

Protein identified that serves as a switch in a key pathway of programmed cell death

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Work led by St. Jude Children's Research Hospital scientists identified how cells flip a switch between cell survival and cell death that involves a protein called FLIP.

The findings solve a riddle that has puzzled scientists for more than a decade regarding the dual nature of caspase-8, an enzyme intimately linked to the cell's suicide pathway but also essential for [cell survival](#) during [embryonic development](#) and the [immune response](#). Researchers identified FLIP and the silencing of another enzyme, named RIPK3, as playing pivotal roles. The study was published in the March 2 advance online edition of *Nature*.

Douglas Green, Ph.D., the paper's senior author and chair of the St. Jude Department of [Immunology](#), said work is already underway to use the findings to generate new cancer treatment targets and fresh insight into the missteps that give rise to certain tumors as well as evidence of how some virus-infected cells escape the pathways designed to dispatch such threats.

"It is a pretty rare thing to 'cure' a lethal mutation in an animal by removing another gene. When that happens, the biology shouts out to us that this is important. We just have to listen," Green said.

FLIP's role was identified after investigators bred mice that lacked genes for both caspase-8 and RIPK3. Previous research identified RIPK3 as responsible for orchestrating cell death via programmed necrosis. Once

viewed as an uncontrolled form of cell death, programmed necrosis is now recognized as a distinct form of [cell suicide](#). The body relies on both programmed necrosis and apoptosis, the more common process, to rid itself of damaged, dangerous or unneeded cells.

While loss of caspase-8 was known to be lethal during embryonic development, in this study investigators showed mice that lacked both caspase-8 and RIPK3 were born at normal rates and appeared developmentally normal early in life.

Investigators went on to show that caspase-8 prevents programmed necrosis by combining with FLIP to form an enzyme complex that disrupts RIPK3 functioning and so prevents death via programmed [necrosis](#). The work also demonstrated that FLIP expression prevents caspase-8 from triggering [cell death](#) via apoptosis, although the exact mechanism must still be determined. Apoptosis relies on caspase enzymes and other molecules to ensure the cell self destructs.

Green said the findings provide insight into the mechanisms at work in neuroblastoma and other tumors that suffer a loss of caspase-8. "We are beginning collaborative experiments to examine these tumors to see if RIPK3 is deleted or blocked," he said. Neuroblastoma arises in cells of the sympathetic nervous system. It is the most common solid tumor in children, accounting for up to 10 percent of all childhood cancers.

Provided by St. Jude Children's Research Hospital

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