Happy accident answers cell signal controversy

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(Phys.org) -- Using a new tool allowing proteins in a living cell to be manipulated in real time, researchers at Johns Hopkins have stumbled across the answer to a longstanding debate about where and how a certain protein is turned on in the cell. Reporting in the February 2012 issue of *Nature Chemical Biology*, scientists show that protein kinase A is also activated in the nucleus rather than inside the cell's body, a challenge to traditional beliefs.

"People have been wondering about nuclear PKA and [the answer] clicked when we saw our results," says Jin Zhang, Ph.D, associate professor of pharmacology at Johns Hopkins. For the most part, those in the field believe that PKA is activated in the cell's cytoplasm, but there is conflicting evidence suggesting it could also be present in the nucleus. Zhang says the answer to the debate clicked for her team when a cell biology technique they were fine-tuning gavethem unusual results.

Zhang and her research team are looking for the best way to see what's happening in live cells in real time. Most recently, they developed a new tool to manipulate the intricate molecular signals within the cell, allowing the researchers to stimulate cellular activities so experiments rely on their timing rather than the cells'. The technique enables the scientists to chemically activate a chain of signals at a precise location and specific time, all of it culminating in the activation of PKA. This causes changes in the cell that lead to a variety of outcomes, from altering metabolism to causing a muscle contraction.

Given the wide range of cellular outcomes possible upon trigger of this chain of signals, Zhang and her team knew they must test their tool under many conditions to see the many different possibilities. They began by stimulating the chain at the edge of the cell. They measured how quickly the signaling chain responded, and engineers collaborating with Zhang came up with a mathematical equation to model the speed of the message going from the cell membrane into the nucleus.

Next, they tested their tool closer to the center of the cell, activating molecules at the edge of the nucleus. They found the response was much faster than anticipated; the mathematical equation did not fit. Thinking about this inconsistency led the team to conclude that the only way to explain their findings was if PKA was activated inside the nucleus, contrary to the traditional understanding of PKA being located and activated outside the nucleus.

According to Zhang, PKA has always been thought to be activated outside the nucleus. Upon activation, it travels into the nucleus to turn on the cell's response. Zhang's data showed the signal from PKA activated at the cell's edge is slow in reaching the inside of nucleus, so the only explanation for a fast response at the nucleus would be if another population of PKA was already there.

"We're collecting information that shows PKA at the nucleus is functional, it's not contamination and not background signal," says Zhang. "These are real functional enzymes that can be activated."

Zhang and her colleagues now aims to find out how PKA at the nucleus differs from traditional PKA. Without doubt, PKA plays a critical role in many cellular processes, says Zhang. This means that nuclear PKA could be a significant and, as yet, untapped source of information about cell function.

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