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Key protein's newly discovered form and function may provide novel cancer treatment target

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Research led by St. Jude Children's Research Hospital investigators suggests that safeguarding cell survival and maintaining a balanced immune system is just the start of the myeloid cell leukemia sequence 1 (MCL1) protein's work.

Nearly 20 years after MCL1 was discovered, scientists have identified a second form of the protein that works in a different location in cells and performs a different function. This newly identified version is shorter and toils inside rather than outside mitochondria where it assists in production of chemical energy that powers cells. The research appears in today's online edition of the scientific journal Nature Cell Biology.

The finding will likely aid the development of cancer drugs. Many cancers feature high levels of MCL1 or extra copies of the gene, and there is widespread interest in the protein for its potential to treat cancer. Until now, however, those efforts have focused solely on MCL1's role on the outer mitochondrial membrane, where it blocks cell death via the apoptotic or cell suicide pathway. This study highlights another role.

"We believe this newly identified form of MCL1 that works inside the mitochondria is probably essential for tumor cell survival. If that proves to be correct, then strategies to block the protein from getting into mitochondria offer a new therapeutic approach for cancer treatment," said Joseph Opferman, Ph.D., an associate member of the St. Jude

Department of Biochemistry and a Pew Scholar in the Biomedical Sciences. He is the paper's senior author.

Opferman has a longstanding interest in MCL1, which belongs to the BCL2 family of proteins that are critical regulators of apoptosis. Unlike other BCL2 proteins, MCL1 is required for embryonic development and for the survival of a variety of normal cell types. The protein is also essential for cancer cell survival.

Until now, however, researchers were unsure how to reconcile MCL1's varied roles with its status as a member of the BCL2 family of proteins. BCL2 proteins were widely believed to work exclusively on the outer mitochondrial membrane.

"In this study, we show that MCL1 has two forms and two important, but completely different functions," said Rhonda Perciavalle, Ph.D., a University of Tennessee Health Science Center graduate student in Opferman's laboratory and the study's first author. Along with working on the outer mitochondrial membrane to help protect cells from apoptosis, investigators demonstrated that MCL1 works internally to facilitate mitochondrial energy production in the mitochondrion's matrix.

Using a variety of laboratory techniques, researchers showed that inside the mitochondrion, MCL1 promotes the normal structure of the inner membrane, where much of the work of energy production is done. The loss of the inner mitochondrial form of MCL1 hampers the ability of cells to produce energy, thus impeding their ability to proliferate.

"The results help explain why the loss of this single pro-survival molecule, MCL1, has such a dramatic impact. We are now working with tumor models to determine if this newly identified form of MCL1 is essential for cancer cells," Opferman said. Perciavalle said the two forms

might work together to protect cancer cells from apoptotic death and to provide them with the fuel and nutrients to sustain their unchecked growth and spread.

Work is also underway to learn precisely how MCL1 functions inside the mitochondria in both normal and cancer cells. Investigators are also interested in the relative importance of the two versions of MCL1 in different tissues under a variety of different conditions.

Provided by St. Jude Children's Research Hospital