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REVIEW

The B7 Family Member B7-H6: a New Bane of Tumor

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Abstract B7-H6 is a ligand of NKp30, which is an activating receptor of natural killer (NK) cells. High expression of B7-H6 is found in certain types of tumor cells, such as lymphoma, leukemia and gastric carcinoma. The expression of B7-H6 can be induced by inflammatory stress in healthy cells. The expression of B7-H6 is significantly correlated with distant metastasis status and post-operative prognosis in cancer patients. The effectiveness of B7-H6 modified antitumor immunotherapy strategies had been verified in tumor-bearing mice, which opened a new door to targeted therapy. In this review, we will focus on the recent development on the roles of B7-H6 in tumor immunity, as well as mechanisms involved in the regulation of B7-H6 expression.

Keywords B7-H6 · NKp30 · Tumor immunity

Natural killer (NK) cells are lymphocytes of the innate immune system that eliminate tumor cells. NK-cell activation is regulated by a delicate balance of activation or inhibition of certain receptors. For example, activation of natural cytotoxicity receptors (NCRs) play important roles in immune surveillance [1–5]. NKp30 is one of the NCRs that can promote recognition and killing of tumor cells by NK cells either independently or together with other stimulatory receptors [1, 2, 4]. Several NKp30 ligands have been identified, among which, B7-H6 is the only membrane-binding ligand. More recently, B7-H6 was found to be a costimulatory molecule and its expression is higher in certain types of tumors. B7-H6 from tumor cells interacts with NKp30 and induces cytotoxic activity [6]. B7-H6 expression could also be induced in healthy cells upon inflammatory and microbial stimulation. This review will focus on the current progresses on the roles of B7-H6 in tumor immunity.

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Characterization of B7-H6 as a Ligand for NKp30

NKp30, a member of CD28 family, is a known NK-activating receptor [2, 6, 7]. The expression of NKp30 has been found in the majority of NK cells, which is involved in the process of tumor cell killing and interaction with antigen presenting cells (eg. dendritic cells) [8]. NKp30 can interact with several molecules, which include Bcl-2 associated athanogene 6 (BAG6, also known as HLA-B-associated transcript 3, BAT3) [8], human cytomegalovirus tegument protein pp65 [9, 10], Duffy-binding-like (DBL)-1α of Plasmodium falciparum erythrocyte membrane protein-1 (PfEMP-1) [11] and a group of heparin sulfate/heparin molecules [12]. However, none of these molecules are expressed on the surface of tumor cells. Brandt et al. identified a surface molecule expressed on tumor cells that binds NKp30 using proteomic approach and named it as DKFZp686O24166 [6]. After protein sequence BLAST and homology analysis, DKFZp686O24166 was designated as B7-H6 due to its comparable identity to B7 family members.

Structure and Expression Profile of B7-H6

Structure of B7-H6

The B7-H6 gene encodes a 454-aa-long type I transmembrane protein with a predicted molecular mass of 51 kDa. The intracytoplasmic domain contains several

signaling motifs, such as an immunoreceptor tyrosine-based inhibition motif (SaYtpL), a SH2 (Src homology 2)-binding domain (YqlQ), and a SH3-binding motif (PdaPilPvsP) [6, 13]. The extracelluar region contains one IgV-like domain and one IgC-like domain. The extracellular domain of NKp30 directly and selectively interacts with the extracellular domain of B7-H6, which was verified by Gordon Joyce et al. using residue mutation strategy [7].

Expression Profile of B7-H6

B7-H6 is selectively expressed on the surface of several types of tumor cells, including melanoma, ovarian cancer, neuroblastoma and primary blood or bone marrow cells derived from different types of hematological malignancies [6, 14]. B7-H6 is undetectable at either protein or transcriptional level in normal tissues or unstimulated healthy peripheral blood mononuclear cells. Salimi et al. reported that higher expression of B7-H6 was observed in skin biopsies of patients with atopic dermatitis [15], suggesting that altered B7-H6 expression pattern exists under inflammatory or disease condition. In consistent with these findings, Matta et al. found that B7-H6 could be induced at the surface of $CD14^{+}CD16^{+}$ proinflammatory monocytes and neutrophils upon stimulation by ligands of Toll-like receptors or proinflammatory cytokines such as interleukin-1β and tumor necrosis factor α, and they also identified a soluble form of B7-H6 (sB7-H6) that was produced by activated monocytes and neutrophils [16]. In addition, Schlecker et al. found that ectodomain shedding of B7-H6 from the surface of tumor cells could be mediated by the metalloproteases "a disintegrin and metalloproteases" (ADAM)-10 and ADAM-17 which suggested another crucial regulatory mechanism of B7-H6 expression [14]. Taken together, these data indicated that the expression of B7-H6 could be regulated by different mechanisms.

