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Targeting immune checkpoint B7-H6 in cancer immunotherapy

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Abstract

Natural killer (NK) cells are central mediators of antitumor immunity and possess the unique ability to recognize and eliminate malignant cells independently of major histocompatibility complex (MHC) restriction. Compared with T-cell-based approaches, NK-cell immunotherapies generally exhibit a more favorable safety profile, highlighting their growing therapeutic potential in oncology. Among the ligands that regulate NK-cell activity, B7-H6 has emerged as a particularly attractive target because of its highly restricted expression in normal tissues and frequent upregulation across diverse malignancies. Initially identified as a ligand for the activating NK-cell receptor NKp30, B7-H6 is now recognized as a multifunctional molecule with roles extending beyond immune recognition. Accumulating preclinical evidence suggests that B7-H6 may contribute to tumor progression by regulating signaling pathways involved in proliferation, survival, migration, invasion, and immune evasion. Furthermore, the existence of soluble B7-H6 adds an additional layer of biological complexity and may influence both NK-cell function and therapeutic responsiveness. In this review, we summarize current knowledge regarding the regulation, expression patterns, and biological functions of B7-H6, with particular emphasis on its dual roles in tumor immunology and cancer cell biology. We discuss the emerging significance of soluble B7-H6, evaluate the current landscape of B7-H6-targeted therapeutic strategies, including bispecific engagers and cellular immunotherapies, and highlight key translational challenges that may influence clinical development. Collectively, current findings position B7-H6 as a promising immuno-oncologic target at the intersection of immune surveillance, immune escape, and malignant progression, warranting continued investigation as a next-generation therapeutic axis in cancer immunotherapy.

Keywords: B7-H6; NKp30; natural killer cells; tumor immunosurveillance; immune escape; soluble B7-H6; cancer immunotherapy; cellular immunotherapy

1. Introduction

The immune system, including both adaptive and innate immune cells, is a natural mechanism by which humans fight against cancer. Natural killer (NK) cells are a type of innate immune cell that can rapidly eliminate abnormal cells, making them key participants in tumor immunosurveillance (1). NK cells have shown their distinct advantages in tumor therapy. NK cells recognize tumor cells in a Major Histocompatibility Complex (MHC)-independent manner. Unlike T cells, NK cells do not require antigen-specific priming through MHC-restricted recognition before exerting cytotoxic activity (2). Consequently, NK cells can respond more rapidly to transformed or stressed cells than conventional T lymphocytes. Moreover, tumor cells are widely reported to evade immune detection by reducing their expression of histocompatibility complex class I molecules (MHC-I or HLA-I) (3). At that time, the MHC-independent function of NK cells became prominently important. NK cells also restrain the development of metastases by producing Interferon-gamma (IFN-γ), which can induce a dormant state in metastatic cells, or by killing circulating tumor cells before they settle in the metastatic niche (4, 5). NK cells have been shown to have lower biological toxicity than T cells because they do not mediate graft-versus-host disease (6, 7). Although T-cell-based therapy has been proven to efficiently eliminate tumors, it is still worth further developing NK-cell-based therapy to meet a wider range of needs.

Among NK-cell activating ligands, B7-H6 occupies a unique position because its expression is largely restricted to malignant and stressed cells, while it is absent from most healthy tissues. Unlike many immune ligands that primarily serve as markers of immune recognition, emerging evidence indicates that B7-H6 also participates in tumor-intrinsic signaling networks regulating proliferation, invasion, and immune evasion. Consequently, B7-H6 has attracted growing interest not only as an NK-cell activating ligand but also as a therapeutic target capable of simultaneously modulating tumor biology and antitumor immunity.

This review summarizes the biological functions of B7-H6, including its regulation, expression patterns, soluble forms, and tumor-intrinsic signaling activities. We further discuss the role of B7-H6 in immune escape, evaluate current therapeutic strategies targeting the B7-H6/NKp30 axis, and highlight the key challenges that must be addressed to enable successful clinical translation.

2. Activation and inhibition mechanisms of NK cells

Understanding the balance between activating and inhibitory signals is essential for appreciating the biological significance of B7-H6 as an NK-cell activating ligand.

NK cells are identified as $CD3^-$ $CD56^+$ cells by flow cytometry, which are usually divided into 2 main subpopulations: $CD56^{bright}$ $CD16^{dim}$ and $CD56^{dim}$ $CD16^{bright}$ (8). $CD56^{dim}$ $CD16^{bright}$ NK cells, the major subtype (⩾90%), circulate in the peripheral blood and specialize in cytotoxicity. $CD56^{bright}$ $CD16^{dim}$ NK cells are more commonly seen in secondary lymphoid tissues, which are more professional in secreting cytokines and chemokines (9, 10). $CD56^{dim}CD16^-$ and $CD56^-CD16^{bright}$ NK cells can also be found in the peripheral blood. After activation, $CD56^{dim}CD16^{bright}$ NK cells lose CD16 from the membrane due to metalloprotease-mediated shedding and become $CD56^{dim}CD16^-$ cells. Also, $CD56^{dim}CD16^{dim}$ cells are identified in patients with antigen-processing (TAP) deficiency. This subpopulation of NK cells is also cytotoxic, but its cytotoxicity is weaker than that of $CD56^{dim}CD16^{bright}$ NK cells. The circulating NK cells can be recruited to the malignant tissue site under the direction of

proinflammatory chemokines produced by other immune cells in the tumor microenvironment (11). Infiltration of NK cells is positively correlated with prognosis in many types of cancer, including colorectal carcinoma, gastric carcinoma, squamous cell lung carcinoma, and squamous cell carcinoma (12, 13).

The best-known hypothesis of the NK-cell activation mechanism, the "missing self" mechanism, was first proposed by Ljunggren in 1990 (14, 15). NK cells degranulate and lyse the target cell when the cell expresses little or no MHC-I. Further study revealed that when the activating signal is stronger than the suppressive signal, NK cells still undergo activation protocols, even in the presence of the MHC-I signal. This mechanism is named "induced self" (16). Conversely, if the net inhibitory signal from different receptors overwhelms the activation signals, the NK cells will remain in tolerance mode. To enhance the cell-killing ability of NK cells, it is essential to shift the signal balance from inhibitory to activating (Figure 1).

