How human NK cells destroy diseased cells and minimize damage to bystanders

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When NK cells encounter cancer or virally infected cells, they adhere to them and quickly congregate their destructive granules on the area of contact with the diseased cell. The granules, which contain molecules that can destroy a cell, are then released onto the target cell to kill it. Scientists at Baylor College of Medicine, Texas Children's Hospital, Rice University, the KTH Royal Institute of Technology and the Karolinska Institute have discovered that congregating the granules before releasing them onto the target cell improves the efficiency of the NK cell attack on diseased cells and minimizes the killing of healthy bystander cells. The results appear in the *Journal of Cell Biology*.

"Although the process of granule convergence itself is established, its contribution to cell destruction by NK cells has not been," said senior author Dr. Jordan Orange, professor of pediatrics and chief of the section of immunology, allergy and rheumatology at Baylor and director of the Center for Human Immunobiology at Texas Children's.

Other cells, such as lymphocytes, mast cells and melanocytes, have structures that are similar to the secretory granules in NK cells; however, in the former cells the secretory structures disperse in many directions, instead of concentrating in one location, before they are released. Here, the researchers investigated the contribution of congregating the granules in one location to the cell-killing activity of NK cells.

In this study, the scientists combined advanced microscopy techniques to determine the interactions between human NK cells and target cells in

laboratory cultures, as well as correlations between granule position in NK cells and target cell death. They used a technique termed ultrasound-guided acoustic trap microscopy, or UGATm, which was developed in Sweden to study immune cells and was refined for the purposes of the present study in Houston.

In a set of experiments, the scientists manipulated the NK cells so they were unable to congregate the granules before attacking target cells.

"Without congregated granules, NK cells still released the granules but were drastically less efficient at killing target cells and damaged more healthy bystander cells than when the granules congregated before release," said Orange. "Therefore, we think that congregating the granules allows NK cells to focus their release onto specific target cells, minimizing damage to bystander cells. This strategy would be efficient when NK cells carry on their normal function of traveling through complex, mostly healthy, tissue seeking and destroying diseased cells."

Therapeutic possibilities

The team is especially excited about the possibility of controlling granule positioning in the setting of established disease – for instance, once a cancerous tumor has grown. Here, once NK cells get into a tumor, the precision attack to protect surrounding cells might be less desirable. Thus, Orange believes that "if we could force NK cells to kill everything around them once they get into a tumor we might be able to improve their ability to destroy more cancer cells. We are hopeful that this could prove to be useful to the growing field of cell therapy in which killer cells designed to find cancer cells are infused into a patient with cancer." Orange's team currently is pursuing these next steps in collaboration with other Baylor College of Medicine investigators.

More information: Hsiang-Ting Hsu et al. NK cells converge lytic

granules to promote cytotoxicity and prevent bystander killing, *The Journal of Cell Biology* (2016). DOI: 10.1083/jcb.201604136