Immune cells kill foes by disrupting mitochondria 2 ways

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When killer T cells of the immune system encounter virus-infected or cancer cells, they unload a lethal mix of toxic proteins that trigger the target cells to self-destruct. A new study shows T cells can initiate cellular suicide, also known as programmed cell death or apoptosis, by a previously unrecognized pathway that starts with the destruction of a key enzyme in mitochondria, the power plant of the cell.

The study, from the lab of Judy Lieberman, a senior investigator at the Immune Disease Institute and Professor of Pediatrics at Harvard Medical School, reveals that T cells use both the novel pathway and the classical apoptotic pathway to interfere with mitochondrial function and induce cell death.

“This work gives us a new understanding of a major T cell defense pathway,” Lieberman says. The results will appear in the May 16 issue of *Cell*.

The Lieberman lab studies cytotoxic T lymphocytes (CTLs), key cells in the immune defense against viral infection and cancer. When CTLs recognize an infected or transformed target cell, they release the contents of cytolytic granules onto the target cell. These granules contain serine proteases called Granzymes, which induce programmed cell death in the target cells. Two major Granzymes, A and B, account for most of the killing activity in granules.

Granzyme B triggers the classical programmed cell death pathway

involving breakdown of the outer mitochondrial membrane, and the release of death-promoting proteins which activate the caspase protease cascade and result in massive DNA damage.

Previous work from the Liebeman lab showed that Granzyme A initiates cell death by a different biochemical pathway. That pathway involves the mitochondria, but does not result in mitochondrial membrane breakdown or caspase activation, and triggers a different type of DNA damage. The current study was aimed at understanding how Granzyme A kills cells.

To identify Granzyme A target proteins in mitochondria, Lieberman and colleagues used proteomics to look at the fate of a large number of mitochondrial proteins after Granzyme A exposure. One protein, NDUFS3, a subunit of the large multi-protein Complex I assembly that participates in energy generation for the cell, disappeared.

Further work established that when Granzyme A was released into a cell, it could enter the mitochondria where it degraded NDUFS3. Further, the investigators showed that loss of NDUFS3 caused mitochondria to produce damaging reactive oxygen, known to be essential for Granzyme A's deadly effects on cells. Destruction of NDUFS3 was sufficient to initiate the toxic effects of Granzyme A on human cells, they showed.

The new demonstrate that while both Granzymes target mitochondria, they do so in very different ways. Lieberman says she is not surprised that immune cells have multiple means of inducing mitochondrial-dependent cell death. "Many viruses and cancers have found ways to be resistant to the caspase-dependent apoptosis pathway triggered by Granzyme B, so it makes sense that immune cells would have a second, parallel pathway to cause cell death," she said.

Source: Harvard Medical School