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Editorial

NKG2D Ligands in Cancer Immunotherapy: Target or Not?

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Introduction

In response to DNA damage or pathogenic stress, epithelial cells were induced to express a class of membrane-bound molecules that can be recognized by the NK cell activating receptor NKG2D [1-3]. In human, these molecules include MHC I chain related family of MIC (MICA and MICB) [4], the unique long 16 (UL16)-binding protein (ULBP) or the retinoic acid early transcript (RAET) family[5-8]. Theoretically, expression of these molecules would evoke the anti-tumor immunity through activation of NK cells and co-stimulation of CD8 T cells, NKT, and subsets of gamma-delta T cells [9]. However, clinical findings of NKG2D ligand expression on tumor cells with disease prognosis are controversy [10-12], which begets the dilemma in whether and how to target NKG2D ligand in cancer immunotherapy.

NKG2D ligands are differentially expressed by human epithelial tumor cells. The most frequently expressed and best characterized human NKG2D ligands are the MIC family molecules, among which MICA is more prevalently expressed. The expression pattern and clinical significance of NKG2D ligands on disease prognosis seem to be cancer-specific. In uveal melanoma, NKG2D ligand MIC(A/B) expression was detected only in primary tumor lesion, in which large infiltration of $NKG2D^+$ lymphocytes was also seen [10]. Metastatic uveal melanoma lesions lost MIC expression and are absent of $NKG2D^+$ lymphocytes. These suggest that MIC expression predicts a favorable clinical outcome for uveal melanoma. Consistently, a study from large cohorts of colorectal patients revealed a positive correlation of NKG2D ligand expression, MIC and RAET1G, with good prognosis [11]. On the contrary, a large patient cohort study from ovarian cancer suggest that tissue levels of NKG2D ligands may predict a poor prognosis, with specific emphasis on the expression of the RAET and ULBP family members [12].

The impact of NKG2D ligand cancer progression is a complex, largely depending on the threshold whether the ligand is predominantly membrane-bound or soluble form. As a mechanism of immune evasion, human malignant cancer cells shed NKG2D ligands through proteolysis activity to produce soluble NKG2D ligand (sNKG2D-L) [13-16]. The loss of membrane-bound NKG2D ligand and concurrent increase in sNKG2D-L pose profound negative imprints in anti-tumor immune responses through mechanism of: 1) reduction of susceptibility of tumor cells to the cytotoxicity of NKG2D-positive lymphocytes due to reduced density of cell surface NKG2D-L; 2) down regulation of NKG2D expression on NK, NKT, γδ and CD8 T cells by sNKG2D-L [13,17-20]; and 3) impairs NK cell homeostatic maintenance [21]. Due to these understandings, whether NKG2D ligand can be used as prognostic marker and therapeutic target has been exploited. Since induction of NKG2D ligand expression is a response to cellular stress and DNA damage to alert the immune system, the prognostic value of tissue expression of NKG2D ligand during early cancer may depend on the tumor immunogenicity and tissue microenvironment of a specific cancer type. As an evitable consequence of tumor shedding NKG2D-L, serum levels of soluble NKG2D ligand hence elevated. It is conceivable that serum levels of sNKG2D-L could provide a significant prognostic value for malignant diseases. Indeed, large patient cohort studies from various types of cancers, including lung, colorectal, breast, ovarian, prostate, and other gastrointestinal cancers, by Salih's group have shown a significant correlation of high serum sMICA or sMICB with metastatic diseases [22,23]. Extensive studies in prostate cancer patients have shown a significant correlation of loss of tumor cell surface MIC expression and increase in serum levels of sMIC and the correlation with disease stages [17]. Serum levels of sMIC were shown more profoundly elevated in men with metastatic prostate cancer [23]. Hence it is suggested that both tissue levels of cell-bound NKG2D ligand and serum levels of soluble NKG2D ligands have to be taken into consideration comprehensively for disease prognosis.

Given these clinical observations, it is conceivable that NKG2D ligand, in particular the most prevalently expressed human MIC, can be targeted for cancer immune therapy. As shedding of NKG2D ligand is a manifestation of human cancer and, in particular, the most predominantly expressed human MIC has no homolog in rodents, existing mouse tumor models cannot be used to as a preclinical model to test the therapeutic effect of targeting human NKG2D ligands. To address this barrier, Liu et al generated lines of engineered TRAMP mice (TRansgenic Adenocarcinoma of the Mouse Prostate) that express two forms of human NKG2D ligand specifically in the prostate. One form is the engineered membrane-bound NKG2D ligand that cannot be shed; the other is the native human NKG2D ligand that can be shed by tumor cells. With these lines of mouse models, Liu et al demonstrated that retaining of membrane-bound NKG2D ligand on tumor cells evoked anti-tumor immune response and prevented tumor development, whereas shedding of NKG2D ligand by tumor cells resulted in elevation of serum sMIC and expedited disease progression to metastasis [21]. Liu et al. further revealed that high levels of sMIC profoundly perturb NK cell homeostatic maintenance as a mechanism to facilitate cancer metastasis [21]. This study provided the proof-of-concept with clinical relevant animal models

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that sustaining membrane-bound NKG2D ligand preserves anti-tumor immunity and hence suggested the significance in stabilizing surface NKG2D-L expression during cancer immunotherapy.

With the understanding of immune suppressive mechanisms of sNKG2D-L, cancer immunotherapy should take the impact of sNKG2D-L into a great consideration. With the promising results of various immunotherapeutic regimens for malignant diseases, such as T cell check point blockade (anti-PD-1 and anti-CTLA4) [24], engineered CAR-T cell adoptive therapy[25], and adoptive NK cell cancer immunotherapy [26], prescreening patients of serum levels of sNKG2D-L may be necessarily to predict potential therapeutic response and to stratify combinatory therapies for a better clinical outcome. Stratifying to sustain membrane-bound NKG2D ligand and/or to eliminate the suppressive effect of sNKG2D-L during cancer immunotherapy is warrant to be the focus of future milestones.

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