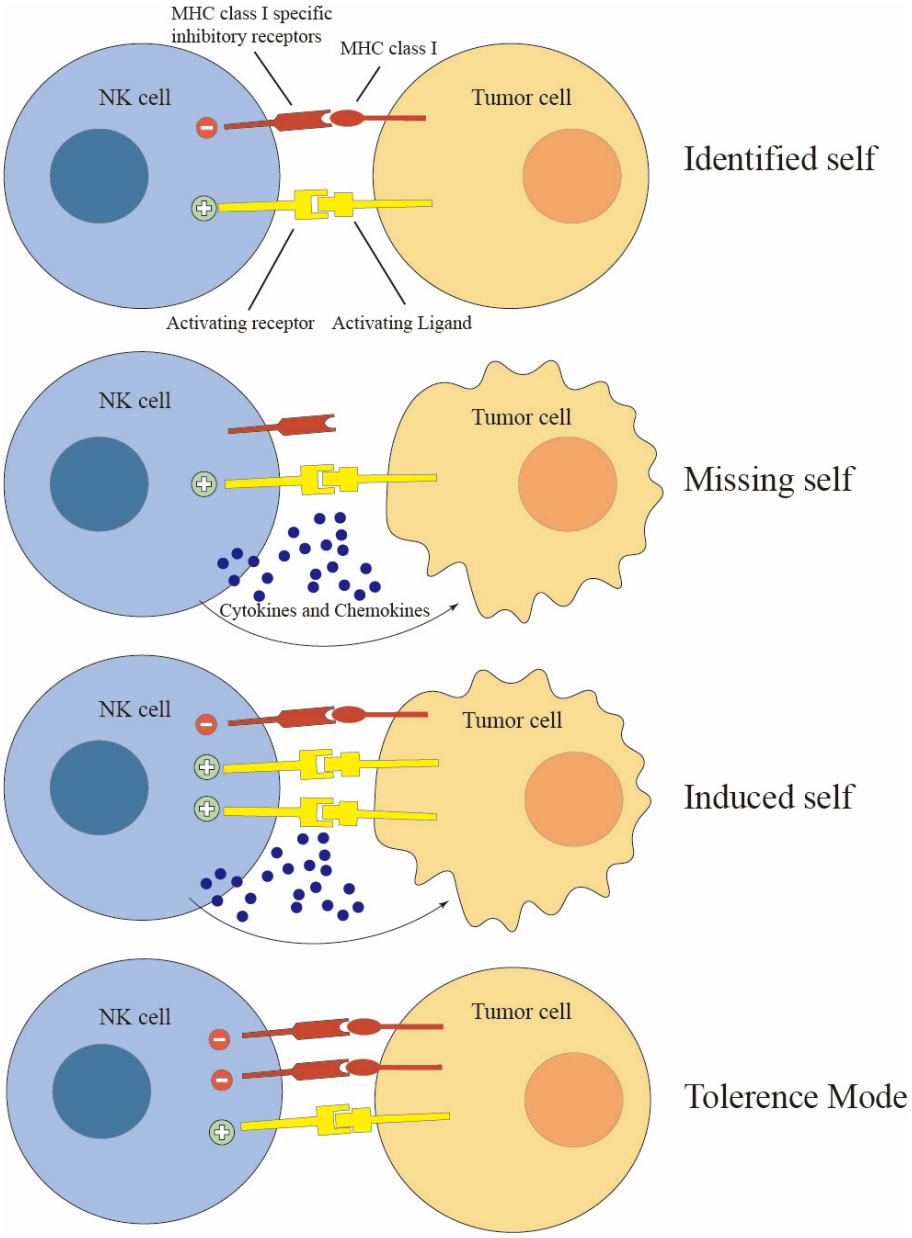


Figure 1. Mode of NK-cell activation and inhibition. *The identification of MHC-I on healthy cells results in NK cells being silenced (Top). Once the activation signal overwhelms the inhibitory signals, regardless of whether the MHC-I molecule is*

identified, NK cells will secrete cytokines and chemokines and initiate the cytolysis program (Middle). On the contrary, NK cells remain in tolerance mode if inhibitory signals dominate (Bottom).

The Killer cell immunoglobulin-like receptor (KIR) family is one of the main groups of receptors that recognize MHC-I to maintain the tolerance phenotype of NK cells. The KIR family includes KIR2DL1, KIR2DL2/3, KIR3DL1, and KIR3DL2. NKG2A, also known as CD159a, and leukocyte immunoglobulin-like Receptor-1 (LIR-1) are other HLA-I receptors, which appear on different subsets of NK cells and also participate in the "self" identification mechanisms of NK cells (17). Interestingly, although there is diversity in HLA-I receptors on NK cells, these receptors use a common downstream signal pathway for inhibition. KIRs, NKG2A, and LIR-1 all contain cytoplasmic immunoreceptor tyrosine-based inhibition motifs (ITIMs). Phosphatase Src homology 2 domain-containing phosphatase 1 (SHP-1) is recruited around ITIMs in response to suppressive stimuli (18, 19). Other ITIM-containing NK inhibitory receptors do not recognize MHC-I. Killer Cell Lectin-like Receptor G1 (KLRG1) is the receptor of N-cadherin and E-cadherin (20, 21). KLRB1 binds the lectin-like molecule LLT1 and LLT1 homologs in humans and mice, respectively (22, 23). IRp60 recognizes phosphatidylserine (PS) and phosphatidylethanolamine (PE) (24). The ligands of sialic acid-binding Siglec-7 (CD238) and Siglec-9 (CD239) are sialoglycans. PD-1 can also be found on NK cells, which can inhibit NK cell activation by binding to PD-L1. TIGIT recognizes CD115 and CD112 (25). Unlike the inhibitory receptors, activation receptors induce diverse signaling cascades (Figure 2).

