**CANCER IMMUNOTHERAPY**

**Natural killers join the fight against cancer**

An antibody overcomes cancer cell immune evasion and activates natural killer cells

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Immunotherapy represents one of the major breakthroughs in the treatment of cancer patients. Current therapies focus on harnessing the adaptive immune system, with great success achieved by interfering with immune checkpoints to unleash antitumor CD8+ T cell responses. There is emerging evidence that cancers develop multiple strategies to escape CD8+ T cell recognition. These tumors, however, can be preferentially attacked by natural killer (NK) cells. NK cells are innate lymphocytes that express activating receptors, including the NK group 2D (NKG2D) receptor, which recognize ligands displayed on the surface of tumor cells and pathogen-infected cells. On page 1537 of this issue, Ferrari de Andrade et al. (1) present an elegant approach to improve NK cell recognition of tumor cells, extending the range of immunotherapies beyond T cells.

The NKG2D–NKG2D ligand axis represents a major activating pathway for human NK cell–mediated recognition of tumor cells and virus-infected cells (2–4). Several strategies targeting NKG2D ligands (5, 6) expressed on cancer cells or the NKG2D receptor (7) on NK cells and certain other immune cells (including CD8+ T cells) have been reported and are now under evaluation in preclinical studies. These approaches are challenging because tumors have evolved mechanisms to escape NK cell surveillance. One major mechanism of tumor escape is the shedding of the NKG2D ligands, major histocompatibility complex (MHC) class I polypeptide–related sequence A (MICA) and MICB, from the tumor cell surface by matrix metalloproteinases (MMPs) and ADAMs (a disintegrin and metalloproteinases), thus impairing NK cell recognition (8–10). Moreover, shed MICA and MICB that might block NKG2D receptor interaction with its cellular ligands are found in the sera of cancer patients, which frequently correlates with poor prognosis and impaired NK cell function.

To circumvent tumor immune escape and to efficiently target NK cells to tumors, Ferrari de Andrade et al. generated a monoclonal antibody (mAb) against MICA and MICB that masks the region of their extracellular domains that is cleaved by MMPs and ADAMs. The use of a mAb that binds to the cleavage site, but does not interfere with the sites for NKG2D receptor binding, preserves the expression of MICA and MICB on tumor cells and allows NKG2D-dependent activation of NK cell effectors. Additionally, the Fc portion of this mAb can mediate antibody-dependent cellular cytotoxicity (ADCC), triggering target-cell killing by NK cells. The application of this mAb greatly reduced the growth of subcutaneous tumors and metastases in an immune-competent mouse model and in an immunocompromised xenograft mouse model in which human NK cells were administered. The study introduces an exciting concept for a therapeutic mAb with the potential to improve NK cell–based cancer immunotherapy.

The biology of NKG2D ligands is complex (4, 10). The MICA and MICB genes are highly polymorphic, and different alleles of these ligands vary in expression and their affinity for the NKG2D receptor. The mAb generated in this study recognizes the most common MICA and MICB variants, which are expressed in many tumors but rarely by healthy cells. Expression of MICA and MICB can be enhanced at the transcriptional level by radiotherapy, histone deacetylase (HDAC) inhibitors, or chemotherapy. The present approach, however, is more specific. Moreover, tumor cells often evolve strategies to down-regulate NKG2D on NK cells or T effector cells in the host. In this respect, tumor cell–produced transforming growth factor β (TGF-β) and kynurenine were shown to transcriptionally down-regulate NKG2D expression on NK cells (11). These effects are transient, and NKG2D expression can be restored by activation of NK cells with cytokines, for example, interleukin-2 (IL-2) and IL-15. Thus, a combination of the MICA-MICB mAb with cytokines that are now being used in the clinic might further increase the therapeutic efficiency of this approach. Additional combinatorial strategies could involve the blockade of inhibitory NK cell pathways such as killer cell inhibitory receptors (KIRs) or NKG2A, which are now in clinical trials in different types of cancer (12) (see the figure).

In humans, NKG2D is not only expressed by NK cells but also by all CD8+ T cells in which a costimulatory function of the NKG2D–NKG2D ligand axis has been reported (13). Ferrari de Andrade et al. used a poorly immunogenic metastatic melanoma model to show that after application of the MICA-MICB mAb, tumor growth control was mainly mediated by NK cells and not by CD8+ T cells. It will be important to assess whether blocking MICA and MICB shedding in more immunogenic tumor models will also elicit an antigen-specific CD8+ T cell response. Accordingly, it is feasible to combine the MICA-MICB mAb with immune checkpoint inhibitors such as anti–PD-1 or anti–PD-L1, engineered immune cells, or antibodies blocking interferon-γ (anti–IFN-γ), tumor necrosis factor (anti–TNF), or interleukin-2 (IL-2) and IL-15. Thus, a combination of the MICA-MICB mAb with cytokines that are now being used in the clinic might further increase the therapeutic efficiency of this approach. Additional combinatorial strategies could involve the blockade of inhibitory NK cell pathways such as killer cell inhibitory receptors (KIRs) or NKG2A, which are now in clinical trials in different types of cancer (12) (see the figure).
as anti–programmed cell death protein 1 (PD-1), anti–PD-1 ligand 1 (PD-L1), or other T cell–based therapies, including the adoptive transfer of engineered T cells to further enhance T cell activation. These combinations would not only enhance both CD8+ T cell and NK cell activation against cancer cells but, in addition, broaden the spectrum of tumor cells that can be attacked.

MICA and MICB expression has been reported in healthy individuals in barrier tissues such as the gut. It is unknown whether these cells also shed NKG2D ligands. Expression and stabilization of MICA and MICB in these tissues could cause excessive inflammation resulting from aberrant immune cell activation and might lead to serious side effects. Additionally, circulating monocytes and tumor-infiltrating myeloid cells in some cancer patients express MICB. Activated T cells can express NKG2D ligands as well (14). Moreover, under homeostatic conditions, NKG2D ligands were detected on mouse endothelial cells and might modulate NK cell function (15). Whether NKG2D ligands on myeloid cells, T cells, and endothelial cells are also stabilized by the MICA-MICB mAb, potentially promoting inflammation, has not been addressed. Undoubtedly, future studies are needed to provide a comprehensive analysis of MICA and MICB expression in homeostatic conditions and during disease.

Bispecific mAbs targeting additional antitumor effector cells, such as CD3+ T cells (which infiltrate solid tumors at higher numbers than NK cells), to MICA- and MICB-bearing tumors could be generated. Moreover, the MICA-MICB mAb could also be engineered into T cells or NK cells for adoptive cell transfer, potentially resulting in efficient tumor cell targeting, provided there is no toxic off-target cell killing. Ferrari de Andrade et al. reveal an innovative approach to counteract a major mechanism of cancer immune escape from NK cell recognition that, if safe in patients, harbors high potential and versatility for future clinical applications. ■

**REFERENCES**

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