SIGNAL TRANSDUCTION

Lewis Cantley, PhD, Chief — The Division of Signal Transduction is a non-clinical division with a focus on determining the molecular mechanisms of cellular responses to growth factors, hormones and other regulators of cell function. The major goal of the Division is to elucidate biochemical mechanisms that control cell growth, cell survival, cell migration and cell cycle entry and to identify defects in these pathways that lead to human diseases such as cancer, insulin resistance, diabetes, obesity, immune defects and cardiac hypertrophy. Importantly, there is a major interest in validating targets, such as protein kinases and lipid kinases, for pharmaceutical intervention in these diseases.

Highlights

Research in the Division of Signal Transduction this year resulted in the discovery of a new metabolic pathway that uncouples glycolysis from ATP production. This research, published in *Science* in 2010, provides a partial explanation for the well-known observation that most cancer cells consume glucose at much higher rates than normal tissues (known as the Warburg Effect in recognition of Otto Warburg, the Nobel Laureate scientist who made this discovery more than 80 years ago). This research has suggested novel ways to target metabolic enzymes for treating cancer. These and other studies from the Division have suggested explanations for links between diabetes, obesity and cancers.

Research from Division members over the past year also provided insight into the biochemical mechanisms by which the frequently mutated oncogenes, K-Ras and PI3K drive tumor formation. These studies have suggested new ways to develop drugs to target these oncogenes and new biomarkers for predicting cancers that are likely to respond to these drugs.

Translational research activities are, indeed, strongly supported by the Division. Dr. Cantley is the Principal Investigator on a Stand Up to Cancer (SU2C) Dream Team Translational Research Grant focused on targeting the PI3K pathway in women's cancers. Under this grant, a team of basic scientists and clinicians are working together to discover approaches that will predict which patients will respond to a new class of drugs called PI3K pathway inhibitors. Their success will contribute to accelerating drug approvals and, ultimately, provide techniques for personalized cancer treatment that can be incorporated into standard practice. Through SU2C's encouragement, the exchange of materials and ideas by team members working in breast, ovarian and endometrial cancers will help us accelerate the cure for all three cancers. As a result, the team's work may demonstrate a new paradigm for women's cancers clinical trials and collaborative translational team science.

STAND UP TO CANCER
standup2cancer.org

Top: Lewis Cantley, PhD

Selected Publications

Vander Heiden MG, Locasale JW, Swanson KD, Sharfi H, Heffron GJ, Amador-Noguez D, Christofk HR, Wagner G, Rabinowitz JD, Asara JM, Cantley LC. Evidence for an alternative glycolytic pathway in rapidly proliferating cells. *Science* 2010; 329:1492-9.

Taniguchi CM, Winnay J, Kondo T, Bronson RT, Guimaraes AR, Alemán JO, Luo J, Stephanopoulos G, Weissleder R, Cantley LC, Kahn CR. The phosphoinositide 3-kinase regulatory subunit p85alpha can exert tumor suppressor properties through negative regulation of growth factor signaling. *Cancer Res* 2010; 70:5305-15.

Engelman JA, Cantley LC. Chemoprevention meets glucose control. *Cancer Prev Res* 2010; 3:1049-52.

Kaneko K, Ueki K, Takahashi N, Hashimoto S, Okamoto M, Awazawa M, Okazaki Y, Ohsugi M, Inabe K, Umehara T, Yoshida M, Kakei M, Kitamura T, Luo J, Kulkarni RN, Kahn CR, Kasai H, Cantley LC, Kadowaki T. Class IA phosphatidylinositol 3-kinase in pancreatic β cells controls insulin secretion by multiple mechanisms. *Cell Metab* 2010; 12:619-32.

Yuan TL, Wulf G, Burga L, Cantley LC. Cell-to-cell variability in PI3K protein level regulates PI3K-AKT pathway activity in cell populations. *Curr Biol* 2011; 21:173-83.

Sasaki AT, Carracedo A, Locasale JW, Anastasiou D, Takeuchi K, Kahoud ER, Haviv S, Asara JM, Pandolfi PP, Cantley LC. Ubiquitination of K-Ras enhances activation and facilitates binding to select downstream effectors. *Sci Signal* 2011; 4:ra13.

Amato S, Liu X, Zheng B, Cantley L, Rakic P, Man HY. AMP-activated protein kinase regulates neuronal polarization by interfering with PI 3-kinase localization. *Science* 2011; 332:247-51.

Tsou P, Zheng B, Hsu CH, Sasaki AT, Cantley LC. A Fluorescent reporter of AMPK activity and cellular energy stress. *Cell Metab* 2011; 13:476-86.

Saci A, Cantley LC, Carpenter CL. Rac1 regulates the activity of mTORC1 and mTORC2 and controls cellular size. *Mol Cell* 2011; 42:50-61.

Honors and Awards

Lewis Cantley, PhD – Received the 2011 Pasarow Award for Cancer Research. He also received the 2011 Katharine Berkan Judd Award for cancer research from Memorial Sloan Kettering Cancer Center.

Faculty

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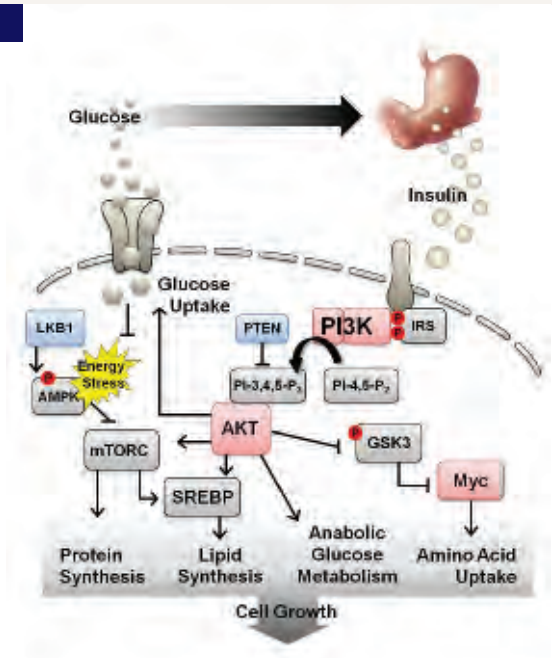
Research from the Division of Signal Transduction is providing biochemical explanations for how obesity and diabetes are linked to increased risk for cancer.