B7-H6 in Tumor Immunity

Clinical Significance of B7-H6 Expression in Tumors

The expression of B7-H6 varies in different types of cancers, which may implicate its different functions under different pathological conditions. In gastric carcinoma, the expression of B7-H6 was similar between tumor tissues and non-tumor tissues, and no correlation was found between B7-H6 expression and clinical characteristics such as age, sex, tumor size, histological classification, lymph node metastasis and distant metastasis. However, Chen et al. showed that B7-H6 expression correlated with tumor differentiation [17], which was consistent with the role of B7-H6 observed in non-small lung cancer [18]. Similarly, in astrocytoma, B7-H6 expression had no predictive value on patient prognosis. However, it could serve as a marker to differentiate the World Health Organization grade level of astrocytoma [19]. In ovarian cancer, Pesce et al. found that the expression of B7-H6 on tumor cells and/or the existence of high concentrations of sB7-H6 in peritoneal/ascitic fluid were associated with low NKp30 expression on NK cells [20]. Moreover, Zhou et al. showed that higher B7-H6 expression in ovarian cancer tissues was positively correlated with tumor metastasis and cancer progression, which supported the notion that B7-H6 expression was involved in the progression of human ovarian cancer [21]. Upregulation of B7-H6 was also found in breast cancer (including those patients with triple-negative breast cancer) [22]. Breast cancer patients with B7-H6 genomic alterations had significantly worse overall survival, and certain clinical factors were associated with B7-H6 expression, which indicated that B7-H6 could be a potential target for breast cancer immunotherapy [22]. In addition, in B-cell non-Hodgkin lymphoma, Wu et al. showed that knockdown of B7-H6 inhibited tumorigenesis and enhanced chemosensitivity via STAT3 signaling pathway [23].

Regulatory Mechanisms of B7-H6 Expression on Tumor Cells

Protease Inhibition Mediates B7-H6 Expression

Protease inhibitors could affect B7-H6 expression on the surface of tumor cells. Two classes of protease inhibitors are involved in the regulation of B7-H6 expression on tumor cells. Histone deacetylase inhibitors (HDACi) and metalloprotease inhibitors regulate B7-H6 expression at transcription and post-transcriptional levels, respectively.

Histone deacetylases (HDACs) are enzymes whose enzymatic activity control the acetylation state of protein lysine residues, especially at the N-terminal extensions of the core histones [24]. Through the influence on chromatin conformation, HDACs are involved in many biological processes, including cell cycle progression, cell survival and differentiation [24–27]. According to a previous study, downregulation of B7-H6 surface protein and mRNA expression in various tumor cell lines could be achieved upon treatment with pan- or class I HDAC inhibitors (HDACi) or HDAC knockdown. The authors attributed the B7-H6 downregulation to reduced histone acetylation at the B7-H6 promoter, resulting in reduced NKp30-dependent tumor cell recognition by NK cells [28].

A disintegrin and metalloproteinases (ADAMs) are a family of proteins with gelatinase activity involved in multiple pathological condition, including autoimmune disease, inflammation, infection and cancer [29–33]. Increased expression of ADAM-family members is found in multiple tumors, and is associated with tumor proliferation, metastasis [34] and prognosis [35, 36], and may serve as effective therapeutic reagents in tumor therapy [37]. Schlecker et al. reported that

ectodomain shedding of B7-H6 from the cell surface of tumor cells was mediated by ADAM-10 and ADAM-17 [14]. Moreover, they also proved that increased B7-H6 surface expression after metalloprotease inhibitor treatment could lead to enhanced NKp30-dependent NK-cell degranulation, which was different from the role of soluble B7-H6 in the setting of sepsis or neuroblastoma [16, 38]. However, regarding the ectodomain structure of B7-H6, it is still unknown whether a single Ig-V like domain at the N-terminal of B7-H6 is sufficient for NKp30 recognition [7].

