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Researchers uncover activation signal for Aurora-A oncogene

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Aurora-A kinase (AurA) is an enzyme that is hyperactive in many cancers and drives tumor cell proliferation. Several AurA inhibitors are currently being tested in clinical trials to see if they slow tumor growth. Now, researchers in the Developmental Therapeutics Program at Fox Chase Cancer Center have identified an activation signal for AurA. They report in the September 7 issue of *Nature Communications* that a quick increase in the calcium concentration in a cell rapidly triggers AurA kinase activity. The discovery may lead to drug combinations that had not previously been considered, and it may provide new insights into how the cell division cycle is timed.

"The results might suggest new ways to combine AurA inhibitors with other drugs to boost their activity," says Erica A. Golemis, Ph.D., Professor and senior author on the study. "Since we now know that AurA activation is controlled in part by calcium, we might combine an AurA inhibitor with drugs that target the calcium machinery in the cell."

AurA is best known for its role in pushing cells through cell division, but in 2007, Golemis was one of the first to report that the protein also functions in non-dividing cells, controlling a process important for cancerous transformation. The signals that turn on AurA kinase activity, however, are not well understood in either dividing or non-dividing cells. Putting together hints from studies in mammalian cells, frog oocytes, and single-celled algae, Golemis's team hypothesized that calcium could be a missing trigger for AurA signaling.

When they tested the idea in human kidney cells, they found that an increase in the amount of free calcium in the cell cytoplasm turned on AurA kinase activity. Together with Roland L. Dunbrack, PhD, a colleague in the Developmental Therapeutics Program, the investigators found that calcium first binds to a small protein called calmodulin, and then together the calcium-calmodulin complex bind to AurA directly.

"Our data might partly explain why AurA is active in tumors," Golemis says. "Tumors frequently have altered calcium signaling, and that altered signaling could be contributing to the oncogenic activity of the kinase."

This work suggests previously unexpected drug combinations, such as targeting AurA and calmodulin together, may have value in improving treatment of cancers with activated AurA. Golemis also thinks the data may offer new insight into the rapid activation of AurA that helps push the cell into mitosis. Once bound to the calcium-calmodulin complex, the AurA protein may change shape enough so that it can bind with other interacting proteins. Thus the calcium-calmodulin binding would act as a quick initial trigger for AurA activity, while the binding to other interacting proteins would allow AurA to have long-term activity.

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