Where the Fat's At

August 25, 2010 |

UC San Diego-led team of scientists create novel map of lipid locations in a single cell

In real estate, location is everything. The same might be said of lipids – those crucial cellular fats and oils that serve as building blocks for cells and as key energy sources for the body.

In a paper published in the September issue of the *Journal of Lipid Research*, a team of scientists, led by researchers at the University of California, San Diego School of Medicine, has mapped for the first time the actual locations of specific lipids within a single cell.

Edward A. Dennis, PhD

"This is groundbreaking analysis," said Edward A. Dennis, PhD, distinguished professor of pharmacology, chemistry and biochemistry at UC San Diego and principal investigator of LIPID MAPS, a national consortium studying the structure and function of lipids. "We've defined not only which lipids are within a particular cell, but also where these lipids are located. That's important because lipids do different things in a cell. They're vital components of membranes. They're involved in communications and signaling, both within cells and between cells. Where they are located – in a cell's nucleus, its mitochondria, membrane or other organelle – is relevant to their function."

And because most serious diseases are linked to specific organelle dysfunction, understanding what lipids do at the subcellular level is essential to elucidating how diseases ranging from

atherosclerosis and arthritis to cancer and diabetes work – and how they might be better treated or prevented.

The focus of the lipid mapping was a cultured mouse macrophage or white blood cell, said Dennis, who also serves as editor-in-chief of the *Journal of Lipid Research*. Alexander Andreyev, PhD, a project scientist in the Dennis lab, extracted and separated organelles of the macrophage using advanced subcellular fractionation techniques. Scientists at collaborating universities then precisely identified and quantified the major lipid categories present with mass spectrometry. More than 220 individual molecular lipid species were identified and analyzed.

The analyses were conducted on macrophages in both resting and activated stages, the latter induced by exposing the cells to a specially synthesized chemical similar to a molecule found in bacteria pathogens. Called KLA, the chemical provokes a signaling cascade inside macrophages, activating their immune system response to infections.

"The idea was to see where targeted lipids were in macrophages at rest and how this changed upon infection," said Dennis. "We discovered that numerous lipids change in abundance in the membrane and in organelles once a macrophage becomes active."

Identifying these changes in specific lipids is expected to provide scientists with a deeper, more sophisticated understanding of how fats are involved in and influence disease processes, said Dennis.

"We've created a new picture of what's happening in cells. Not an image, but a view at the molecular level where drugs interact and diseases are cured."

The findings are part of the larger, on-going LIPID MAPS project, which received a second five-year renewal grant in 2008 for almost $38 million. The LIPID MAPS project is, in some ways, akin to the earlier Human Genome Project to inventory genes and similar endeavors with proteins (proteomics) and metabolites (metabolomics). It brings together researchers in a dozen research laboratories at nine universities, medical research institutes and life sciences companies. UC San Diego serves as lead institution and information clearinghouse.

"We've now identified many hundreds of lipids," said Dennis, "but we have the capability of detecting many thousands. This has been a trail-blazing experiment. We can now go deeper into the cell."

Co-authors of the study are Eoin Fahy, Xiang Li, Yihua Zhao and Shankar Subramaniam, San Diego Supercomputing Center, UC San Diego; Ziqiang Guan, Andrea Ryan and Christian R.H. Raetz, Department of Biochemistry, Duke University Medical Center; Samuel Kelly, Hyejung Park, Elaine Wang and Alfred Merrill, School of Biology, Georgia Institute of Technology; Jeffrey G. McDonald, Bonne M. Thompson and David W. Russell, University of Texas Southwestern Medical Center; and Steven Milne, David Myers and H. Alex Brown, Department of Pharmacology, Vanderbilt University.

This study was supported by the LIPID MAPS Large Scale Collaborative Grant from the National Institutes of Health.

# # #

Media contact: Scott LaFee, 619-543-6163, slafee@ucsd.edu