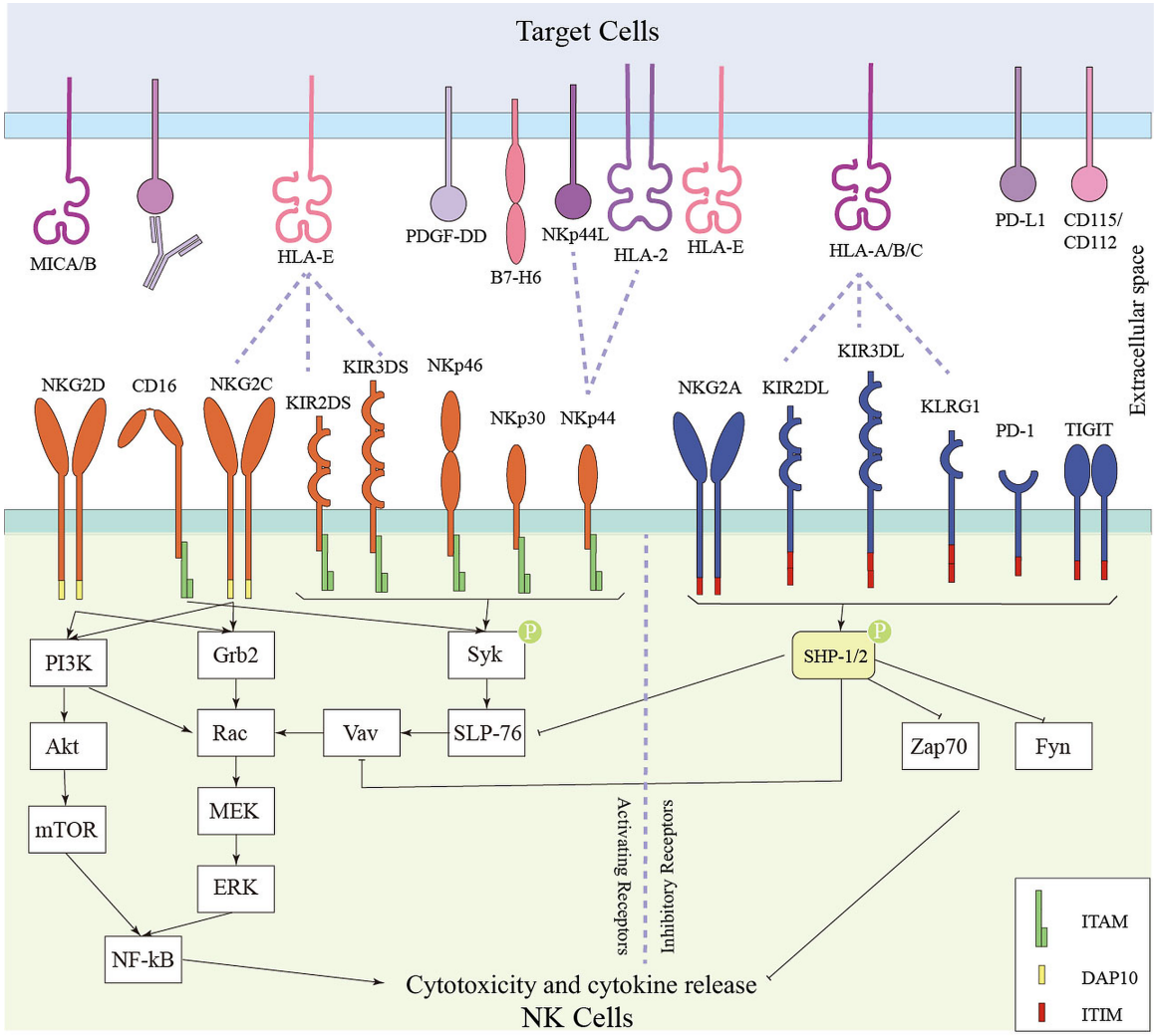


Figure 2. NK-cell receptors induced intracellular signaling pathways. *Inhibitory receptors recognize their ligands and recruit and phosphorylate SHP-1/2, thereby inhibiting the Syk, Zap70, and Fyn pathways. The ITAM and DAP10 motifs initiate the PI3K and Grb2 cascades, inducing cytotoxicity and cytokine release in NK cells via NF-κB regulation.*

Groups of activation receptors contain an immunoreceptor tyrosine-based activation motif (ITAM). Among those receptors, KIR2DS, KIR3DS, NKG2C (CD159c) are closely related to MHC-I receptor counterparts, while CD16, NKp30 (CD337), and NKp46 (CD335) are not MHC-I receptor-related. CD16, NKp30, and NKp46 are expressed on most resting NK cells (26). After recognizing the Fc region of immunoglobulin, CD16 induces phosphorylation of ITAMs on the gamma domain of the high-affinity IgE receptor (FcεRIγ) and the CD3ζ chain, thereby triggering Antibody-dependent cell-mediated cytotoxicity (ADCC) (27, 28). It is an important tumor elimination approach in multiple monoclonal antibodies (mAb) in clinical practice, such as cetuximab, trastuzumab, and rituximab (29).

NKp30, NKp44, and NKp46 are classified as natural cytotoxicity receptors (NCRs), which are uniquely expressed by NK cells. NKp46 is highly conserved in mammals, but its ligands expressed on normal or tumor cells have yet to be identified (30, 31). The platelet-derived growth factor DD (PDGF-DD), secreted by many tumor types, is a widely studied ligand of NKp40. NKp30 will be discussed in detail in the next section. The best-known NK activation receptor lacking ITAM motifs is NKG2D (32, 33). Its ligands, MHC-I chain-related gene A (MICA), MHC-I chain-related gene B (MICB), and UL16-binding protein (ULBP), activate NK cells by phosphorylating the NKG2D-associated adapter protein DAP10, thereby stimulating the Phosphoinositide 3-kinase (PI3K) signaling cascade (34, 35). Tumor cells usually achieve immune escape by downregulating NK-cell activation signals, thereby shifting the NK cell from an activated to an inhibitory state.

Collectively, NK-cell activation is governed by the dynamic integration of stimulatory and inhibitory signals, creating a framework in which tumor-associated ligands such as B7-H6 can critically influence antitumor immune responses.

3. B7-H6 is a tumor-specific NK activation ligand

B7-H6 (NCR3LG1), a 51-kDa transmembrane protein with an IgV-IgC-like structure, was first identified in 2009 as an activation ligand for NK cells recognized by NKp30 (36, 37). The IgV-like domain has two glycosylation sites, and the IgC-like domain has four (38). B7-H6 contains an immunoreceptor tyrosine-based inhibition motif, an Src homology 2-binding domain, and an SH3-binding motif in the intracellular site, supporting unique intracellular functions (39, 40). B7-H6 is a tumor-specific marker that is undetectable in normal tissues at the mRNA level. But it is widely expressed in tumors, such as lymphoma, leukemia, ovarian carcinoma, brain cancer, breast cancer, and renal cell carcinoma, at both the mRNA level and protein level (41). Such tumor specialties make B7-H6 a potential therapeutic target for anti-tumor therapy. Expression of B7-H6 is closely related to histone deacetylases (HDACs).

