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Detailed studies reveal how key cancer-fighting protein is held in check

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St. Jude Children's Research Hospital scientists have mapped the structural details of how p53 attaches to its regulatory protein, called BCL-xL, in the cell. The protein p53 is a key activator of the cell's protective machinery against genetic damage, such as the mutations that drive cancer cells' explosive growth.

The detailed understanding of how these two molecular puzzle pieces fit together will help scientists design drugs that release p53 in cancer cells, triggering their suicide, called apoptosis.

The findings appear in the current online journal *Nature Structural & Molecular Biology*. The research was led by co-corresponding authors Richard Kriwacki, Ph.D., a member of the St. Jude Structural Biology department, and Douglas Green, Ph.D., chair of the St. Jude Immunology department.

In guarding the cell against genetic damage, the p53 machinery functions both in the nucleus of the cell and in the cell's gel-like cytosol. When this machinery detects irreparable damage to the cell, p53 is unleashed to trigger apoptosis. In about half of all cancers, this machinery is rendered inoperable by mutation of p53, enabling cancer cells to proliferate despite their genetic malfunctions.

The protein BCL-xL is a central inhibitor of the p53 machinery, binding both p53 and other molecules—called BH3 proteins—that also drive apoptosis.

"The molecular details of how BCL-xl performs this dual inhibitory function were not understood," Kriwacki said. "Having those details has enabled us to determine exactly how BCL-xl can restrain or inhibit apoptosis through interactions with BH3-domain-containing proteins, as well as p53."

In their studies, the researchers used a structural analysis technique called NMR spectroscopy to map the 3-D structure of p53 binding to BCL-xL. Their experiments also revealed in detail how one region of the p53 protein, called the DNA-binding domain, serves double duty in the machinery. It enables p53 to attach to DNA in the cell's nucleus, helping the cell repair genetic damage. The same domain also acts as an attachment point for BCL-xL in the cytosol.

"The structural details that we report are novel," Kriwacki said. "And they provide the key insights for really dissecting the dual roles of BCL-xl in inhibiting apoptosis. Those roles are inhibiting the BH3-containing proteins on the one side, and p53 on the other. Also, through these studies we solidified the mechanistic understanding for how p53 functions in the cytosol, which complements its pro-apoptotic role in the nucleus."

The findings will help scientists design cancer-fighting drugs, Kriwacki said. In many cancers, p53 is prevented from triggering apoptosis by its attachment to BCL-xL. Drugs are currently being tested that bind to BCL-xL to free BH3 proteins to trigger apoptosis. However, Kriwacki said, new drugs could be developed—based on knowledge of p53's attachment to BCL-xL—that also block BCL-xL from binding p53.

"Our hypothesis is that many cancers have normal p53, but it is being tied up by BCL-xL," he said. "If it could be released, it could play its role in triggering apoptosis. A drug that could block both of BCL-xL's anti-apoptotic functions could potentially more profoundly induce

apoptosis in cancer cells."

Kriwacki also said that the paper was significant because it emphasizes the importance of the role that p53 plays in the cytosol of the cell, in addition to its role in the nucleus; his further studies are seeking to map that molecular machinery in great detail.

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