Jekyll and Hyde: Cells' executioner can also stave off death

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An enzyme viewed as an executioner, because it can push cells to commit suicide, may actually short circuit a second form of cell death, researchers at Emory University School of Medicine have discovered.

The finding could shift drug discovery efforts, by leading scientists to rethink how proposed anti-cancer and anti-inflammatory drugs that target the enzyme, called caspase 8, are supposed to work. The results are described in this week's *Nature*.

Caspase 8 has been described as "the killer you can't live without." This enzyme plays a key role in apoptosis, a form of cellular suicide important for the development of all multicellular organisms, and in defense against viral infections. Mice lacking caspase 8 die before birth, because their blood vessels and blood-forming stem cells fail to develop properly. In the Nature paper, Emory researchers show that mice without caspase 8 develop normally if they also lack another enzyme called RIP3.

"The surprising aspect is that caspase 8 appears to have two functions: one that initiates apoptosis and a second that restrains an independent programmed death pathway," says senior author Ed Mocarski, PhD, Robert W. Woodruff Professor of Microbiology and Immunology at Emory Vaccine Center and Emory University School of Medicine.

Graduate student William Kaiser, in Emory's Microbiology and Molecular Genetics program, is the first author of the paper. Other

Emory authors include Tamara Caspary, PhD, assistant professor of human genetics, as well as students and postdoctoral fellows from both Emory labs.

"It's remarkable to be able to rescue mice from embryonic death," Caspary says. "I was surprised that the mice are even born, since these enzymes are basic parts of the cellular machinery."

In humans, a lack of caspase 8 has been linked to immune disorders and skin diseases such as eczema, while too much caspase 8 activity has been connected with diabetes. In addition, several experimental anti-cancer and anti-inflammatory drugs aim to alter caspase 8 levels in order to induce death in cancer cells or reduce inflammation.

"Until recently, scientists viewed programmed cell death mainly as apoptosis, a program of self-destruction deliberately set in motion through signals cells receive from outside," Mocarski says.

For example, apoptosis ensures that white blood cells responding to an infection don't multiply indefinitely. White blood cells have built-on triggers on their surfaces that activate caspase 8, which unleashes a cascade of enzymes that break down the contents of the cell.

In contrast to apoptosis, necrosis was seen as unregulated death by neglect, until the discovery of an alternative form of cell death, driven by RIP3, called programmed necrosis. This looks like necrosis under the microscope, but like apoptosis is orchestrated by the cell from within rather than occurring because of injury or infection. Mocarski's group recently showed that RIP3 enables cells to sabotage themselves if they are infected by a virus, an activity where apoptosis was once thought to be the most important.

"For several years, the puzzle was: what are the non-apoptotic functions

of caspase 8, since there are numerous systems that are impacted by not having it," Mocarski says. "Now we have to consider that the absence of caspase 8 is actually revealing death by RIP3."

Mice lacking both caspase 8 and RIP3 have blood vessels and blood cells that look healthy. However, a few months after birth, they develop swollen lymph nodes, because their white blood cells do not go through apoptosis normally. Other scientists have shown that mice that have caspase 8 missing only in the skin have chronic skin inflammation, a condition resembling eczema in humans.

"Our results indicate that whatever caspase 8 was doing in the skin, removing RIP3 takes care of it," Mocarski says.

More information: W.J. Kaiser, J.W. Upton, A.B. Long, D. Livingston-Rosanoff, L.P. Daley-Bauer, R. Hakem, T. Caspary and E.S. Mocarski. RIP3 mediates the embryonic lethality of caspase-8-deficient mice. *Nature* (2011).

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