Other Mechanisms Involved in B7-H6 Expression

Textor et al. mapped a functional binding site for Myc, a proto-oncogene overexpressed in certain tumors, in the promoter region of B7-H6. Either pharmacological inhibition or siRNA/shRNA-mediated knock-down of c-Myc or N-Myc could significantly decrease B7-H6 expression in a variety of tumor cells including melanoma, pancreatic carcinoma and neuroblastoma cell lines. Moreover, they also observed that inhibition or knock-down of c-Myc in tumor cells impaired NKp30-mediated degranulation of NK cells [39]. Xu et al. suggested that promoter methylation could be an epigenetic basis for deregulation of certain B7 family genes in breast cancer [22].

B7-H6-Mediated Tumor Immunotherapy

Because B7-H6 can induce NKp30-dependent NK activation and cytokine secretion [6], therapeutic interventions based on NKp30-B7-H6 interaction may provide a new strategy for tumor treatment. Li et al. previously suggested that B7-H6 binds NKp30 through the complementarity-determining region (CDR)–like loops of its V-like domain in an antibody-like interaction and this interaction provides a template for designing molecules to stimulate NKp30-mediated cytolytic activity for tumor immunotherapy [13]. However, according to most recent studies, an inverse correlation was found between soluble B7-H6 level and NKp30 expression in patients with ovarian cancer [20] and high-risk neuroblastoma [40], while no relationship was found between the soluble B7-H6 generated by ectodomain shedding and the expression of NKp30 [14]. Other strategies have been developed in order to overcome these obstacles, Kellner et al. generated a fusion protein consisting of the ectodomain of B7-H6 and the CD20 single-chain fragment variable 7D8, and named it as B7-H6:7D8. In the functional assay, they found that B7-H6:7D8 could stimulate NKp30 mediated NK cell cytotoxicity [41]. Recently, genetic modification of T cells with tumor-targeting chimeric AgRs (CARs) and adoptive transfer of CAR-modified T cells has emerged to treat cancer. Zhang et al. developed chimeric antigen receptors (CAR) based on NKp30 and found that these NKp30 CAR expressing T cells produced IFN-γ and killed B7-H6 ligand-expressing tumor cells. Moreover, they also proved that these NKp30 CAR expressing T cells could help to establish tumor immunity in vivo [42]. Bi-specific T cell engagers (BiTE) strategy is a novel T cell mediated immunotherapy that utilizes a fusion protein to link tumor cells and T cells with anti-tumor specificity. Wu et al. showed that B7-H6-specific BiTEs direct T cells to mediate cellular cytotoxicity and IFN-γ secretion upon co-culturing with B7H6$^+$ tumors. Furthermore, B7H6-specific BiTE exhibited no self-reactivity to pro-inflammatory monocytes. In vivo, B7-H6-specific BiTE greatly enhanced the survival of RMA/B7H6 lymphoma bearing mice by activating perforin and IFN-γ effector. In addition, long term survivor mice were protected against a RMA lymphoma tumor re-challenge [43].

B7-H6 antibody itself may have important therapeutic potentials. Matta et al. isolated mouse monoclonal antibodies against human B7-H6 and found that all four antibodies blocked the activation of NK cells while two antibodies directly blocked the binding of B7-H6 to NKp30 and the other two antibodies 4E5.5 and 17B1.3 did not inhibit the direct interaction of B7-H6 with NKp30 [16, 44]. Elucidating the inhibitory mechanisms of the latter two antibodies could be helpful for designing better B7-H6- based tumor immunotherapy. Therefore, Xu et al. analyzed the crystal structure of the inhibitory antibody 17B1.3 in complex with the ectodomain of B7-H6 and found that 17B1.3 could bind to a site on B7-H6 that was completely distinct from the binding site for NKp30. They concluded that the bulky 17B1.3 antibody most likely targeted the NK cell–target cell interface that were required for NK cell activation [44].

Conclusions

B7-H6, a promising molecule of B7 family, can bind its receptor NKp30 to exert anti-tumor effects by helping NK cells to recognize abnormal cells. However, hurdles remain before B7-H6 based therapy can be used in the clinic. There are only a few longitudinal studies using cancer patients to elucidate the correlation between B7-H6 and tumor development and progression [17, 18]. Furthermore, activation of NKp30 can result in death of immature DCs [45], which hampers the application of NKp30 chimeric T cells [46]. Although previous studies showed that NKp30 isoforms exerted different effects on tumor immune response [40, 47], the exact roles of NKp30 isoforms in tumor immunotherapy remain largely unknown. Nonetheless, recent discoveries on NKp30 and B7-H6 interaction paved the way to the development of novel therapeutic strategies for cancer treatment.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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