Novel checkpoint molecule of natural killer cell anti-tumor immunity revealed

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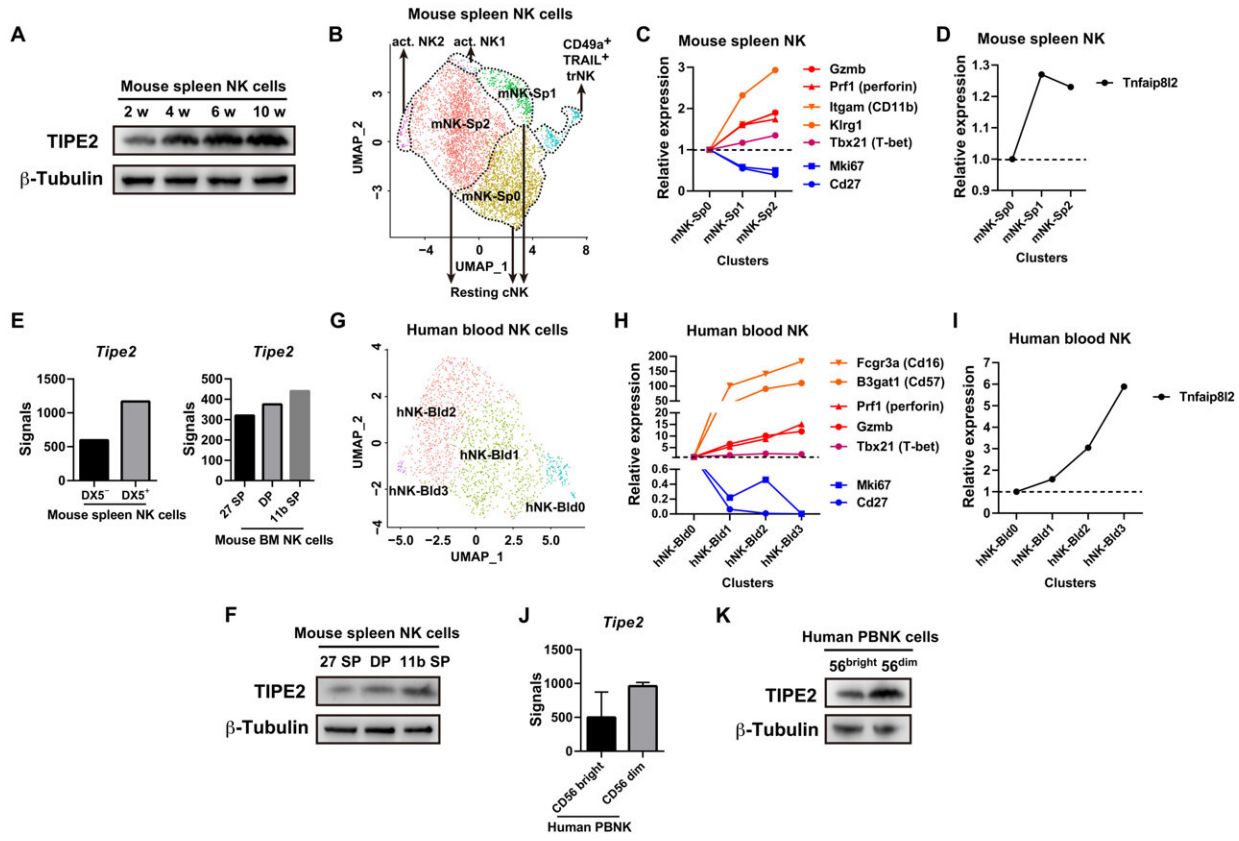

Fig. 1. TIPE2 expression correlates with NK cell maturation in both mice and humans.(A) TIPE2 expression of purified splenic NK cells from 2-, 4-, 6-, or 10-week-old wild-type mice was examined by Western blot. (B) UMAP of splenic NK cells from Tipe2WT/WT mice. Cells are color coded according to the defined subset. (C) Relative expression of the indicated genes in the defined subsets from (B). (D) Tipe2 relative expression levels were shown for clusters from (B). (E) Tipe2 transcript levels of purified DX5− or DX5+murine liver NK cells or CD27 SP, DP, or CD11b SP murine bone marrow NK cells obtained

from the dataset GSE43339 or the Immunological Genome Project database (www.immgen.org), respectively. (F) TIPE2 expression of purified CD27 SP, DP, or CD11b SP splenic NK cells from wild-type mice was examined by Western blot. (G) tSNE of human peripheral blood NK cells. Cells are color coded according to the defined subset. (H) Relative expression of the indicated genes in the defined subsets from (G). (I) Tipe2 relative expression levels were shown for clusters from (G). (J) Tipe2 transcript levels of purified CD56bright or CD56dimperipheral blood NK cells from healthy donors were obtained from the dataset GSE79939 (61). (K) TIPE2 expression of purified CD56bright or CD56dim peripheral blood NK cells from healthy donors was examined by Western blot. (A, F, and K) Data are representative of at least two independent experiments. Credit: DOI: 10.1126/sciadv.abi6515

Currently, immunotherapy is revolutionizing tumor therapy. However, most patients can't benefit from available immunotherapy strategies due to limited efficacy and safety, especially those with solid tumors.

Natural killer cells (NK cells) are cytotoxic innate immune cells that play an important role in immune surveillance against tumors. However, the underlying mechanisms are still poorly understood.

Dr. Tian Zhigang's group from the Shenzhen Institute of Advanced Technology (SIAT) of the Chinese Academy of Sciences reported that tumor necrosis factor-α (TNF-α)-induced protein-8 like-2 (TIPE2) suppressed NK cell maturation and anti-tumor immunity. This finding indicates that TIPE2 is a checkpoint molecule of NK cells, and targeting TIPE2 may benefit NK-based tumor immunotherapy.

Their study was published in *Science Advances* on Sept. 15.

Previous studies of Dr. Tian's group have already revealed the roles of checkpoint receptors T cell immunoglobulin and immunoreceptor

tyrosine-based inhibitory motif domain (TIGIT) and A3AR on NK cell functions in tumor surveillance, tissue injury and regeneration.

Based on these studies, they searched for checkpoint molecules during NK cell maturation, the process during which NK cells acquired optimal functions.

The researchers conducted single-cell transcriptomic analysis of both human and mouse peripheral NK cells at the steady state. They found that human and mouse NK cells comprised several sub-populations correlating with the NK cell maturation process from "immature" NK cells to "mature" NK cells. Importantly, TIPE2, a molecule previously reported to mediate immune tolerance, increased its expression along with the NK cell maturation process.

The researchers also investigated the role of this molecule in NK cell biology. They found that in NK-specific TIPE2 deficient mice, the levels of mature NK cells increased, and NK cells displayed enhanced effector functions, indicating that TIPE2 suppressed NK cell functional maturation.

Furthermore, NK-specific TIPE2 deficient mice showed better control of tumor growth in vivo, accompanied by increased tumor infiltration of NK cells, and by enhanced effector functions of tumor-infiltrating NK cells.

These results suggested a promising approach of targeting TIPE2 for NK cell-based immunotherapies.

More information: Jiacheng Bi et al, TIPE2 is a checkpoint of natural killer cell maturation and antitumor immunity, *Science Advances* (2021). DOI: 10.1126/sciadv.abi6515

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