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Cocktail Boosts Immune Cells in Fighting Cancer

Natural killer cells (or NK cells), as part of the body´s immune system, can effectively fight cancer. Unfortunately, they quickly lose their aggressiveness and hence are unable to reject solid tumors. Scientists from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have now discovered a cocktail consisting of three different immune mediators that leaves NK killer cells active over a long period of time. In mice, cocktail-boosted NK cells let tumors shrink. The cocktail was able to persistently activate human NK cells, too.

Fighting cancer using the body's own defense system is a promising treatment approach. Immune therapies have even become clinical routine in treating a few cancers such as malignant melanoma and prostate cancer. Natural killer cells (or NK cells) are considered to be particularly suitable weapons against cancer. They are part of the innate immune system and respond to a wide range of cancer cells of diverse origin. Moreover, NK cells also kill tumor cells that have lost a specific target and go unnoticed by other immune cells.

"The big problem in using NK cells for therapy is their rapid loss of activity, hence their aggressiveness," says Dr. Adelheid Cerwenka. Together with her team at the German Cancer Research Center (DKFZ), Cerwenka is trying to develop cancer therapies based on NK cells. "Although there are good treatment results for certain types of blood cancer, NK cells have been clinically effective in fighting solid tumors only in a few cases," the immunologist explains.

Cerwenka's team has now been the first to enhance the NK cells' deadly potential in mice using a cocktail of three different immune mediators (interleukins 12, 15, and 18). NK cells that were activated in the culture dish and then injected into cancerous mice significantly slowed down tumor growth. The animals survived significantly longer and in one quarter of animals the tumors even regressed completely. By contrast, NK cells without prior treatment were ineffective.

The NK cells pretreated with the cocktail initially multiplied strongly in the mice. The researchers found it particularly remarkable that the NK cells appear to be re-stimulated by other immune cells in the bodies of the affected mice and were thus kept in an active state. Even after three months, the DKFZ immunologists still found active, functional NK cells in mice, even after the tumors had already been rejected. "We previously thought immunological memory exists only in cells of the adaptive immune system," says Cerwenka.

However, NK cells were only able to let tumors shrink if the mice had undergone prior radiation treatment. The scientists found a lot more NK cells at their site of action in tumor tissue in irradiated mice than in control animals. Cerwenka and colleagues do not yet know the precise molecular reason for this observation. "The good thing is that we might be able to achieve this effect in a potential clinical application by combining the cocktail-treated NK cells with radiation therapy."

Cocktail-treated human NK cells also display all molecular signs of sustained activation in cell culture. Adelheid Cerwenka and her team have already started testing the effectiveness of killer cells in fighting human cancer cells. "We hope to advance the development of NK cell therapies against cancer with our novel approach," says Cerwenka.

Jing Ni, Matthias Miller, Ana Stojanovic, Natalio Garbi and Adelheid Cerwenka: Sustained effector function of IL-12/15/18 preactivated NK cells against established tumors. Journal of Experimental Medicine 2012, DOI: 10.1084/jem.20120944

- **The body's defense system is made up of the innate and the adaptive immune systems. The innate system is responsible for immediate defense of the body. Cells of the innate system do not have specific receptors but respond to a broad spectrum of pathogens (using phagocytes, granulocytes) or transformed body cells (using NK cells). By contrast, T and B lymphocytes, which are part of the adaptive immune system, are equipped with highly specific receptor molecules directed against protein components of specific pathogens. If these long-lived cells, which form a sort of memory of the immune system, encounter this specific invader again, they first have to multiply before they can mount an effective defense. Therefore, several days pass before the adaptive immune defense is ready to fight the attack.*

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