Biography of Lewis C. Cantley

Lewis Cantley cites the discovery of the phosphoinositide 3-kinase (PI3K) pathway as the most surprising of his research team's discoveries. This discovery, made more than a decade ago, opened a window on the way biochemical signaling pathways control normal cell growth and how they can trigger the development of cancer when they are defective. Crucially, his work has also enabled researchers to use the genetic blueprints of signaling proteins to predict their cellular targets, with a view to finding new cancer therapies.

Cantley, a professor of systems biology at Harvard Medical School and chief of the Division of Signal Transduction at Beth Israel Deaconess Medical Center, has received numerous awards in recognition of these achievements. Most recently he received the Caledonian Prize of the Royal Society of Edinburgh in 2002. He has well over 300 publications to his name, including research papers, reviews, and book chapters. Cantley was duly elected to the National Academy of Sciences in 2001. His inaugural article in this issue of PNAS describes how the tumor suppressor LKB1 protein kinase directly activates another protein kinase called AMP-activated kinase. This process regulates programmed cell death in response to conditions that deplete cellular ATP and elevate AMP. The work could explain the apparent paradox where LKB1 acts as a tumor suppressor and yet cells that lack it are resistant to cancer-causing oncogenes (1).

Enigmatic Enzymes

Cantley was born on February 20, 1949, and obtained a B.S. in chemistry, *summa cum laude*, from Wesleyan College in West Virginia in 1971. This was an exhilarating time to be starting a career in biochemical research. "Growing up in the 1960s, I was inspired by the early work of Jacque Monod and colleagues that provided the first real insight into the biochemical basis for cellular regulation by sugars and also provided models for regulation of proteins through conformational changes," he said. "I was also excited by the work of Peter Mitchel and Efraim Racker in elucidating how mitochondria can generate ATP from pH gradients, and the work of Edwin Krebs and Edmund Fischer in elucidating the role of protein kinases in control of carbohydrate metabolism."

Lewis C. Cantley

After completing his undergraduate degree, Cantley moved on to Cornell University in Ithaca, NY, to earn his Ph.D. in biophysical chemistry. Under the direction of Gordon Hammes he concentrated on protein conformational changes and enzyme kinetics. "This background provided me with some insight into the biochemical, structural, and dynamic bases for protein interactions that control cellular processes," he said. His Ph.D. research involved the use of fluorescent nucleotide analogs and the application of the emerging technology of fluorescence resonance energy transfer (FRET) to monitor nucleotide binding sites on coupling factor 1 involved in ATP synthesis (2). He focused on the structure and mechanism of enzymes that transport small molecules across cell membranes and so helped pioneer the use of FRET in studies of membrane proteins (3–5).

Cantley relocated to Massachusetts in 1975 to take on a postdoctoral position at Harvard University under the guidance of Guido Guidotti. Here, Cantley's research on the plasma membrane sodium pump led to the discovery that vanadate, an impurity in commercial ATP, actually inhibits the pump. He showed that vanadate acts as a transition state analog for phosphoenzyme hydrolysis and thus traps the enzyme in the act of catalysis (6, 7), a finding that led to the reinterpretation of previously published research.

In 1978, Cantley took the post of assistant professor in Harvard's Department of Biochemistry and Molecular Biology and subsequently became associate professor in 1981. A full professorship in physiology came from Tufts University School of Medicine in 1985, and Cantley held the position until 1992. He and his colleagues, Malcolm Whitman, David Kaplan, Tom Roberts, and Brian Schaffhausen, laid important groundwork during this time, examining the biochemical mechanisms of cellular responses to oncogenes and growth factors. The researchers made their seminal discovery regarding the PI3K pathway in 1985.

"At the time we made this discovery, relatively little was known about phosphoinositides, other than as intermediates in inositol-1,4,5-trisphosphate production," Cantley said. His team found that PI3K catalyzed an unexpected reaction: the phosphorylation of phosphatidylinositol at the D-3 position of the inositol ring (8). This finding consequently led to the discovery of a new signal transduction pathway. PI3K activation turned out to be critical for oncogene-mediated cell transformation and for insulin-dependent stimulation of glucose uptake and metabolism (10, 11).

