTLA-4 (Ipilimumab) + IL-2	Melanoma	6/36 CR, 84-month follow-up [113]
	Anti-CTLA-4 (Ipilimumab) + gp100 peptide		4/56 CR, 92-month follow-up [113]
	Anti-CTLA-4 (Ipilimumab) after vaccination with GM-CSF	Ovarian	6/11, 1x CR, 5x SD [120, 121]
Cellular vaccines	Vaccinia virus encoding B7-1	Melanoma	3/12, 1x PR, 2x SD [111]
	Adenocarcinoma cell line engineered to express B7-1 and HLA-A	NSCLC	6/19, 1x PR, 5x SD [112]

CR complete remission/response, *OR* objective response, *PR* partial response, *SD* stable disease

Increased B7-H4 expression in tumor tissues and in the blood of patients represents a realistic opportunity to design novel immunotherapies, by regulating the immune response through manipulating the expression of B7-H4 and/or its receptor. Furthermore, B7-H4 might be used as a diagnostic, prognostic, or predictive marker, but its expression pattern has still to be investigated in a huge series of tumor samples. So far, efficient neutralizing antibodies directed against B7-H4 are not available. The use of B7-H4-specific siRNA in activated hepatic stellate cells (HSC) has been shown to restore effector T cell function in mice [109], and down modulation of B7-H4 in breast cancer cell lines increased caspase activity and leads to apoptosis of tumor cells [110].

Earlier on, cellular vaccines encoding the normally not expressed B7-1 molecule in melanoma and NSCLC cancer have led to some clinical efficacy with mostly stable disease outcome in some patients [111, 112].

Recently, combinations of immunotherapies targeting the co-inhibitory molecules with co-stimulatory molecules or tumor-associated antigen are investigated, which might lead to an improved immune response. The data in melanoma patients for the combination of anti-CTLA-4 along with IL-2 or with gp100 peptide treatment are very promising: 6/36 complete responder and 4/56 complete responder at 84-month and 92-month follow-up, respectively [113]. Several actively recruiting clinical trials for therapy of RCC and melanoma with combination therapy of B7 receptors are ongoing, such as anti-PD1 combined with anti-CTLA-4 and anti-PD-1 along with sunitinib or pazopanib, both tyrosine kinase inhibitors (web: National Cancer Institute: Clinical trials).

Conclusions and future perspectives

The B7 family members are widely expressed on tumor cells and cell populations of the tumor microenvironment. The co-inhibitory B7-H ligands promote the suppression of host anti-tumor response, whereas the co-stimulatory molecules might affect growth and survival of malignant cells. An increased knowledge of the balance between co-stimulatory and co-inhibitory pathways in tumors and the immune cell infiltration will shed further light on the relationship between immunity and cancer, but also provide insights into the management of malignancies as well as the development of novel immunotherapeutics. In addition, the receptor identification will also be an important issue in order to understand the (patho)physiological role of the B7-H family members.

The improved survival of patients upon modulating these pathways might be both due to the increased destruction of tumor cells and an improved homeostasis of the immune system, which results in a reconstitution of an efficient immune texture with indirect anti-tumor effects.

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Conflict of interest The authors declare no conflict of interest.

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