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B7x—from bench to bedside

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ABSTRACT

B7x is an immune checkpoint molecule which belongs to the B7 family of ligands which includes PD-L1, PD-L2, B7-H3 and HHLA2. B7x belongs to the Immunoglobulin superfamily and its protein structure is similar to other members with a N terminus peptide, IgV and IgC like extracellular domain with four cysteine residues. Its receptor is yet to be identified. B7x inhibits T cell proliferation and expansion by IL-2 dependent and non-IL-2 dependent pathways. Even though high levels of B7x mRNA can be detected in most tissues its protein expression is highly limited suggesting significant post translational control. In vivo data, show that B7x plays an important role in limiting autoimmunity in the peripheral tissues and fine-tuning autoimmune responses. B7x is highly expressed in various cancers and in prostate cancer its expression is corelated with poorer outcomes. Local production of IL-6 and IL-10 in various cancers promotes B7x expression and tumor immune evasion. B7x is especially expressed in PD-L1 negative tumors suggesting that this may be an important method of immune evasion in these tumors. Currently drug development, targeting B7x through various mechanisms including monoclonal antibodies and antibody drug conjugates are in development in cancers and increasing B7x expression with fusion proteins in autoimmune diseases is underway.

INTRODUCTION

Immunotherapy has revolutionised the field of cancer therapeutics over the last decade. Immune checkpoint blockade (ICB) with cytotoxic T-lymphocyte antigen (CTLA-4), programmed death receptor (PD-1) and programmed death-ligand (PD-L1) antibodies has produced long and durable responses with a relatively low side effect profile. The clinical success has further fuelled a growing interest in developing newer checkpoint inhibitors. Since most patients are ineligible for ICB and even in those who receive CTLA-4, PD-1/PD-L1 therapy, only a small percentage respond. The third group of the B7 family, namely B7-H3, B7x and Human Endogenous Retrovirus-H Long Terminal Repeat-Associating Protein 2 (HHLA2), represents alternate immune checkpoints and has generated a considerable amount of interest. In this review, we will focus on B7x.

B7x (B7-H4/VTCN1//B7S1/B7 homolog 4) was discovered in 2003 using Expressed Sequence Tagged databases for proteins with homology to other members of the B7 family (table 1). Human B7x (hB7x) is located on chromosome 1p12/13.1 and inhibits T-cell proliferation and cell cycle arrest.[1] The genomic DNA of hB7x contains six exons and five introns and the coding region spans 849 base pairs.[1 2] Exon 6 is used for alternative splicing to generate two different protein products, soluble B7x (sB7x) and cell surface B7x. A B7x pseudogene located on chromosome 20p has also been described by Choi *et al*.[2] B7x is evolutionary conserved and shares 87% of its amino acid (AA) sequence with mouse B7x, which is located on the F2 region of chromosome 3 and also codes for six exons and five introns.[1 2] The hB7x protein consists of 282 AA and shares varying level of similarity with other members of the B7 family: B7-1 (12%), B7-2 (13%), B7h (16%), PD-L1 (18%), PD-L2 (18%) and B7-H3 (24%).[1 3 4]

STRUCTURE

B7x belongs to the immunoglobulin superfamily and its protein structure is similar to the other members of the B7 family. It consists of a N-terminus signal peptide, an IgV and IgC-like extracellular domain with four conserved cysteine residues and a transmembrane domain.[1] Even though there are reports that B7x is anchored to the cell membrane via Gp1 linkage,[4] treatment with phosphatidylinositol-specific phospholipase C did not change its expression levels.[2] The crystal structure of B7x IgV domain is similar to other B7 family members. The hB7x IgV domain consisted of 'β-sandwich' folding formed by a 'back sheet' (ABED strands) and a 'front sheet' (C″C′CFGA′ strands) stabilised by a disulfide bond between B and F strand.[5]

FUNCTION

B7x regulates T-cell proliferation and expansion via interleukin-2 (*IL-2 dependent and non-IL-2*)-dependent pathways. B7x expression on EL4 cells inhibits CD8+ T-cell proliferation, cytokine secretion and inhibits cytolytic activity.[1 3] The inhibition of T-cell proliferation is by cell cycle arrest, rather than T-cell apoptosis and can only be partially reversed by increased co-stimulation through CD28.[3 4] Cell surface B7x suppresses Th1-derived and

Table 1 Homology between hB7x and other members of the B7 family

	HB7x[1] (%)
B7-1	12
B7-2	13
B7h	16
PD-L1	18
PD-L2	18
B7-H3	24

hB7x, human B7x; PD-L, programmed death-ligand.