Cantley's research further revealed that a phosphoinositide kinase copurified with several oncoproteins and, even more surprising, produced a set of previously unknown phosphoinositides (8, 9). "At first, the findings were viewed with considerable skepticism by both the cancer research community and by the lipid signaling community," he said.

Cantley's subsequent research as professor of both cell biology and systems biology at Harvard Medical School (1992 to present) overcame the research community's initial skepticism about the PI3K pathway. His team bolstered their results by further characterizing the mechanism by which growth factors and oncogenes activate PI3K and by elucidating pathways downstream of PI3K (11). The researchers' finding that these lipids interact directly with proteins and control many cellular events (12) took Cantley's research far beyond what he anticipated. "I think there is still much to be learned about the role that phosphoinositides play in cellular regulation," he said.

Signaling Structures

Another major focus of Cantley's research is the structural basis for specificity of protein–protein interactions in the signal transduction cascades that control

This is a Biography of a recently elected member of the National Academy of Sciences to accompany the member's Inaugural Article on page 3329.

cell growth and survival. Cantley and his student Zhou Songyang developed an oriented peptide library approach (13) that revealed the structural basis for regulated interaction of signaling proteins. The technique allows researchers to determine the optimal phosphopeptides for binding to various protein domains. Cantley's team further modified the technique to determine optimal substrates for protein kinases (14–16). This technique has also led to a widely adopted bioinformatics approach for predicting signaling pathways on the basis of primary sequences (17).

Cantley's laboratory has considered one aspect of these processes in particular: the mechanism by which protein phosphorylation controls the assembly of signaling complexes. "Through the work of my laboratory and others, it has been possible to determine structures of protein–peptide complexes and thus explain how specificity in signaling is maintained," said Cantley.

Collaborations and the sharing of ideas between laboratories are extremely important, Cantley asserts. "I virtually never turn down an opportunity to collaborate," he said, "because I always learn new technologies and obtain new points of view. The most fun part of my day is proposing new models to explain unexpected observations and then seeing if someone can find a weak point in my argument."

Breaking the Mold

Today, Cantley is still actively involved in studying the biochemical signaling pathways that regulate normal mammalian cell growth and the defects that can cause cell transformation. The major theme underlying his research remains the desire to understand the structural and biochemical basis for cellular regulation. "Much of my research in the past 15 years has focused on understanding the biochemical basis for how lipid kinases and protein kinases control cellular functions such as cell metabolism, cell growth, cell division, cell death, and cell movement," he said. Indeed, the research that led to his inaugural PNAS paper emerged from an attempt to understand why loss of a gene that encodes a protein kinase can result in tumor formation in humans.

In his inaugural article, Cantley reports that this kinase (LKB1) phosphorylates and turns on another protein kinase, AMP-activated protein kinase, which was already known to regulate cellular responses to stresses due to nutrient or oxygen deficiency. This discovery provides a new link between cancer and energy metabolism. Such research helps scientists incrementally elucidate the biochemical pathways that control responses to growth factors and hormones. "My goal has been to take the mystery out of complex cellular responses by providing explanations based on physical and chemical properties of components," Cantley said, "By elucidating these pathways we reveal new protein targets for developing drugs for treating diseases such as cancer and diabetes."

"Ultimately, I am never satisfied with an observation unless I can propose a biochemical model in which steps in the pathway make sense on a structural, kinetic and biochemical basis." He added, "Knowing a genetic pathway is exciting, but I need to understand the biochemical basis for the pathway."

One of Cantley's personal philosophies is never to assume that the ideas or models for biological functions that have been published in journals or textbooks are complete or even necessarily fundamentally correct. "Biological systems are incredibly complex, and our present insights into the mechanisms by which these systems are self-regulated are very primitive," he confessed. "There are many opportunities for future scientists to make major unexpected discoveries in cellular regulation. One must have the courage to trust one's own data and form new models that break the mold."

David Bradley, *Freelance Science Writer*

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