

## **Researchers uncover marker important to effectiveness of natural killer T cells**

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Natural killer T cells, or NKT cells, are potent warriors against solid tumor cancers. However, the potential for this small subset of white blood cells has been limited by the lack of understanding of how they can be multiplied outside of the body and still be used to effectively target tumors.

Researchers from Baylor College of Medicine have now identified a molecular marker of NKT cells with high potential for proliferation and developed a method using molecular costimulation to expand these cells ex vivo (outside the body), then use them for effective cancer immunotherapy. Their study appears in the current issue of the *Journal of Clinical Investigation*.

Natural killer T cells localize to tumors, where they attack the tumors themselves, and they also can be engineered, or enhanced, to go after proteins and other markers that are selectively present in the tumor but not in normal tissue. One type of molecular enhancer, called chimeric antigen receptor (CAR), when used with T cells demonstrated success in clinical trials in fighting certain types of leukemia and lymphoma. However, CAR T cells have so far showed little activity in solid tumors, in part due to poor localization of T cells to the tumor site. Because of natural anti-tumor properties and ability to localize to the tumor tissues, NKT cells represent an attractive alternative for CAR-directed immunotherapy of cancer.

"NKT technology is quite powerful and offers a significant potential for



treatment of cancer, including solid tumors," said Dr. Leonid Metelitsa, professor of pediatrics at Baylor, Texas Children's Cancer Center and the Center for Cell and Gene Therapy at Baylor, Texas Children's Hospital and Houston Methodist. "But for it to be most effective, we have to find the best way to expand the cells ex vivo while preserving their ability to persist once delivered back to patients. If they can persist in the body for a long time, they have much longer therapeutic activity and this is essential for fighting cancer."

Previous research has shown that there is a certain subset of T cells that have a better ability to proliferate and persist, offering greater therapeutic benefits. This subset is called central memory T cells and is characterized by the expression of the surface molecule CD62L.

However, in NKT cells freshly derived from blood, CD62L was not present or it was expressed at a very low level, Metelitsa said. But after expanding, or multiplying, the NKT cells using technology developed in his lab and then studying the characteristics of the new cells, Metelitsa and his research team identified the presence of CD62L in these new cells at higher levels.

"We consistently identified a subset of cells present at very high numbers after the first 12 days of expansion, and critical to this subset of cells was the presence of CD62L. In fact, they became the majority of the new cells," Metelitsa said.

In addition, Metelitsa said that CD62L NKT cells were responsible for further propagation of NKT cells in culture, important for achieving large numbers of cells that will be necessary for treating cancer patients. However, extensive culture led to eventual decline of CD62L expression in NKT cells.

Using a mouse model of lymphoma, researchers delivered the expanded



CAR-NKT cells positive for CD62L as well as cells negative for the molecule to the mice, and found that mice could be cured only with the CD62L-positive therapy.

With CD62L identified as a marker that is important to the effectiveness of NKT cells, researchers turned their focus to costimulation of NKT cells to maintain the subset with a high percentage of CD62L-positive cells in the prolonged culture. Costimulation involves interaction of receptors on NKT cell with activating molecules on an antigenpresenting cell to increase the NKT cell's immune functions.

"We have known that costimulation is an important part of immune response and immunotherapy but in this case we did not know which costimulatory molecules would be important for the expansion and persistence of CD62L-positive NKT cells," said Gengwen Tian, a research assistant in pediatrics – oncology at Baylor and first author on the paper.

After testing more than 100 combinations in the lab, Tian and researchers in Metelitsa's lab, discovered the particular combination of an antigen-presenting molecule, CD1d, with costimulatory molecules that induced prolonged persistence and better therapeutic activity of NKT and CAR-NKT cells in the mouse models. These costimulatory molecules are CD86, 4-1BBL and OX40L.

"When we developed an antigen-presenting cell clone that expressed CD1d with all of these costimulatory molecules at certain levels, NKT cells maintained a high percentage of CD62L even in a prolonged culture," Metelitsa said.

In vivo testing of CAR-NKT <u>cells</u> that were expanded with the original method or with the optimal costimulation demonstrated significantly higher therapeutic activity of the latter in mouse models of



neuroblastoma and lymphoma.

"Our goal now is to optimize our NKT cell expansion protocol so that we can obtain FDA approval to initiate clinical trials," Metelitsa said.

**More information:** Gengwen Tian et al. CD62L+ NKT cells have prolonged persistence and antitumor activity in vivo, *Journal of Clinical Investigation* (2016). DOI: 10.1172/JCI83476

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