The expression of B7-H6 was significantly induced or reduced by HDAC knockdown or HDAC3 overexpression, respectively (42). In addition to the membrane-binding type, B7-H6 also exists in soluble form. Matta et al. identified a soluble form of B7-H6 (sB7-H6), which could also associate with exosomes, is strictly expressed by activated monocytes and dendritic cells under inflammatory conditions, but can hardly be detected on the cell membrane of healthy donor PBMC (37, 43). Another type of sB7-H6 is generated by A disintegrin and metalloprotease (ADAM)-mediated protein shedding (Figure 3).

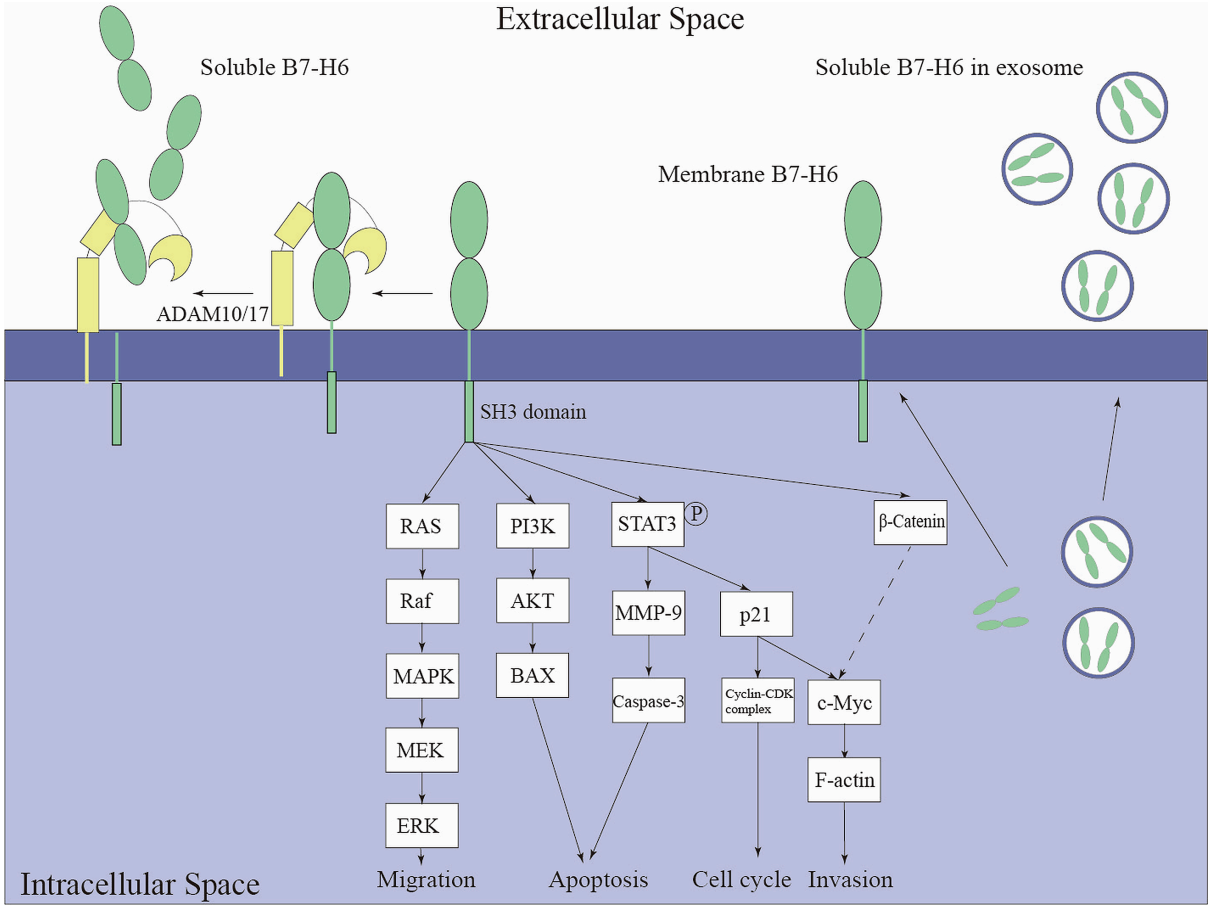


Figure 3. The intracellular signaling and Expression of membrane-bound B7-H6 and the formation of soluble B7-H6. *B7-H6 can be expressed on the cell membrane and acts as a ligand for NKp30. The B7-H6 membrane-associated form contains an intracellular SH3 domain, enabling it to participate in multiple intracellular signaling pathways, including Ras/Raf, PI3K/Akt, and STAT3, thereby regulating the migration, survival, proliferation, and invasion of cancer cells. B7-H6 is also present in the peripheral blood in a soluble form. There are two different ways to secrete soluble B7-H6. Soluble B7-H6 could be secreted by exosomes. The membrane-type B7-H6 can be digested by ADAM10/17. Then, the shed B7-H6 will be released into the tumor environment and the circulatory system.*

More specifically, ADAM-10 and ADAM-17 cleave the extracellular domain of B7-H6, potentially resulting in immune escape in melanoma (44). The ADAM inhibitor could significantly increase the membrane level of B7-H6 in the B7-H6 overexpression cell line. The shed-off part of B7-H6 was about 30 kDa, corresponding to the full-length extracellular domain. Furthermore, ADAM-10 and ADAM-17, as sheddases located on the extracellular membrane, are activated and cleave the target protein in the extracellular region. Moreover, two types of sB7-H6 were found in the peripheral blood of pregnant women (45). The function of those sB7-H6 in the pregnancy process remains ambiguous.

The existence of both membrane-bound and soluble forms of B7-H6 highlights the biological complexity of this molecule. Whereas membrane-associated B7-H6 primarily functions as a ligand for NKp30-mediated immune recognition, soluble B7-H6 may exert distinct immunological and tumor-promoting effects. The relative abundance, origin, and biological activity of these different B7-H6 species are likely to influence both tumor progression and therapeutic responsiveness. Consequently, understanding the mechanisms governing B7-H6 expression, shedding, and extracellular release has become an important area of investigation in cancer immunology.