Th2-derived cytokines (interferon (IFN), IL-2, IL-4 and IL-10) from naïve T cells.[2] The underlying mechanism by which B7x inhibits IL-2 production may be related to the downregulation of JunB, a component of the AP-1 transcription family that is usually activated after T-cell activation.[4]

B7X EXPRESSION IN NORMAL AND DISEASE STATES

Normal tissue: B7x protein is not detected in most healthy tissues; however, high levels of B7x mRNA are observed in lung, liver, pancreas, spleen, thymus, kidney, prostate, testes and skeletal muscle suggesting post-transcriptional regulation of its expression.[2–4 6] B7x mRNA is expressed on professional antigen presenting cells (APCs), bone marrow-derived dendritic cells (DCs), peritoneal macrophages and splenic B cells and broadly distributed in non-lymphoid tissue.[4] Unlike other members of the B7 family, B7x is not expressed on cells from the haematopoietic origin.[1 3 7 8] B7x expression is lost rapidly in vitro culture.[9] A soluble B7x-Ig protein binds to activated but not naive T cells and B-cell activation in mice with lipopolysaccharide, and IL-4 leads to B7x downregulation.[4] B7x has been mostly shown to have cell surface expression, but it can also translocate from the surface to the nucleus.[10]

Autoimmunity: B7x has a vital role in suppression of autoimmune responses. Inhibition of B7x exacerbated autoimmune encephalomyelitis (EAE) in mice.[4] Treatment with B7xIg effectively ameliorated the progression of relapsed and chronic EAE with decreased CD4 T cells within the central nervous system and spleen and a concurrent increase in the number of T regulatory cells (Tregs).[6] In a diabetes model, transfection of diabetogenic T cells into B7x-deficient mice resulted in a more aggressive disease state characterised by an earlier onset of disease with higher glucose levels due to increased IFN-γ and IL-17 production. However, complete abrogation of diabetes was observed after introduction of diabetogenic T cells into mice known for overexpression of B7x, although evidence of insulitis remained.[6] Similarly in an autoimmune kidney disease model, B7x knockout mice developed severe renal disease while B7xIg decreased kidney damage and inflammation.[11] These results show that B7x plays an important role in suppressing autoimmunity in the periphery and for fine-tuning the response to inflammation.

Cancer: Several observational studies show that the B7x protein is selectively expressed in higher levels in cancers including ovarian, renal cell cancer, pancreatic cancer, hepatocellular carcinoma (HCC), gastric cancer, lung cancer, glioma, breast, prostate cancer, urothelial cancer, cervical cancer and melanoma[12–21] (table 2). In vivo and in vitro studies in lung and ovarian models have shown that both local cytokine production of Il-6, IL-10 and hypoxia promote B7x expression. In ovarian cancer cells, tumour-associated macrophage (TAM) stimulated Tregs to secrete IL-6 and IL-10, which, in turn, promote B7x expression on APCs.[19 22] In addition, production of IL-10 and TNF-α by the TAMs also increases B7x expression in lung cancer models. IL-4 is known to suppress B7x expression,[23] whereas IL-6, which is found in abundance in the tumour microenvironment (TME) with IL-10, activates signal transducer and activator of transcription 3 which then binds to B7x promoter and enhances gene expression.[24] Xenograft studies in a breast cancer model with B7x deficiency protected from the development of lung metastasis, whereas a colon cancer model with high B7x expression had a sixfold increase in pulmonary metastasis.[25 26] B7x expression was upregulated in myeloid DCs, plasmacytoid DCs, $CD14^{+}HLA\text{-}DR^{hi}$ cells and $CD14^{+}HLA\text{-}DR^{lo/-}$ cells in the peripheral blood of patients with HCC compared with healthy donors. Furthermore, B7x expressed on early CD8+ tumour infiltrating lymphocytes (TILs) promoted T-cell exhaustion via Eomesodermin, a transcription factor associated with T-cell exhaustion.[27] These preclinical findings suggest that B7x expression in tumours helps in tumour immune evasion.

