Researchers Describe First Functioning "Lipidome" of Mouse Macrophage

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For the first time, scientists have described not only the identities and quantities of fat species in a living mammalian cell – in this case, a mouse macrophage or white blood cell – but they also report how these lipids react and change over time to a bacterial stimulus triggering the cell's immune response.

Writing in the December 17 issue of the *Journal of Biological Chemistry*, lead authors Edward A. Dennis, PhD, distinguished professor of pharmacology, chemistry and biochemistry at the University of California San Diego School of Medicine and Shankar Subramaniam, PhD, Joan and Irwin Jacobs Endowed Chair in Bioengineering and Systems Biology and Chair of Bioengineering at the Jacobs School of Engineering, said the work culminates more than seven years of effort by scientists in LIPID MAPS, a national consortium of 12 research laboratories at nine "core" universities, medical research institutes and life sciences companies collaborating to study the structure and function of lipids.

The scientists said the "omics" and systems biology approach to mammalian metabolomics is the first of its kind and sheds new light on the important role of lipid molecules in physiological processes and pathologies associated with inflammation. UC San Diego serves as lead institution and information clearinghouse for the effort. Dennis is principle investigator.

Edward A. Dennis, PhD

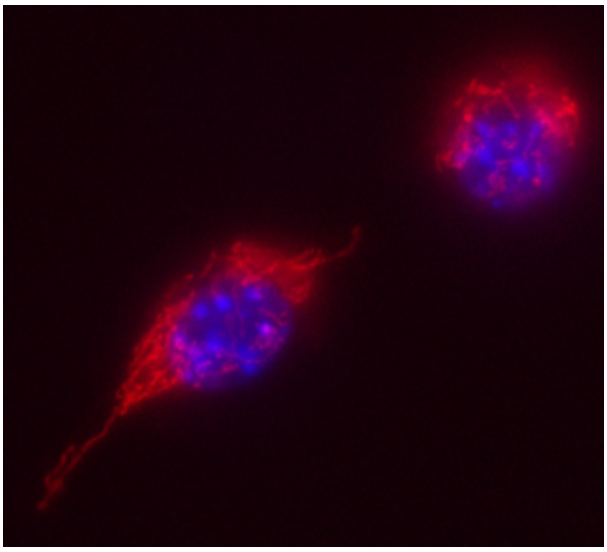
"This paper is the essence of what we originally proposed," said Dennis. "This is our big, initial study, though we've published many other papers and have more in the pipeline." All nine core facilities in LIPID MAPS participated in the study.

Until relatively recently, lipid research has not received the same degree of attention as, say, genes or proteins. But fats are indisputably crucial to cell operations and overall health. Lipids represent major structural and metabolic components of cells and perform essential functions, such as membrane construction, energy production and intracellular communications.

"They're also a key in virtually all diseases," said Dennis. "Any condition involving inflammation involves lipids. It's hard to think of a disease, including cancer, in which lipids don't play some role."

Likewise for the subject of the research: the mouse macrophage.

"It would have been simpler to do this with yeast or bacteria," said Dennis, "but the macrophage is found in every kind of mammalian tissue (under different names). It's a major player in the immune system."



two mouse macrophages. Nuclei are blue, mitochondria red. A newly completed "lipidome" of all of the fat species in the macrophage shows how the cells change under different disease conditions.

Moreover, scientists were able to study natural macrophages obtained from a live, well-established mouse model, rather than relying upon cultured cells. The model could also be genetically modified to test various hypotheses.

Previous studies have produced increasingly expansive and detailed "parts lists" of lipids. In October, for example, Dennis and colleagues published a paper that identified and quantified almost 600 distinct fat species circulating in human blood.

The new paper goes further. It chronicles the activity of more than 400 fat species in a macrophage after exposure to an endotoxin – a molecule found on the surfaces of bacteria that is recognized by macrophages and which triggers the cell's infection-fighting functions.

Each hour for 24 consecutive hours, scientists measured minuscule increases or decreases of targeted lipids, an indication of greater or lesser activity.

"The result is a temporal model of infection at the level of a single cell," said Dennis.

Similar experiments were conducted with macrophages exposed to a statin (a popular class of cholesterol-lowering drugs) and with macrophages simultaneously exposed to both an endotoxin and a statin.

"We chose to use a statin because we know it blocks production of cholesterol (a type of lipid), but statins also produce some anti-inflammatory effects. We wanted to see what else happens. And in fact, we saw some unexpected changes in certain metabolites."

Metabolites are the players and products of metabolism – the set of chemical reactions in cells that produce and sustain life.

Dennis said the findings lay the foundation for on-going and future projects to eventually produce a human "lipidome," a complete inventory of all fat species in the human body and how they work together.

"We only have three more years of the LIPID MAPS project," Dennis said. "But this is really just the beginning."

Co-authors of the paper are Raymond A. Deems of the Department of Chemistry and Biochemistry at UC San Diego; Richard Harkewicz of Department of Pharmacology, UC San Diego School of Medicine; Oswald Quehenberger and Gary Hardiman of UCSD's Department of Medicine, School of Medicine; H. Alex Brown, Stephen B. Milne and David S. Myers of the Department of Pharmacology, Vanderbilt University School of Medicine; Christopher K. Glass of the UCSD's Department of Medicine and Department of Cellular and Molecular Medicine, School of Medicine; Donna Reichart of UCSD's Department of Cellular and Molecular Medicine, School of Medicine; Alfred H. Merrill, Jr., M. Cameron Sullards and Elaine Wang of the Schools of Biology, Chemistry and Biochemistry and the Petit Institute of Bioengineering and Bioscience at Georgia Institute of Technology; Robert C. Murphy of the Department of Pharmacology, University of Colorado Denver; Christian R.H. Raetz, Teresa Garrett, Ziqiang Guan and Andrea C. Ryan of Department of Biochemistry, Duke University Medical Center; David W. Russell, Jeffrey G. McDonald and Bonne M. Thompson of Department of Molecular Genetics, University of Texas Southwestern Medical Center; Walter A. Shaw of Avanti Polar Lipids, Inc.; Manish Sud, Yihua Zhao, Shakti Gupta, Mano R. Maurya and Eoin Fahy of the San Diego Supercomputer Center at UC San Diego.
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