Beyond epigenetic regulation, cellular stress pathways, inflammatory signaling, and oncogenic transformation have been proposed to contribute to the induction of B7-H6, although the underlying mechanisms remain incompletely defined. Although the regulatory mechanisms governing B7-H6 expression remain incompletely understood, current evidence suggests that B7-H6 expression reflects a state of cellular stress associated with malignant transformation rather than normal tissue homeostasis. The highly restricted expression pattern of B7-H6, together with its inducibility under pathological conditions, provides a strong rationale for its development as a selective immunotherapeutic target.

4. Regulation of B7-H6 expression in cancer

Although B7-H6 is widely recognized as a tumor-associated ligand for the activating NK-cell receptor NKp30, the mechanisms governing its expression remain incompletely understood. Unlike many immune regulatory molecules that are constitutively expressed in normal tissues, B7-H6 expression is largely absent under physiological conditions and becomes induced in response to pathological stress (37). This restricted expression pattern suggests that B7-H6 functions as a stress-associated molecule that signals cellular transformation and tissue damage to the immune system.

Current evidence indicates that B7-H6 expression is regulated at multiple levels, including epigenetic, transcriptional, and post-translational mechanisms. Among the best-characterized regulators are histone deacetylases (HDACs), which participate in chromatin remodeling and gene transcription. Experimental studies demonstrated that HDAC inhibitors can modulate B7-H6 expression and alter tumor-cell recognition by NK cells, whereas HDAC3 overexpression suppresses B7-H6 levels (46,47). These findings suggest that epigenetic mechanisms play an important role in controlling the availability of B7-H6 on the tumor cell surface. These observations suggest that epigenetic therapies may increase tumor susceptibility to NK-cell-mediated immune surveillance by enhancing B7-H6 expression.

In addition to epigenetic regulation, inflammatory and stress-associated signals have been proposed to contribute to B7-H6 induction, although the regulatory mechanisms remain incompletely defined (48). Chronic inflammation, a hallmark of many malignancies, is characterized by persistent cytokine production, oxidative stress, and tissue remodeling. These processes may create a microenvironment favorable for B7-H6 expression, thereby linking inflammatory signaling to NK-cell recognition of transformed cells.

Cellular stress responses associated with malignant transformation may also contribute to B7-H6 upregulation. Tumor cells are frequently exposed to genomic instability, oncogene activation, metabolic stress, hypoxia, and DNA damage, all of which activate stress-response pathways that alter surface ligand expression. Similar to other stress-induced NK-cell ligands, B7-H6 may function as a molecular indicator of cellular distress (37), allowing NK cells to identify and eliminate potentially dangerous cells before malignant progression occurs. However, the specific signaling pathways connecting these stress responses to B7-H6 transcription remain largely undefined and warrant further investigation.

Beyond transcriptional regulation, post-translational mechanisms also influence the biological availability of B7-H6. A major regulatory process involves ADAM10- and ADAM17-mediated proteolytic shedding, which releases the extracellular domain of B7-H6 into the tumor microenvironment and circulation (49). This process reduces membrane-associated B7-H6 while generating soluble B7-H6 species that may possess distinct immunological functions. Consequently, B7-H6 expression is not solely determined by transcriptional activity but also by dynamic regulation of protein stability and surface retention.

Collectively, current evidence suggests that B7-H6 expression is controlled by a complex network of epigenetic regulation, inflammatory signaling, cellular stress responses, and post-translational processing. A deeper understanding of these regulatory mechanisms will not only provide insight into the biological role of B7-H6 during tumor development but may also reveal new opportunities to enhance the efficacy of B7-H6-targeted immunotherapies by increasing target expression or preventing its loss through proteolytic shedding. The diverse mechanisms regulating B7-H6 expression suggest that this molecule is more than a passive marker of malignant transformation. Accumulating evidence suggests that B7-H6 may actively contribute to tumor progression through both immune-dependent and tumor-intrinsic mechanisms, as discussed below.

5. Biological roles of B7-H6 in cancer

Although B7-H6 was initially characterized as an immune recognition ligand, accumulating evidence indicates that it also participates directly in tumor cell biology. Emerging studies suggest that B7-H6 contributes to several hallmarks of cancer, including sustained proliferation, resistance to apoptosis, enhanced migratory capacity, and metastatic dissemination. These observations have shifted the perception of B7-H6 from a passive immune marker to an active regulator of malignant behavior. The expression patterns, biological functions, and clinical associations of B7-H6 across different malignancies are summarized in Table 1.

Table 1: Molecular and clinical significance of B7-H6 across human malignancies.

Tumor types	Expression	Biological functions	Prognostic association	Proposed Mechanism	Ref
Hepatocellular Carcinoma (HCC)	Upregulated	Promotes proliferation, migration, and invasion	Conflicting; associated with both aggressive behavior and improved survival in different cohorts	STAT3 activation; MMP9 induction	51, 56, 60
Breast Cancer	Upregulated	Promotes tumor progression and survival	Worse overall survival	PI3K/Akt signaling; apoptosis regulation	40,54
Ovarian Cancer	Upregulated	Associated with metastasis and immune escape	Poor survival and disease progression	NKp30-suppression via soluble B7-H6	58
Glioma/Medulloblastoma	Upregulated	Enhances migration and invasion	Not established	c-MYC activation; PI3K/Akt; ERK/MAPK; MMP2/9	53,57
Non-Hodgkin Lymphoma (NHL)	Upregulated	Promotes proliferation, migration, and invasion	Limited clinical data	Ras/MEK/ERK signaling	52
Non-small cell lung cancer (NSCLC)	Variable	Associated with tumor differentiation	No significant association with survival	Not clearly defined	59
Cervical Cancer	Upregulated	Regulates proliferation and migration	Unknown	NKp30-dependent signaling interactions	50

Abbreviations: HCC, hepatocellular carcinoma; NSCLC, non-small cell lung cancer; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; ERK, extracellular signal-regulated kinase; MMP, matrix metalloproteinase; STAT3, signal transducer and activator of transcription 3.