A large retrospective study conducted on B7x expression on 948 prostate cancer samples showed that stronger intensity correlated with biochemical, clinical recurrence and death from prostate cancer. B7-H3 and B7x are highly expressed in human prostate cancer and was associated with disease spread and poor outcomes.[12] B7x expression was evaluated in 259 renal cell carcinoma (RCC) cases and the protein was present in 59.1% of nephrectomy specimens.[13] In this study, higher B7x expression was associated with adverse clinical and pathological features, including constitutional symptoms, tumour necrosis, and advanced tumour size, stage and grade. Interestingly, B7x was preferentially expressed on the endothelium of RCC tumour vasculature (81.5%) but not on normal renal tissue vessels (6.5%).[13] B7x was detected in 95.4% (165/173) of primary breast cancers and in 97.6% (240/246) of metastatic breast cancers, with the staining intensity being greater in invasive ductal carcinomas followed by invasive lobular carcinomas than in normal breast epithelium. Increased staining was associated with negative progesterone status and history of neoadjuvant chemotherapy, but unlike RCC there was no correlation with higher expression and clinicopathological features.[14] A meta-analysis of studies relating to B7x expression in ovarian cancer reported a pooled HR of 1.30 (95% CI:

Table 2 Human B7x expression in cancer

Tumour	Positive B7x expression	References
Lung cancer	69% (128/185) and 68% in discovery and validation cohort	29
Pancreatic cancer	92% (33/36) in tumour samples 20% (1/5) in tumour-negative samples	20
	61.9% (39/63) in pancreatic tumour samples	40
HCC	HBV related: HCC: 68.67% (57/83)	41
	93 HCC cases: mean sB7x: 49 ng/mL versus 31.66 ng/mL in healthy volunteers	42
Breast cancer	95.4% (165/173) primary breast cancer 97.6% (240/246) metastatic breast cancer	14
Gastric cancer	25.8% (31/120)	43
	71% (71/100)	44
Renal cancer	59.1% (153/259) in tumours 81.5% in RCC endothelium versus 6.5% in normal tissue vessels	13
	RCC sB7x concentration of 14.4 ng/mL versus 2.7 ng/mL in healthy volunteers	13
Thyroid	95.3% (61/64)	45
Glioma	Not reported	24
Prostate cancer	99% (805/814); 15% with strong intensity	12
Melanoma	96.5% (28/29) primary tumours 89.7% (26/29) metastatic tumours	15
Ovarian cancer	100% in all 103 samples	46
Urothelial cancer	75.8% (42/67)	47

HBV, Hepatitis B virus; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma.

1.17 to 1.45, p<0.05) between higher B7x expression and worse progression-free survival.[28] Hence, B7x protein is widely expressed in various cancers, and in some cancers, it is associated with adverse clinical features.

Co-expression of B7x with other immune checkpoints

Since PD-L1 is expressed only in a minority of cancers, it stands to reason that the other members of the B7 family could be expressed or co-expressed to promote tumour immune evasion. In 392 primary non-small-cell lung cancers (NSCLC) samples, B7x was expressed in 69% of tumours. The co-expression of PD-L1 with B7x was infrequent at 6% and the majority (78%) of PD-L1-negative cases expressed B7x, HHLA2 or both. The triple-positive group (PD-L1, B7x and HHLA2) had more TIL infiltration than the triple-negative group.[29] In another study using multiplex quantitative immunofluorescence (QIF), PD-L1, B7-H3 and B7x expression was determined in 90 small-cell lung cancer (SCLC) samples. PD-L1, B7-H3 and B7x were expressed in 7.3%, 64.9% and 2.6%, respectively, of SCLC with limited co-expression and were not associated with the level of TILs. Elevated B7x expression was associated with shorter 5-year overall survival. The levels of CD3+, CD8+ and CD20+ TILs and the ratio of total/effector T cells were significantly lower in SCLC than in NSCLC. High levels of CD3+, but not CD8+ or CD20+ TILs, were significantly associated with longer survival.[30] In triple-negative breast cancer, an immune cold microenvironment is defined by expression of B7x and a fibrotic stroma signature while immunoreactive microenvironment was associated with CD8+ T cells, a type 1 IFN signature, indoleamine-2,3-dioxygenase 1 and PD-L1.[31] Hence, B7x co-expression can define TME and B7x is expressed in PD-L1-negative tumours for immune evasion with important clinical implications.

