Medical Xpress

Molecule acts as umpire to make tough life-or-death calls

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Researchers have demonstrated that an enzyme required for animal survival after birth functions like an umpire, making the tough calls required for a balanced response to signals that determine if cells live or die. St. Jude Children's Research Hospital scientists led the study, which was published online and appears in the May 22 edition of the scientific journal *Cell*.

The work involved the enzyme receptor-interacting protein kinase 1 (RIPK1). While RIPK1 is known to be involved in many vital cell processes, this study shows that its pivotal role in survival after birth is as an inhibitor of two different pathways that lead to the death of cells. Functioning properly, the pathways provide a way to get rid of dangerous, damaged or unneeded cells.

By removing different components of each pathway in different combinations, researchers demonstrated that after birth RIPK1 helps cells maintain a balanced response to signals that promote either pathway. "We are learning that in disease this balancing act can be perturbed to produce damage and cell death," said the study's corresponding author Douglas Green, Ph.D., chair of the St. Jude Department of Immunology.

The results resolve long-standing questions about RIPK1's role in cell survival and provide clues about how the disease-fighting immune system might use these pathways to contain infections. The findings have also prompted researchers to launch an investigation into whether RIPK1 could be harnessed to kill cancer cells or provide insight into tumor development. RIPK1 is already the focus of drug development efforts designed to limit cell damage following heart attack, stroke or kidney injury.

"This study fundamentally changes the way we think about RIPK1, a molecule that we care about because it is required for life," Green said. "The results helped us identify new pathways involved in regulating programmed cell death and suggest that we might be able to develop cancer therapies that target these the pathways or engage them in other ways to advance treatment of a range of diseases."

The study is one of two involving RIPK1 being published in the same edition of *Cell*.

The St. Jude report builds on previous research from Green's laboratory regarding regulation of the pathways that control two types of programmed cell death. One, called apoptosis, is driven by an enzyme named caspase-8. It forms a complex with a protein named FADD as well as other proteins that prompt cells to bundle themselves into neat packages for disposal. The other, called necroptosis, involves a different

pathway that is orchestrated by the enzyme receptor-interacting protein kinase 3 (RIPK3). Researchers knew that before birth, RIPK1 worked through RIPK3 to trigger cell death by necroptosis, but until now the enzyme's primary role after birth was uncertain.

For this study, researchers bred mice lacking different combinations of genes for ripk1, ripk3, caspase-8, FADD and other components of both the apoptotic and necroptotic pathways.

Mice lacking ripk1 died. Mice missing two genes – ripk1 plus ripk3 or ripk1 plus caspase-8 or FADD – also died soon after birth. Mice survived and developed normally, however, when researchers removed three genes – ripk1, ripk3 and either caspase-8 or FADD. "The fact that the mice survived was totally unexpected and made us rethink how these pathways worked," Green said.

Added Christopher Dillon, Ph.D., a postdoctoral fellow in Green's laboratory: "Knocking out two genes to restore balance following the loss of another gene, in this case RIPK1, is exceedingly rare." Dillon and St. Jude postdoctoral fellows Ricardo Weinlich, Ph.D., and Diego Rodriguez, Ph.D., are the paper's first authors.

The finding established RIPK1's premier role in cell survival as inhibition of apoptosis and necroptosis.

The results also demonstrated that other pathways must exist in cells to maintain a balanced response to signals pushing for cell death via apoptosis or necroptosis. Evidence in this study, for example, suggested one possible new pathway that triggered necroptosis using interferon and other elements of the immune response to infections.

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