Researchers discuss disrupting NKG2A:HLA-E interactions for enhanced anti-cancer immunity

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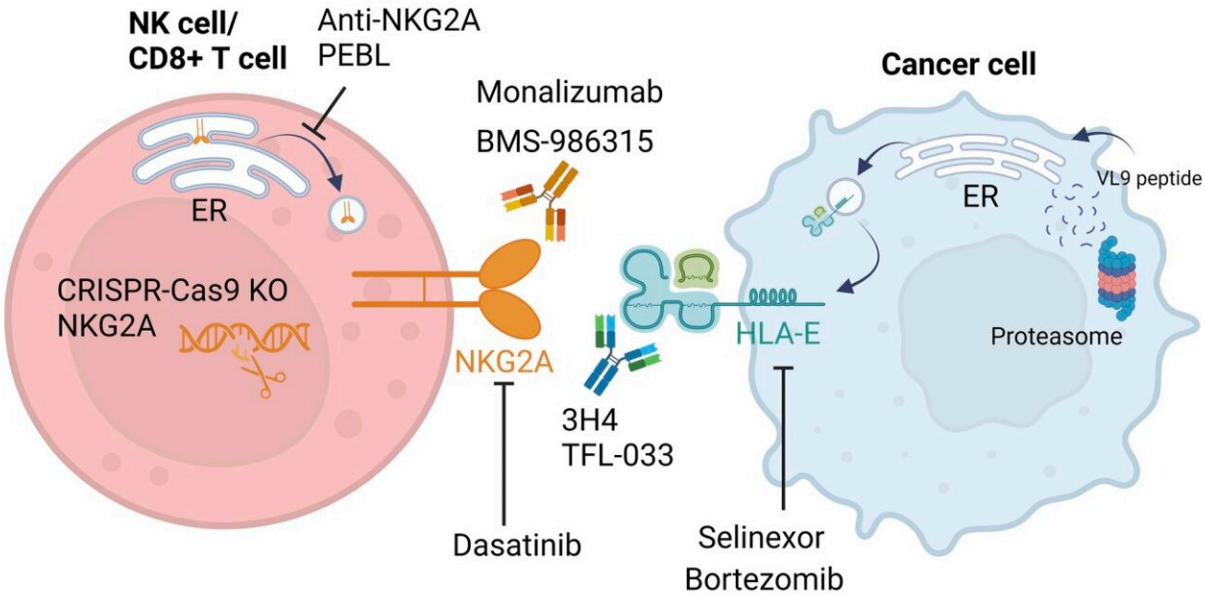

Cancer therapeutics targeting the NKG2A:HLA-E axis. The NKG2A:HLA-E interaction can be inhibited by antibodies targeting either NKG2A (monalizumab, BMS-986315) or HLA-E (3H4, TFL-033). Small molecule inhibitors bortezomib and selinexor have been shown to reduce surface expression of HLA-E, sensitizing tumor cells to NK cell cytotoxicity. The proteasome inhibitor bortezomib induces endoplasmic reticulum (ER) stress, potentially leading to impaired peptide loading which is crucial for expression of HLA-E at the cell surface. The precise mechanism behind the downregulation of surface HLA-E by selinexor has not yet been described. Expression of NKG2A on the surface of NK cells can also be manipulated by CRISPR-Cas9 knock-out

(KO), anti-NKG2A protein expression blocker (PEBL) that can retain NKG2A in the ER, and the tyrosine kinase inhibitor dasatinib that can induce NKG2A downregulation. Overall, either blockade or downregulation of NKG2A and HLA-E relieves NK cell inhibition and improves lysis of tumor cell targets. Created with https://www.biorender.com/. Credit: *Oncotarget* (2024). DOI: 10.18632/oncotarget.28610

A new editorial titled "Strategies to disrupt NKG2A:HLA-E interactions for improved anti-cancer immunity" has been published in *Oncotarget*.

Two studies using CRISPR screens in cancer cells identified HLA-E as a critical negative regulator of NK cell interactions with cancer cells. Consistent with this, IFNγ signaling was associated with NK cell resistance due to increased STAT1 activation and enhanced HLA-E expression. This effect is also evident in the murine homolog of HLA-E, Qa-1b, which was upregulated by inflammatory signals across all cell types tested.

In addition to inflammatory signals, researchers Jack G. Fisher, Lara V. Graham, and Matthew D. Blunt from Clinical and Experimental Sciences, Faculty of Medicine at the University of Southampton, UK, recently demonstrated that surface expression of HLA-E is increased by lymph node-associated signals IL-4 and CD40L on primary chronic lymphocytic leukemia (CLL) cells.

Additionally, two recent studies have shown that HLA-E can protect circulating tumor cells from NK cell lysis via NKG2A, suggesting that targeting the NKG2A axis could be a promising strategy for preventing metastasis in solid tumors.

"In conclusion, there is strong preclinical evidence that disruption of

NKG2A interactions with HLA-E can stimulate both NK cell and cytotoxic T cell effector functions against cancer," the researchers state.

More information: Jack G. Fisher et al, Strategies to disrupt NKG2A:HLA-E interactions for improved anti-cancer immunity, *Oncotarget* (2024). DOI: 10.18632/oncotarget.28610