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Protein targeted for cancer drug development is essential for normal heart function

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St. Jude Children's Research Hospital scientists have discovered that a protein used by cancer cells to evade death also plays a vital role in heart health. This dual role complicates efforts to develop cancer drugs that target the protein, but may lead to new therapies for heart muscle damage. The research appeared in the June 15 edition of the scientific journal *Genes & Development*.

The protein, MCL1, is currently the focus of widespread cancer drug development efforts. MCL1 is best known as an inhibitor of death via the cell's suicide pathway in a process called apoptosis. The protein is elevated in a variety of cancers, and a number of MCL1 inhibitors are in the cancer drug development pipeline worldwide. The protein has also been linked to drug resistance in cancer patients. Until now, however, MCL1's role in heart muscle cells was unclear.

"Our study shows that MCL1 is required for normal cardiac function and that the protein may be critical in protecting the heart from apoptosis," said Joseph Opferman, Ph.D., an associate member of the St. Jude Department of Biochemistry and the paper's corresponding author. Unlike skin or blood cells, heart muscle cells cannot be replaced, so even a small loss through apoptosis can be devastating. In this study, knocking out MCL1 in mice led to death from cardiomyopathy within weeks.

"These findings suggest that cancer-related drug development efforts should focus on reducing MCL1 expression in target cells rather than eliminating the protein's function completely," Opferman said.

The results also have implications for treating heart muscle damage following heart attacks or other insults. While limiting MCL1 in cancer cells might aid in destroying them, providing higher levels of the protein in heart muscle cells might benefit a patient recovering from a heart attack or other heart damage. "These findings have broad implications for human health," Opferman said.

MCL1 belongs to a protein family involved in regulating apoptosis. The body uses apoptosis to rid itself of damaged, dangerous or unneeded cells. MCL1 prevents apoptosis by blocking the activity of other members of the same protein family that promote the process.

This research builds on previous work from Opferman's laboratory that identified a second form of MCL1. That form works inside rather than outside the mitochondria and helps to produce the chemical energy that fuels cells. Mitochondria are specialized structures inside cells that serve as their power plants.

The latest results suggest both forms of MCL1 are necessary for normal heart function, said the paper's first author Xi Wang, a University of Tennessee Health Science Center graduate student working in Opferman's laboratory.

When investigators knocked out the mouse version of the human MCL1 gene in the heart and skeletal muscle of both embryonic and adult mice, the animals rapidly developed lethal cardiomyopathy. Without MCL1, researchers found that muscle fiber in heart muscle cells was replaced by fibrous tissue, and the pumping ability of the animals' hearts diminished. Loss of MCL1 was also associated with a rise in apoptosis sufficient to cause fatal heart muscle weakness.

To better understand MCL1's role in normal heart function, researchers blocked apoptosis by deleting genes for the proteins Bak and Bax as well

as MCL1. Bak and Bax promote apoptosis. Knocking out all three genes restored normal heart function in the mice. The animals lived longer, but mitochondria in the heart muscle did not look or function normally. These results suggest that normal heart function requires both forms of MCL1. "The question is whether, with time, you would see deleterious effects from the loss of MCL1 separate from apoptosis," Opferman said.

Provided by St. Jude Children's Research Hospital

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