In addition to acting as the ligand for NKp30, B7-H6 also has intracellular regulatory functions. (**Figure 3**) When soluble NKp30 was co-cultured with the B7-H6-positive cervical cancer-derived cell lines, SiLA and HeLa, the proliferation and migration were significantly retarded (50). Knockdown of B7-H6 significantly attenuated tumor proliferation, migration, and invasion in the HepG2 and SMMC-7721 cell lines (51). Moreover, B7-H6 promotes cell proliferation, migration, and invasion via the Ras/MEK/ERK Pathway. Overexpression of B7-H6 in Jurkat and Raji cell lines significantly increased MEK and ERK phosphorylation (52). However, the MEK1/2 inhibitor can only partially reverse the cell migration and invasion. This reminds us that B7-H6 regulates tumor migration, proliferation, and invasion through multiple pathways. These pathways may function independently. Accumulating evidence revealed the relationship between B7-H6 and the PI3K/AKT pathway. Knockdown of B7-H6 in glioma stem-like cells decreased the expression of c-Myc and inactivated the PI3K/Akt and ERK/MAPK signaling pathways. RNMT (RNA guanine-7-methyltransferase) played a key role in c-Myc expression and was also downregulated by B7-H6 inhibition. C-Myc was known to regulate the PI3K/Akt and ERK signaling pathways. Moreover, enhanced c-Myc expression induced by B7-H6 also reorganizes F-actin, thereby improving the migration and invasion of Daoy cells (53). Furthermore, cell cycle regulatory proteins, such as cyclin D1, cyclin-dependent kinases 4 (CDK4) and CDK6, and phospho-Rb expression were significantly decreased upon B7-H6 inhibition (51). Knockdown of B7-H6 inhibits cell proliferation and promotes apoptosis, while it upregulates the expression of β-catenin, caspase-3, and Bax in MDA-MB-231 cells (54). Those proteins are also regulated by the PI3K/AKT and Ras/MEK/ERK pathways. Therefore, in addition to the Ras/MEK/ERK pathway, B7-H6 may regulate cell proliferation and invasion via the c-Myc/PI3K/Akt pathway.

Further studies have found that B7-H6 activates the STAT3 pathway (42). Cellular stress responses may also contribute to B7-H6 upregulation. In particular, therapeutic stress has been shown to enhance tumor sensitivity to NK-cell cytolysis by upregulating B7-H6 (55). B7-H6 promotes proliferation and invasion of HCC cells by inducing MMP-9 expression and STAT3 activation (56). The expression levels of MMP-2 and MMP-9 decreased upon B7-H6 knockdown in glioma cells (57). That research revealed that the pro-tumorigenesis function of B7-H6 may be mediated by the STAT3 pathway, promoting anti-apoptosis and pro-proliferation in cancer cells, but this function appears to depend on pathological conditions. In clinical practice, B7-H6 is closely associated with patient prognosis and survival. In a study on a cohort of 1100 breast cancer patients, the upregulation of B7-H6 at the mRNA level is significantly associated with worse overall survival (40). In ovarian cancer, high-level expression of B7-H6 in tumor tissues is correlated with a worse survival rate, tumor metastasis, and progression (58). However, in astrocytoma, gastric carcinoma, and non-small cell lung cancer (NSCLC), this protein expression does not confer prognostic significance (51). But in NSCLC, B7-H6-positive carcinomas were significantly correlated with the degree of differentiation but not with the three-year survival rate (59). In a study of hepatocellular carcinoma (HCC), high B7-H6 levels are associated with smaller tumor size and better survival (60). Therefore, the biological consequences of B7-H6 expression appear to be context-dependent and may vary with tumor type and microenvironmental conditions. Collectively, these findings suggest that B7-H6 may serve as a context-dependent indicator of tumor progression and clinical outcome. The prognostic significance of B7-H6 appears to be highly context-dependent. Differences in tumor lineage, immune cell infiltration, quantification methods, and the relative contributions of membrane-bound versus soluble B7-H6 may account for the inconsistent clinical associations reported across malignancies. These observations suggest that B7-H6 should not be viewed as a universal prognostic biomarker, but rather as a context-specific indicator whose biological and clinical relevance may vary according to tumor type and microenvironmental conditions.

Collectively, these findings suggest that B7-H6 functions as more than an NK-cell ligand. Through engagement of Ras/MEK/ERK, PI3K/Akt, c-Myc, and STAT3 signaling networks, B7-H6 appears capable of promoting multiple hallmarks of cancer, including sustained proliferation, resistance to apoptosis, and invasive behavior. These observations support an emerging model in which B7-H6 serves both immunological and tumor-intrinsic functions. This dual functionality places B7-H6 at a unique intersection between tumor immunology and cancer cell biology. Traditionally, B7-H6 has been viewed primarily as a danger-associated ligand that facilitates NK-cell recognition and elimination of transformed cells through NKp30 activation. However, accumulating evidence indicates that B7-H6 also exerts direct tumor-intrinsic effects by regulating signaling pathways involved in proliferation, survival, migration, and invasion. Moreover, proteolytic shedding and the generation of soluble B7-H6 may enable tumors to attenuate NK-cell surveillance while preserving or even enhancing protumorigenic functions. Consequently, B7-H6 may act as a molecular bridge linking immune surveillance, immune escape, and malignant progression. This integrated model offers a potential explanation for the context-dependent clinical associations observed across tumor types and highlights why therapeutic targeting of B7-H6 may simultaneously influence both tumor cells and the antitumor immune response.

The role of B7-H6 in tumor immune escape has gradually emerged through a series of experimental and clinical studies. The shedding of B7-H6 was considered one of the mechanisms by which tumor cells escape immune surveillance. The inhibition of ADAM-mediated B7-H6 shedding significantly increased NK-cell cytotoxicity (44). Furthermore, a high level of sB7-H6 was detected in peritoneal/ascitic fluid from ovarian cancer patients, which was associated with low NKp30 expression on NK cells (58). In high-risk neuroblastoma, sB7-H6 in serum inhibited NK-cell functions when co-cultured with NK cells in vitro (61). In hemodialysis patients, elevated serum sB7-H6 levels are associated with a higher risk of infection, and circulating sB7-H6 levels increase in patients with infectious complications (62). Therefore, B7-H6 may be related to inflammatory responses. However, there are 2 forms of B7-H6, and those studies haven't explicitly stated the functional form of sB7-H6 in sera. Therefore, we can't confirm the immunosuppressive function of cell-shed sB7-H6 in cancer progression. On the other hand, a recent study demonstrated that human recombinant sB7-H6 with an Fc tag has high NKp30-binding capacity and can induce both TNF-α and IFN-γ production (63). Whether cell-shed sB7-H6 can also induce NK-cell-mediated cytokine production and cytotoxicity remains to be experimentally verified. The biological significance of soluble B7-H6 (sB7-H6) remains one of the major unresolved questions surrounding the B7-H6/NKp30 axis. A prevailing hypothesis proposes that sB7-H6 functions as a decoy ligand that chronically engages NKp30, leading to receptor downregulation and reduced NK-cell responsiveness. This model is supported by studies demonstrating an inverse relationship between circulating sB7-H6 levels and NKp30 expression in cancer patients.

