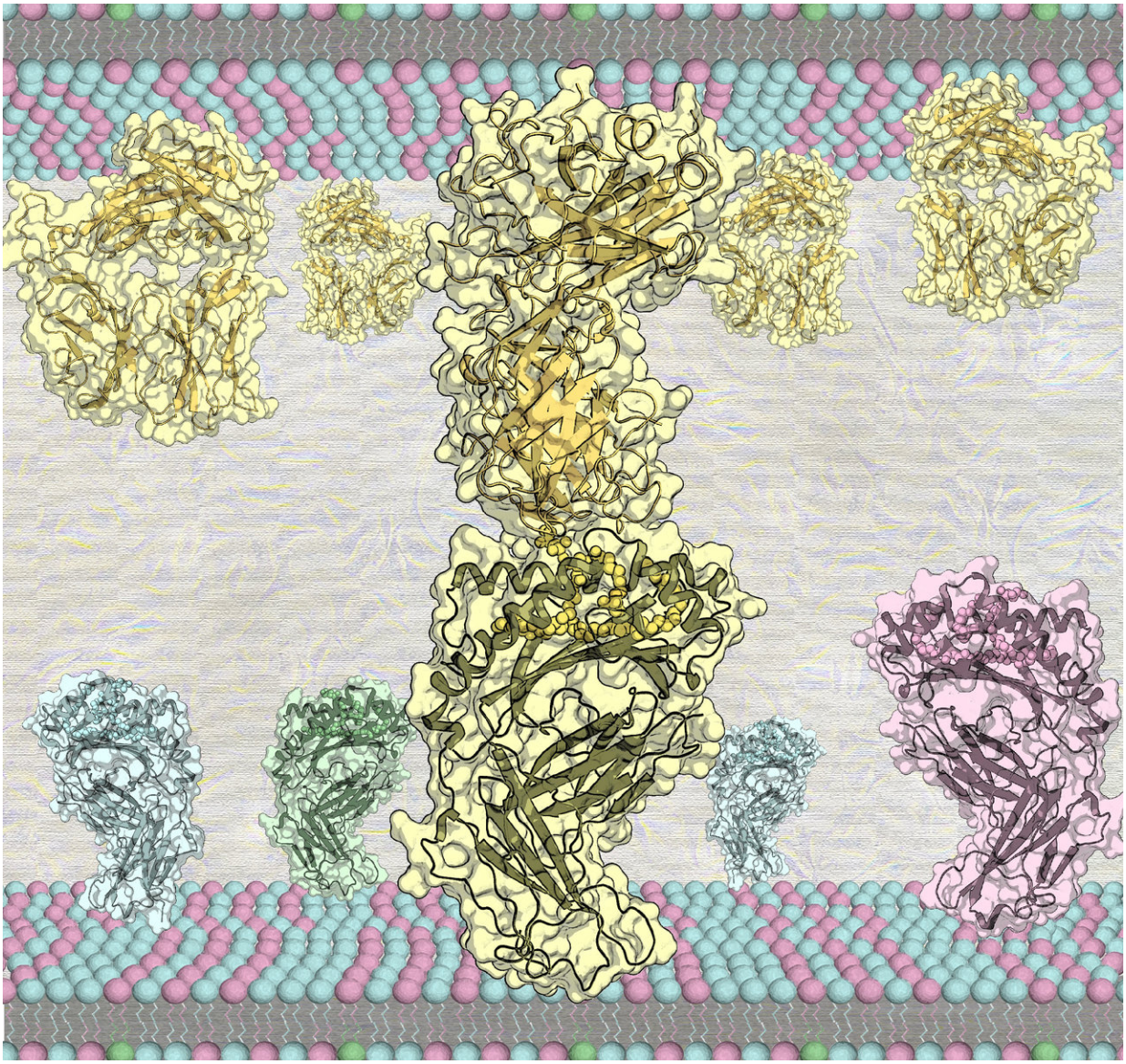
Medical Xpress

The skinny on lipid immunology

October 20 2017



T-cell Receptors (gold, upper) on the surface of T-cells selectively bind the lipid antigen presenting molecule on dendritic cells, CD1b (lower), presenting a rare cellular phospholipid (gold), over common phospholipids found in membranes

(pink, cyan and green), which in turn induces an autoimmune response. Credit: Shahine et al.

Phospholipids - fat molecules that form the membranes found around cells - make up almost half of the dry weight of cells, but when it comes to autoimmune diseases, their role has largely been overlooked. Recent research has pointed to a role for them in numerous diseases, including psoriasis, contact hypersensitivities and allergies. In a new study published in *Science Immunology*, researchers from Brigham and Women's Hospital and Monash University in Australia reveal new insights into the basis for T cell receptor (TCR) autoreactivity to self-phospholipids, with implications for autoimmune diseases.

"Lipids have been under appreciated in immunology," said co-corresponding author D. Branch Moody, MD, a principal investigator in the Division of Rheumatology, Immunology and Allergy. "We've been interested in autoimmune diseases for decades, and it's thought that in certain autoimmune diseases like psoriasis, multiple sclerosis and type 1 diabetes are driven by particular tissues. The search for the particular molecules, known as antigens, that trigger autoimmune diseases has focused on proteins and peptides, but we should also be thinking about lipids as candidate antigens for autoimmune disease."

For 30 years, researchers have known that T cells play an important role in autoimmune disorders, but it was thought that T cells could only respond to proteins. Previous studies conducted by investigators at the Brigham provided the first hint that a T cell could also respond to lipids. The newly published study suggests that many T cells can respond lipids, and illuminates the physical structures that make this recognition of lipids possible.

T cells are activated when another key part of the immune system, dendritic cells, present them with an antigen. Moody and his colleagues, Ildiko Van Rhijn and Tan-yun Cheng, set out to detect what molecules were being captured and presented, stimulating a T cell response. Using structural biology, Jamie Rossjohn and Adam Shahine of the Australian Research Council Centre of Excellence in Advanced Molecular Imaging at Monash University in Australia showed how a protein on the surface of dendritic cells - known as CD1b - binds to lipids. This complex of CD1b and a lipid then binds to a T cell receptor, activating an immune response.

"The advanced imaging facilities of the Australian Synchrotron have allowed us to generate three-dimensional models of T-cell receptor interaction against CD1b and lipid antigens," said Shahine. "These results highlight the role of CD1b in a phospholipid-mediated immune response, and grant us a deeper understanding of the mechanisms of lipid-based autoimmune disease."

The work may have implications for specific forms of autoimmune disease, including systemic lupus erythematosus. Previous studies have found that patients with lupus have antibodies that bind to phospholipids, which cause clotting and strokes. The new study shows that T cells also recognize phospholipids, opening up new perspectives on T cell and antibody cooperation in this disease.

"We now have these beautiful, three-dimensional images of how three different molecules can interact, which explains some detail about which part of the lipid matters. Knowing the precise structure of the complexes involved in this process could be useful for designing new kinds of lipids that could turn on or off the immune response," said Moody.

More information: *Science Immunology* (2017). DOI: 10.1126/sciimmunol.aao1384

Provided by Brigham and Women's Hospital