Enzyme's Second Messenger Contributes to Cell Overgrowth

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Scientists at the University of California, San Diego (UCSD) School of Medicine have uncovered a novel pathway by which hormones elevated in inflammation, cancer and cell injury act on cells to stimulate their growth.

The research team led by Joan Heller Brown, Ph.D., professor and chair of the department of pharmacology at UCSD, has demonstrated in a mouse model that a newly discovered subtype of the phospholipase C (PLC) family of enzymes, called PLC-epsilon, has the unique ability to activate a second and distinct signaling pathway that cells require for proliferation. The study is currently on line in advance of publication by the *Proceedings of the National Academy of Science* (PNAS.)

The studies reported in the PNAS demonstrate that "in the cell, hormones that activate small G proteins are highly dependent on PLC-ε to generate second messengers," said Heller Brown. "In addition, and more surprisingly, we discovered that this enzyme is required for cell growth because it serves a second function when activated by hormones."

Many intracellular signaling proteins work as molecular "switches." The reception of a signal activates them and causes them to pass the signal through the cell, after which they can be switched off until another signal is received. G proteins are a commonly used form of switch, activated by the binding of guanine nucleotides.

PLC's normal role is delivering signals from outside the cell to inside the cell by generating "second messengers" that tell cells to contract and secrete. But these signals alone are not enough to cause cells to increase their growth. The first author of the paper, Simona Citro, Ph.D., and colleagues found that PLC-ε uniquely activates a second and distinctly different signaling cascade. This second signal catalyzes activation of a Ras family of small G proteins associated with cell growth.

"In combination with the first set of signals, this can lead to cell proliferation and could contribute to inflammation or cancer if left unchecked," said Citro.

"PLC plays a critical role in physiological processes including heart function, cell secretion and blood pressure control, so one would not normally want to block its activity," added Heller Brown. The UCSD researchers' discovery may enable scientists to target this novel PLC isoform or inhibit only its second function, preventing pathological responses while leaving PLC's critical positive role intact.

Additional contributors to the study include a co-contribution by a senior author Alan V. Smrcka as well as Sundeep Malik and Emily A. Oestreich, Department of Pharmacology and Physiology, University of Rochester; Julie Radeff-Huang, UCSD Department of Pharmacology; and Grant G. Kelley, Departments of Medicine and Pharmacology, State University of New York Upstate Medical University, Syracuse. The study was funded by the National Institutes of Health.

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Media Contact: Debra Kain, 619-543-6163, ddkain@ucsd.edu

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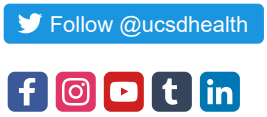
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