However, accumulating evidence suggests that the effects of sB7-H6 may be more complex than simple receptor blockade. Recombinant sB7-H6 has been shown to retain NKp30-binding activity and stimulate cytokine production under certain experimental conditions, raising the possibility that soluble B7-H6 may exert context-dependent immunomodulatory effects. These apparently conflicting findings may reflect differences in molecular origin, post-translational modification, concentration, or mode of release. For example, ADAM-mediated shedding, exosome-associated secretion, and inflammation-induced soluble isoforms may possess distinct biological properties. Clarifying these differences will be critical for understanding how B7-H6 contributes to immune escape and for optimizing future B7-H6-targeted therapeutic strategies. Collectively, current evidence suggests that soluble B7-H6 may function as both a biomarker of disease progression and a regulator of antitumor immunity, although its precise biological role remains to be fully elucidated.

6. Current anti-B7-H6 antibody therapy

The tumor-restricted expression pattern of B7-H6 has spurred the development of diverse therapeutic platforms to exploit the B7-H6/NKp30 axis. Unlike broadly expressed immune targets that raise concerns about on-target, off-tumor toxicity, B7-H6 offers an opportunity to selectively target malignant cells while simultaneously enhancing immune effector functions. Consequently, multiple antibody-based, cellular, and immune-engaging strategies have been developed to leverage B7-H6's unique biological properties. A diverse range of B7-H6-targeted therapeutic platforms has been developed, including bispecific engagers, immunoligands, CAR-based cellular therapies, and cytokine-enhanced immune approaches. The major strategies currently under investigation are summarized in Table 2.

Table 2: Current B7-H6-targeted therapeutic strategies.

Strategy	Format	Mechanism	Outcome	Ref
NK-cell engager	B7-H6/NKp30 immunoligand	NK activation	Enhanced cytotoxicity	64
HER2-B7-H6 immunoligand	Fusion protein	HER2 targeting + NK activation	Improved ADCC	65
B7-H6/CD3 BiTE	T-cell engager	T-cell recruitment	Tumor elimination	66
TZ47 CAR-T	CAR-T	Direct targeting	In vivo efficacy	67
Humanized anti-B7-H6 antibody/scFv design	CAR-T	Reduced immunogenicity	Improved translation	68
Human scFv CAR-T	CAR-T	Alternative epitope	Strong efficacy	69
IL-15-enhanced BiTE	BiTE + cytokine	T/NK activation	Superior efficacy	71

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; BiTE, bispecific T-cell engager; CAR, chimeric antigen receptor; IL-15, interleukin-15; NK, natural killer.

Pekar et al. generated a bispecific IgG-like NK-cell engager that fused the high-affinity N-terminal IgV domain of B7-H6 with antigen-binding fragments (Fabs) derived from cetuximab, an EGFR monoclonal antibody (64). The high-affinity N-terminal IgV domain of B7-H6 was obtained by affinity maturation. This bispecific IgG-like NK-cell engager increased NK-cell cytotoxicity and the release of IFN-γ and TNF-α compared with human IgG Fc (HFC), thereby promoting ADCC. A HER2/B7-H6 fusion antibody is also constructed to trigger NK-cell killing of HER2-positive breast cancer cells (65). The B7-H6:HER2-scFv shows good efficacy in enhancing NK-cell cytotoxicity and in improving ADCC when combined with trastuzumab and cetuximab [61]. Several different bispecific T-cell engagers (BiTEs) were also generated. Wu et al. fused the anti-B7-H6 scFv with a CD3ε-specified scFv to lead T cells to mediate cell killing and cytokine release against B7-H6-positive tumor cells (66). The elimination effect was observed in both murine melanoma and ovarian cancer models. In vivo, perforin and IFN-γ levels increased following B7-H6/CD3 BiTE treatment, resulting in improved survival (66). They also constructed a B7-H6-specific CAR-T cell based on TZ47, which showed good tumor-elimination efficacy in the in vivo ovarian cancer model (67). Since TZ47 is a mouse IgG, Choi et al. humanized it to reduce its immunogenicity (68). Later in 2017, Hua et al. published a new human B7-H6-targeting scFv that binds a different epitope than TZ47 and generated a new CAR-T based on this antibody. This scFv can bind to both soluble and membrane-bound B7-H6, and the CAR-T also showed sufficient anti-cancer activity (69). BCL-2 overexpression, B7-H6-targeting CAR-T also showed promising therapeutic outcomes both in vitro and in vivo, alone and in combination with venetoclax (a

BH3-mimetic small-molecule drug targeting BCL-2) against small-cell lung cancer (70). A recent study constructed BiTEs combined with the IL-15/IL-15Ra sushi fusion protein against B7-H6-positive cell lines. The cytotoxicity reached 90% in vitro, and tumor size was reduced by 79% in vivo. However, the BiTEs with the IL-15/IL-15Ra sushi fusion protein showed higher toxicity at high concentrations in vivo (71).

Taken together, these studies demonstrate that B7-H6 can be successfully targeted through multiple therapeutic modalities, including NK-cell engagers, bispecific antibodies, CAR-T cells, and cytokine-enhanced immune platforms. Although most evidence remains preclinical, the breadth of successful approaches highlights B7-H6's versatility as an immunotherapeutic target and provides a strong rationale for continued clinical development.

7. Clinical development status of B7-H6-targeted therapies

Despite the growing body of preclinical evidence supporting B7-H6 as an attractive immunotherapeutic target, clinical translation remains in its early stages. To date, most B7-H6-directed approaches have been evaluated primarily in cell-line systems and xenograft models (66, 67), with only limited progression into human clinical studies. The most advanced clinical program is represented by a B7-H6/CD3 bispecific T-cell engager evaluated in a phase I clinical trial (ClinicalTrials.gov identifier: NCT04752215). Although study completion and status updates have been reported, efficacy and detailed safety outcomes have not yet been publicly disclosed, making it difficult to assess the true clinical potential of B7-H6-targeted therapy.