B7x as a prognostic and predictive marker. Several studies have reported that B7x expression levels have predictive and prognostic value.[27 32–35] Detectable levels (>0.1 ng/mL) of sB7x were observed in 53 patients with RCC compared with 18 controls. The median (range) observed concentration of sB7x for patients with RCC was 14.4 ng/mL (0.1–56.9) in comparison to 2.7 ng/mL (0.2–37.1) in the controls.[32] In gastric cancer, the median concentrations of sB7x were significantly higher than those in healthy controls (16.85 vs 10.46 ng/mL; p=0.008) and high sB7x expression was associated with lower OS.[35] A meta-analysis of nine studies assessing B7x expression via enzyme-linked immunosorbent assay (two studies), immunohistochemistry (six studies) and QIF (one study) demonstrated that B7x was an unfavourable prognostic factor in NSCLC, as higher B7x expression was associated with lymph node metastasis, advanced stage, poor differentiation and poor OS (HR=2.03, 95% CI=1.41 to 2.92, p<0.001).[34] Another meta-analysis also reported that B7x expression was associated with worse OS (HR=1.79, 95% CI 1.56 to 2.06, p<0.001) across many cancers.[33] Based on these findings, B7x is expressed in many cancers and higher sB7x levels are associated with poor prognosis.

DRUG DEVELOPMENT

The mounting evidence that B7x is expressed in a wide variety of human malignancies, and that its detection in either tumour samples or the blood serves as an adverse prognostic marker makes it an attractive drug target. B7x can be targeted through various mechanisms like monoclonal-blocking antibodies (mAbs), single chain fragment variables (scFvs), antibody–drug conjugate (ADCs), CD3 bispecific antibodies (BiTE) and chimeric antigen receptor T cells (CAR-Ts).[9 36 37] Anti-B7x mAbs have been demonstrated to inhibit tumour growth in vivo by blocking B7x-mediated immunosuppression and by killing tumour cells through antibody-dependent cell-mediated cytotoxicity (ADCC).[5] Anti-B7x scFvs have been shown to delay the growth of ovarian cancer cell line, OVCAR5, in NSG (NOD scid gamma mouse) mice.[9] Since B7x is expressed in breast cancer, a B7x *scFv/CD3 BiTE* has shown activity in preclinical models.[38] Leong *et al* generated a B7x ADC with monomethyl auristatin that also led to tumour regression in triple-negative breast cancer xenograft models.[37] In addition, B7x-targeted CAR-T cells capable of recognising both human and murine B7x led to tumour regression in xenograft models; however, lethal toxicity was observed 6–8 weeks post-treatment. Post mortem analysis showed a case of on target/off toxicity as significant damage was observed in ductal and mucosal epithelial tissues with B7x expression.[36]

Currently, a phase Ia/Ib clinical trial (NCT03514121) with FPA150, a fully hB7x mAB with enhanced ADCC, in patients with advanced solid tumours is underway. The early results of this trial presented at the American Society of Clinical Oncology conference in 2019 reported a favourable side effect profile in 24 patients treated with FPA150 antibody in advanced solid cancers. Aside from Grade 1–2 diarrhoea and fatigue, the only grade 3 treatment related adverse event (TRAE) event reported was hypertension. Anti-tumour response has not yet been reported.[39] In rheumatoid arthritis, AMP-110, a fusion protein containing extracellular domain of B7x plus Fc portion of IgG has been studied in two phase clinical trials (NCT01878123 and NCT02277574), although results have not been reported yet. The combination therapy of anti-B7x with PD-1 antibody blockade is a promising approach because B7x inhibition causes upregulation of PD-1 on CD8+ TILs. In murine models, combination therapy has been proven to be more efficacious than monotherapy with B7x and PD-1 alone.[27] Hence, targeting B7x in cancers and autoimmune diseases is an active area of drug development.

CONCLUSION

B7x is an immune checkpoint of the B7 family, inhibits T-cell proliferation and function, and has significant homology in protein structure to other members namely, PD-L1, B7-H3 and HHLA2. The receptor for B7x is yet to be discovered. Despite high mRNA expression in most tissues, its protein expression is very limited. Preclinical models show that B7x is critical in regulating peripheral autoimmunity and autoimmune diseases can be reversed by upregulating B7x in animal models. Trials in human are testing this proof of concept. Due to its wide expression in cancer tissues, B7x is also an attractive target for cancer immunotherapy-blocking antibodies such as mAbs, scFvs, ADCs, CD3 BiTEs and CAR-Ts. Further research is needed to answer important questions regarding the receptor for B7x, conditions of upregulation of B7x in human tissues. Development of B7x-based therapeutics in autoimmune conditions and cancer is currently underway, and the results can be expected in the near future.

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