Researchers correct the record about behavior of important human protein tied to cancer

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In a study to be published this week, a research team is challenging a prevailing belief about the behavior of a human protein linked to the formation of cancer, possibly breathing new life into the search for therapies that will inhibit that protein from "turning on" genes involved in abnormal cell proliferation.

"The body is made up of cells that communicate with each other and with external cues via receptors at their surfaces. To generate cellular responses, signaling pathways are activated that initiate movement of proteins to specific locations inside the cells, notably the nucleus, where DNA is situated," said Diane Lidke, assistant professor at the University of New Mexico School of Medicine's department of pathology and lead author on the paper to be published Jan. 29 in the Journal of Biological Chemistry.

One particular pathway, the extracellular signal-regulated kinase (ERK) pathway, is altered in about 30 percent of all human cancers, said Lidke, who worked on the project during a postdoctoral stint in the lab of Thomas Jovin at the Max Planck Institute for Biophysical Chemistry. "It has been suspected for a long time that alterations of the ERK pathway could be the founding mutation behind cancers, and this was shown recently for melanoma."

ERKs act as messenger molecules by relaying signals that are received

from outside the cell to the administrative core, the nucleus. To do so, ERK must move from its home in the intracellular fluid to the nucleus of the cell, turn on several genes while turning off others, which in turn finally tells the cell to divide or differentiate.

ERK's entry in the nucleus is unconventional, because the protein lacks the ability to bind to the known nuclear import proteins, Lidke said.

For more than a decade, scientists in this intense field of research thought that two molecules of ERK had to pair with each other after being activated in order to enter in the nucleus.

In this study, Lidke and her colleagues showed that that protein pairing - known as dimer formation - is, in fact, not necessary for ERK to move into the nucleus after all.

"Instead, the process was found to be dependent solely on the rate at which stimuli activate the ERK," explained Philippe Lenormand, staff scientist at the University of Nice and the senior author on the paper.

But how the team came to this conclusion goes back to 1998, when a leading research group generated a mutant form of ERK while studying the three-dimensional shape of the molecule. In order to understand the normal function of a protein, mutants are made to compare how certain tweaks alter their functions.

At the time, that group reported observing the mutant entering the nucleus of a cell abnormally. Yet, years later, when Lidke's team and other scientists working independently performed experiments with the same mutant, they didn't observe anything different about how it entered the nucleus: It went in the same way normal ERK does.

"Our work has clarified this field by reconciling existing data that

seemed conflicting at first glance," said Lenormand. "The entry in the nucleus of the mutant and the exchange in and out of the nucleus were slower than normal ERK," which could explain why the 1998 observations resulted in the conclusion that the mutant never made it inside. It was all about timing.

Lidke said that the fact that the mutant is activated with delay correlates well with the delayed entry in the nucleus: "As a consequence, it is the first time that a delay in activation is reported to trigger a delay in nuclear entry of ERK, indicating that ERK entry in the nucleus is a direct consequence of activation."

The discovery was made possible by the use of high-resolution microscopy techniques that allow the behavior of proteins to be observed in the living cell.

Having demonstrated that it is the activation of the mutant that is impaired, the team expects a renewed interest in the ERK mutant molecule to reveal details of ERK activation inside the cell.

Having a better understanding of the process by which ERK nuclear migration is regulated ultimately may pave the way to the development of therapies that manipulate it and, therefore, control how it affects genes involved in abnormal cell proliferation. This is also very important in light of clinical trials of potent and specific chemicals that block the activation of ERK.

So far, none of those blockers has proved successful against cancer, likely because ERK activity results from a balance between activation and feedback-inhibition. By reducing the activation, the feedback-inhibition is also reduced; hence, ERK activity is kept at a threshold that allows cancer cells to adapt to the drug treatment and continue growing.

So, the next question is this: Can we prevent ERK from entering nucleus altogether while avoiding some of these activation/feedback regulations?

"The improved understanding of ERK signaling by this study will open new lines of research," Lenormand said. "This is important, because this signaling pathway is deregulated in many cancers and essential for cognition, memory formation and cell differentiation."

More information: The resulting article, which can be read in full at www.jbc.org/content/285/5/3092, has been named a "Paper of the Week" by the *Journal of Biological Chemistry*.

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