X-ray protein probe leads to potential anticancer tactic

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Researchers at Emory University School of Medicine have identified a new type of potential anticancer drug. The compound, named FOBISIN, targets 14-3-3 proteins, important for the runaway growth of cancer cells.

The researchers were using X-rays to see how FOBISIN fits into the clamp-shaped 14-3-3 protein structure. Unexpectedly, the X-rays induced the compound to be permanently bonded to the protein. The finding suggests that compounds like FOBISIN can be used in combination with radiation to trigger potent anticancer activity.

The results were published online Sept. 9 in Proceedings of the National Academy of Sciences Early Edition.

Senior author Haian Fu, PhD, has been studying 14-3-3 proteins for two decades. He is professor of pharmacology and of hematology and oncology at Emory University School of Medicine, and the director of the Emory Chemical Biology Discovery Center.

"Targeting 14-3-3 proteins could be especially valuable because they can impact multiple pathways critical for cancer cell growth," he says. "14-3-3 proteins have been shown to be dysregulated in a number of cancer types, including lung cancer and breast cancer."

14-3-3 proteins act as adaptors that clamp onto other proteins. Fu and co-workers Jing Zhao, PhD,postdoctoral fellow, and Yuhong Du, PhD,

assistant professor and associate director of the Discovery Center, sorted through thousands of chemicals to find one (FOBISIN: Fourteen-three-three Binding Small molecule Inhibitor) that prevents 14-3-3 from interacting with its partners.

14-3-3 proteins are found in mammals, plants and fungi. In humans, they come in seven varieties, and FOBISIN appears to inhibit interactions by all seven. A 14-3-3 proteins' ability to clamp depends on whether the target protein is phosphorylated, a chemical modification that regulates protein function. FOBISIN's inhibitory power also requires the presence of phosphorylation in the molecule.

Fu's group teamed up with the laboratory of Xiaodong Cheng, PhD, co-senior author, professor of biochemistry and a Georgia Research Alliance Eminent Scholar, to examine how FOBISIN fits into its targets.

Scientists use X-rays as a tool to probe protein structure. If a protein and a drug that targets it can be crystallized together, the X-ray diffraction pattern from the crystals reveals the 3D arrangement of the atoms and how the drug interacts with the protein. Research assistant professor John Horton, PhD, and research associate Anup Upadhyay, PhD, in the Cheng laboratory used synchrotron X-ray radiation from the Advanced Photon Source at Argonne National Laboratory for this purpose.

"In this case, the X-rays had an unexpected effect: they caused FOBISIN to become covalently attached to the 14-3-3 protein," Cheng says.

The finding suggests that compounds like FOBISIN could be developed as "pro-drugs" that upon exposure to radiation, permanently stick to and inhibit their targets. A common strategy in fighting cancer is to combine drugs and radiation so that the drugs increase cells' sensitivity to radiation. Here, the radiation would activate the drug.

"These compounds could be used in combination with other strategies to enhance the tumor selectivity of the treatment," Fu says.

More information: J. Zhao, Y. Du, J.R. Horton, A.K. Upadhyay, B. Lou, Y. Bai, X. Zhang, L. Du, M. Li, B. Wang, L. Zhang, J.T. Barbieri, F.R. Khuri, X. Cheng and H. Fu. Discovery and structural characterization of a small molecule 14-3-3 protein-protein interaction inhibitor. *PNAS* Early Edition (2011).

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