In immune cells, 'super-res' imaging reveals natural killers' M.O.

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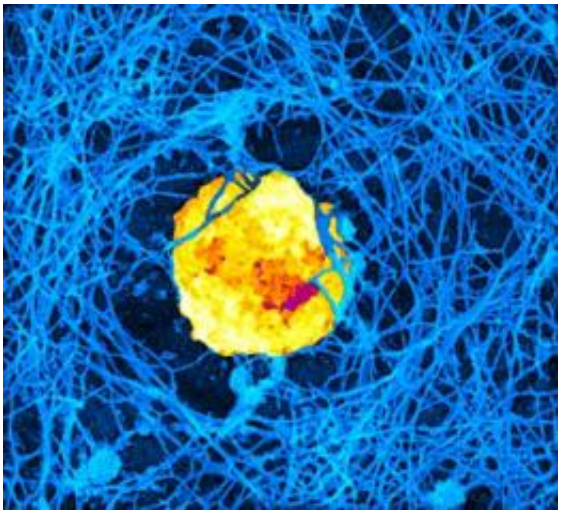

Electron micrograph image shows a lytic granule (yellow) within the actin network (blue) at the immune synapse of a natural killer cell. Credit: Gregory Rak and Jordan Orange, Children's Hospital of Philadelphia

Making use of a new "super resolution" microscope that provides sharp images at extremely small scales, scientists have achieved unprecedented views of the immune system in action. The new tool, a stimulated emission depletion (STED) microscope, shows how granules from natural killer cells pass through openings in dynamic cell structures to destroy their targets: tumor cells and cells infected by viruses. Deeper understanding of these biological events may allow scientists to devise more effective treatments for inherited diseases that impair the immune

system.

"This new technology enables researchers to see individual elements previously below the physical limits of imaging using light," said study leader Jordan S. Orange, M.D., Ph.D., who holds the Jeffrey Modell Endowed Chair in Pediatric Immunology Research at The Children's Hospital of Philadelphia. Previously, microscopes could not "see" objects smaller than 200 nanometers (a nanometer is one millionth of a millimeter). The STED microscope at Children's Hospital uses a unique arrangement of lasers and fluorescence to image fine structures, such as protein filaments, smaller than 60 nanometers.

The current study appears Sept. 13 in the online, open-access journal *Public Library of Science Biology* (*PLoS Biology*).

Orange, who runs a clinical program at Children's Hospital for pediatric primary immunodeficiency diseases, has long researched the biology of natural killer (NK) cells at the immunological synapse—the site where the NK cell attaches to its target cell and delivers cell-killing molecules. A crucial component of this highly regulated process is filamentous actin (F-actin), a structural protein in NK cells that forms a dense network through which cell-killing molecules called lytic granules move into the synapse.

The conventional view was that F-actin was not present at the center of the network, where granules are secreted through the synapse. Now under super-resolution, the current study, performed in both live human cells and cell lines, reveals that F-actin pervades the synapse, but leaves openings just large enough to allow granules to pass through. "At the same time, F-actin appears to be dynamically interacting with the granules to move them toward their targets," Orange added.

Orange compared the F-actin filaments to the rails of a roller coaster,

but one that quickly rearranges itself to guide a rider through a narrow tunnel. Further studies of NK function, Orange said, will investigate energy utilization and biological mechanisms that allow the lytic granules to navigate the immunological synapse. He added, "As we better understand how this process is regulated, we will work toward manipulating immune response to treat immune deficiency disorders."

More information: "NK cell lytic granule secretion occurs through a pervasive actin network at the immune synapse," *PLoS Biology*, published online Sept. 13, 2011, www.plosbiology.org/article/in … journal.pbio.1001151

Provided by Children's Hospital of Philadelphia

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