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How killer immune cells avoid killing themselves

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After eight years of work, researchers have unearthed what has been a well-kept secret of our immune system's success. The findings published online on June 9th in *Immunity* offer an explanation for how specialized immune cells are able to kill infected or cancerous cells without killing themselves in the process.

The focus of the study is a molecule known as perforin, whose job it is to open up a pore in cells targeted for destruction. With that pore in place, proteases known as granzymes can enter target cells and destroy them.

Perforin is one of the most critical ingredients for a functional immune system. Without it, mice succumb to viral illness and lymphoma. Humans born without a working perforin gene develop an aggressive immunoregulatory disorder in the first few months of life and usually die unless treated with cytoxic drugs or a bone marrow transplant.

But perforin itself is an incredibly destructive molecule. "Perforin forms a massive pore," said Ilia Voskoboinik of the Peter MacCallum Cancer Centre in Australia. "It allows almost any protein to diffuse into a target cell. A few hundred molecules of perforin is sufficient to obliterate any cell."

When the immune cells known as cytotoxic lymphocytes (including cytotoxic T lymphocytes and natural killer cells) are activated, "they produce a massive amount of perforin, yet the cells are fine,"

Voskoboinik said. The question was: how do our immune cells manage such toxic cargo without endangering themselves?

Before perforin is released, the cells that produce it have to transport it from one part of the cell to another. That transport chain starts in a component of the cell known as the endoplasmic reticulum (ER). From there, it moves to the Golgi and into secretory granules where it is packaged together with granzymes. It is those secretory granules that ultimately fuse with the plasma membrane of the cytotoxic cell and allow its release into the junctions between the immune cell and the cell it aims to kill.

Scientists used to think perforin had an inhibitory domain within its structure that was only removed once they were safely stored in the secretory granules. (The acidic environment within secretory granules keeps perforin inactive until its release.) But Voskoboinik's team purified perforin and found that the protein was always active regardless of whether they had removed the supposed inhibitory domain or not.

"It seeded doubt about how perforin is inhibited," he says. "It was a puzzle. Perforin was fully functional but for some reason it couldn't kill the cell [in which it was synthesized]."

The real danger zone for the cell when it comes to perforin is the ER, Voskoboinik explained. Conditions there should be ideal for perforin to work, but something keeps it from doing so. The new study links that protection to a single amino acid at one end of the perforin protein. When that amino acid is substituted with another, perforin doesn't make it to the Golgi compartment, it builds up in the ER, and the cell dies.

"Perforin goes from zero to extremely high levels within 24 hours and it has everything it needs to be functional," Voskoboinik said. "The cell relies on a really efficient transport system to move perforin away from

the danger zone and as a result the cell is absolutely protected."

The findings "close a chapter" in our understanding of the immune system that has existed in the field since perforin was discovered almost 25 years ago, Voskoboinik says. "It was one of those things that was out there on Olympus untouched. Everyone would just stare at it. That's what got us interested."

Provided by Cell Press