'Rheostat' identified that helps regulate cell death versus survival decisions

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Authors Richard Kriwacki, PhD, and Aaron Phillips, PhD, identified how an unstructured or intrinsically disordered region (IDR) in Bcl-xL provides greater flexibility for monitoring conditions and determining cell fate. Credit: St. Jude Children's Research Hospital

St. Jude Children's Research Hospital scientists have determined how a protein's disordered region serves as a molecular rheostat to help regulate cell survival.

The survival drama is played out millions of times each day in cells throughout the body. The results have long-term consequences for human health and well-being, since the surveillance system is tasked to eliminate unneeded and unwanted cells, including cancer cells. Until now, however, scientists did not understand how the mechanism involved in this process monitors cellular conditions. The findings appear as an advance online publication today in the journal *Nature Chemical Biology*.

The research focused on the Bcl-xL protein, a member of the Bcl-2 family of proteins that promotes cell survival and inhibits programmed cell death (apoptosis) when cells are healthy. Previous research from St. Jude showed Bcl-xL promotes cell survival by binding and inhibiting the activity of p53 and other proteins that drive apoptosis. Bcl-xL is commonly over-expressed in cancer to prevent a cell's natural ability to undergo apoptosis.

Expanding on research from other scientists, St. Jude investigators have identified how an unstructured or intrinsically disordered region (IDR) in Bcl-xL provides greater flexibility for monitoring conditions and determining cell fate. Researchers showed that just like rheostats can be adjusted to dim or brighten a room in response to changing conditions, the chemical modification, or adjustment, of the Bcl-xL IDR shifts the balance from blocking to promoting apoptosis.

"Proteins often include structured and unstructured regions, called intrinsically disordered regions," said corresponding author Richard Kriwacki, Ph.D., a member of the St. Jude Department of Structural Biology. "This study reveals how an intrinsically disordered region in a protein can play a regulatory role by acting as a sensor for what is happening in the cellular environment to either restrain or promote apoptosis.

"This research deepens our understanding of a basic mechanism that controls cell fate," he said.

Researchers used nuclear magnetic resonance (NMR) spectroscopy and other tests to determine how modification of the protein's IDR influenced cell survival.

For example, investigators reported that "adjusting" an amino acid in the intrinsically disordered Bcl-xL loop through chemical attachment of a phosphate group—akin to adjusting the regulatory knob of a rheostat—encouraged apoptosis. Such tagging is called phosphorylation. The phosphate group promotes binding of the IDR to the p53 binding site on Bcl-xL. The interaction not only blocks p53 binding, but NMR results revealed that it also distorts and weakens Bcl-xL binding of BH3 proteins, which, along with p53, can trigger apoptosis.

"NMR spectroscopy provided insight that was essential for understanding the mechanism that helps control cell-fate decisions," Kriwacki said. "The atomic-level images from NMR allowed us to track how modification of the intrinsically disordered region of Bcl-xL led to increased levels of pro-apoptotic proteins (p53 and BH3 proteins) to drive programmed cell death.

"The evolution of internal IDRs within Bcl-xL and Bcl-2 enables the proteins to flexibly respond to diverse apoptotic signals, fine tuning their regulatory functions," he said. "Modifications of the intrinsically disordered regions, in response to different stressors in the environment, are a means to tune the anti-apoptotic activity of Bcl-xL and Bcl-2 to changing cellular conditions."

For example, chemotherapeutic agents promote phosphorylation of the IDR of Bcl-2 and enhances cell death. "This highlights how the kind of regulatory fine-tuning described in this paper plays a role in cancer

treatment," Kriwacki said.

More information: Ariele Viacava Follis et al. Regulation of apoptosis by an intrinsically disordered region of Bcl-xL, *Nature Chemical Biology* (2018). DOI: 10.1038/s41589-018-0011-x

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