The lack of clinical data highlights a broader challenge frequently encountered during immunotherapy development. While xenograft models have consistently demonstrated potent antitumor activity of B7-H6-targeting antibodies, BiTEs, and CAR-based cellular therapies, these models incompletely recapitulate the complexity of the human tumor microenvironment. Human tumors exhibit substantial heterogeneity in antigen expression, immune-cell infiltration, stromal composition, and immunosuppressive signaling, all of which may significantly influence therapeutic responses. Furthermore, xenograft systems often fail to accurately model soluble B7-H6 dynamics, antigen shedding, and long-term immune adaptation, factors that may become critical determinants of efficacy in patients.

The clinical development of B7-H6-targeted therapies can also be viewed in the context of other NK-cell-directed immunotherapeutic strategies. Therapeutic agents targeting NKG2D ligands, NKp46, CD16, NKG2A, and TIGIT have already entered clinical development and, in some cases, demonstrated encouraging early clinical activity (30). Compared with these targets, B7-H6 has the distinct advantage of being highly restricted in normal tissues or largely restricted to malignant and stressed cells, potentially reducing the risk of on-target, off-tumor toxicity. At the same time, uncertainties regarding expression heterogeneity, the biology of soluble B7-H6, and inducible expression under inflammatory conditions remain important translational considerations (47). Consequently, future clinical studies will be essential not only to establish efficacy but also to define optimal patient-selection strategies, combination regimens, and biomarkers to maximize the therapeutic potential of the B7-H6/NKp30 axis.

8. Discussion

Beyond demonstrating clinical efficacy, several biological and translational challenges must be addressed before B7-H6-targeted therapies can be successfully integrated into routine oncology practice. These include uncertainties regarding target heterogeneity, the biological consequences of

soluble B7-H6, the mechanisms of therapeutic resistance, and the identification of predictive biomarkers to guide patient selection.

Currently, most B7-H6-targeting therapies focus on T-cell activation. However, a recent study has disclosed that B7-H6 expression is significantly increased on T cells, especially on CAR-T cells, in response to activation. B7-H6-mediated NKp30-dependent NK-cell activation resulted in depletion of activated T cells and limited the antitumor activity of CAR-T cells (72). Although there are no experimental results demonstrating T-cell depletion after T cells are activated by B7-H6-targeting T-cell engagers, there is a theoretical risk of T-cell elimination by NK cells, which could compromise the therapeutic efficacy of these engagers. Therefore, the development of B7-H6 target therapy based on activating NK cells might be more efficient. Furthermore, shedding B7-H6 is known as an immune escape strategy for cancer cells. For this reason, immunotherapy may lose efficacy. Therefore, B7-H6-targeting treatment combined with shedding inhibition may yield better outcomes. Another important consideration is the heterogeneous expression of B7-H6 across tumor types and even within individual tumors. Antigen heterogeneity may facilitate immune escape through selective pressure during treatment, potentially limiting the durability of therapeutic responses. Future studies should therefore investigate strategies to overcome antigen-loss variants, including dual-targeting approaches and combination immunotherapies.

What's more, there is a limited number of studies that have explored the drug-combination potential of B7-H6-targeting therapy. A study has shown that a B7-H6/CD3 T-cell engager can more effectively suppress tumor growth in combination with an anti-PD-1 drug. The combination of anti-PD-1 and B7-H6 reduced the effective concentration of both drugs (73). In addition to anti-PD-1, many other drugs are worth testing in combination with anti-B7-H6 antibodies. This direction needs more attempts. Also, B7-H6 is a highly tumor-specific surface marker. Therefore, B7-H6 is potentially a target for a tumor-specific drug delivery system, but this remains untested. B7-H6 retains considerable therapeutic potential. The development of robust predictive biomarkers also remains a major unmet need. While B7-H6 expression is frequently used as a selection criterion, it remains unclear whether expression level alone adequately predicts therapeutic responsiveness. Integrating tumor B7-H6 expression with measures of NK-cell infiltration, NKp30 expression, soluble B7-H6 concentration, and immune microenvironment characteristics may provide a more comprehensive framework for patient stratification.

B7-H6 occupies a unique position at the intersection of tumor immunology and cancer cell biology. Beyond functioning as a ligand for NKp30-mediated immune recognition, accumulating evidence suggests that B7-H6 actively contributes to tumor progression by regulating proliferative, survival, and invasive signaling networks. This dual role distinguishes B7-H6 from many conventional immunotherapeutic targets and creates opportunities for therapeutic strategies that can simultaneously enhance antitumor immunity and disrupt tumor-intrinsic oncogenic programs.

Despite substantial progress, several fundamental questions remain unanswered. The upstream signaling pathways that induce B7-H6 expression remain incompletely characterized; the biological functions of distinct soluble B7-H6 species remain controversial; and the mechanisms by which B7-H6 activates intracellular oncogenic pathways are poorly understood. Emerging evidence suggests that membrane-bound and soluble B7-H6 may exert distinct biological functions, yet their relative contributions to tumor progression and immune regulation remain unclear. Notably, soluble NKp30 has been reported to inhibit tumor growth, whereas inhibition of ADAM-mediated B7-H6 shedding can suppress tumor cell proliferation, highlighting the complex and potentially divergent roles of different

B7-H6 forms. Whether the protumorigenic activities attributed to B7-H6 are mediated primarily by membrane-associated or soluble species remains unresolved. Clarifying the molecular mechanisms governing B7-H6 signaling, shedding, and functional diversification will be essential for refining therapeutic strategies, identifying predictive biomarkers, and determining which patient populations are most likely to benefit from B7-H6-targeted interventions.

Collectively, current evidence positions B7-H6 as a unique immuno-oncologic target that integrates immune surveillance, immune escape, and tumor-intrinsic signaling. Continued investigation into the regulation, biological functions, and therapeutic exploitation of the B7-H6/NKp30 axis will likely facilitate the development of next-generation immunotherapies that simultaneously enhance antitumor immunity and disrupt malignant progression.

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Declarations

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