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**Scientists at CeMM discover a new fundamental feature in the organization of biological matter.**

**(Vienna, 18 June 2015) An unexpected order in the molecular regulation of the constituents of the fat part of our cells is revealed in two simultaneous publications appearing from the laboratory of Prof. Giulio Superti-Furga in the renowned scientific journals *Cell* and *Cell Reports*. The two studies, from scientists at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences investigated the role of lipids in the immune response. Marielle Köberlin, Berend Snijder, Leonhard Heinz and colleagues discovered that the regulation of lipids in the cell membrane follows a surprising circular, ring-like organizational pattern and that this pattern is linked to various cellular functions. In particular, the scientists found that the ability of cells to mount an immediate immune response is influenced by the cell’s lipid composition to a degree that far exceeds what had been known to date and can be predicted by this new regulatory “code”.**

Essential to our immune system are so-called macrophages that act as sentinels and can ‘eat’ and destroy pathogens. The first contact between an invading pathogen and macrophages occurs at the cell surface of the macrophage. As for all cells in the human body, this cell surface is made up of two oppositely oriented layers of lipids, called a lipid membrane, and membrane proteins, including receptors that recognize pathogens. While much is known about the role of the many proteins involved in this process, cellular membranes contain hundreds of chemically distinct lipids, for which little is known in terms of regulation and function, and in particular their possible influence on the cell’s immune response.

**Membrane lipids follow a higher-level organization**

The team around Giulio Superti-Furga at the CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, has been interested in the organizational principle of biological matter, such as cell constituents, and in processes related to the primary response of cells to pathogens.

In the systematic study published in *Cell*, the team discovered that the amount and composition of lipids of different lipid types, follows a higher-level organization. The authors report that in cells certain lipids increase or decrease together with other lipids, a process they call lipid co-regulation. Visualization of the regulatory interdependence between hundreds of different lipid species, revealed that the organization forms a near perfect circular network of co-regulated lipids, exposing for the first time a “code” underlying the cellular lipids, or the “lipidome”.

Interestingly, based on the “circular lipidome” the researchers are now able to decipher the role of hundreds of different lipid species in the immune response, revealing which lipids act to stimulate and which act to dampen the inflammatory response of macrophages. The predictive power of the circular lipidome was put to test with cells from patients suffering from lipid storage disorders, caused by inherited mutations in genes involved in lipid metabolism. The authors found that they could accurately predict the inflammatory response of cells of these patients, only based on the measured differences in lipid composition.

**Further insights into the lipid´s role in the immune response**

In their second study published in the journal *Cell Reports,* the team provides a detailed functional characterization of a protein called SMPDL3B, a lipid-modifying enzyme. In a collaborative effort involving researchers from CeMM, the Medical University of Vienna and the National University of Singapore, the authors discovered that SMPDL3B is located on the surface of macrophages where it strongly affects the cellular lipid composition, thereby providing a novel mode of regulation for the immune response.

Senior Author Giulio Superti-Furga, who is Principal Investigator at CeMM and Professor for Medical Systems Biology at the Medical University of Vienna says: “Not only do these studies reveal a wide, unexpected role for lipids in innate immune signaling, but establish that global studies, looking at many molecules at the same time, can reveal new fundamental principles on how biological matter is organized. The circularity of lipid co-regulation discovered at CeMM is likely to enter the biochemistry textbooks.”

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**Studies:**

A Conserved Circular Network of Coregulated Lipids Modulates Innate Immune Responses

Marielle S. Köberlin, Berend Snijder, Leonhard X. Heinz, Christoph L. Baumann, Astrid Fauster, Gregory I. Vladimer, Anne-Claude Gavin and Giulio Superti-Furga

Cell 162, July 2, 2015: 1-14. DOI: <http://dx.doi.org/10.1016/j.cell.2015.05.051>

The Lipid-Modifying Enzyme SMPDL3B Negatively Regulates Innate Immunity

Leonhard X. Heinz, Christoph L. Baumann, Marielle S. Köberlin, Berend Snijder, Riem Gawish, Guanghou Shui, Omar Sharif, Irene M. Aspalter, André C. Müller, Richard K. Kandasamy, Florian P. Breitwieser, Andreas Pichlmair, Manuela Bruckner, Manuele Rebsamen, Stephan Blüml, Thomas Karonitsch, Astrid Fauster, Jacques Colinge, Keiryn L. Bennett, Sylvia Knapp, Markus R. Wenk, and Giulio Superti-Furga

Cell Reports 11, June 30, 2015: 1–10. <http://dx.doi.org/10.1016/j.celrep.2015.05.006>

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