MS11-O2 Cholesteryl esters are a new class of ligands for lipid antigen presentation by CD1c proteins

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Presentation of lipid antigens to T cells is negotiated by CD1 proteins (Cluster of differentiation 1). CD1 proteins are a family of MHC class I-like glycoproteins, distinguished into five different classes that differ in substrate specificity and intracellular trafficking. Determining their individual substrate specificity and unique features is instrumental to understanding their roles in host defense and immune regulation.

We have studied the CD1c isoform and determined the 2.4 Å structure of CD1c in the presence of lipid ligands, differentiating this isoform from other CD1proteins. The ligands are enclosed in binding pockets, resulting in significant changes in shape of CD1c between ligand bound and unbound forms. Computational simulations starting with this structure explore the lipid-binding pocket to suggest the potential of CD1c to present acylated sterols.

We confirmed the prediction for two lipid classes: cholesteryl esters similar to those accumulating in foamy macrophages and in solid tumors, relevant in the context of autoimmune disorders and cancer, and acylated steryl glycosides relevant in bacterial infections such as lime disease and tuberculosis. The findings open up new avenues for research into the role of CD1c in human immunity.

Mansour S, Tocheva AS, Cave-Ayland C, Machelett MM, Sander B, Lissin NM, Molloy PE, Baird MS, Stübs G, Schröder NW, Schumann RR, Rademann J, Postle AD, Jakobsen BK, Marshall BG, Gosain R, Elkington PT, Elliott T, Skylaris CK, Essex JW, Tews I, Gadola SD. "Cholesteryl esters stabilize human CD1c conformations for recognition by self-reactive T cells." Proc Natl Acad Sci USA. 113 (2016), E1266-75.

Keywords: Immunity, glycoprotein, CD1, lipid, antigen

MS11-O3 Structure of the full-length VEGFR-1 extracellular domain in complex with VEGF-A

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Vascular Endothelial Growth Factors (VEGFs) regulate blood and lymph vessel development and are thus essential for vessel homeostasis. VEGFs activate three receptor tyrosine kinases (RTKs), VEGFR-1, -2, and -3. Mutation of these receptors gives rise to distinct disease profiles documenting signal diversity among VEGF receptors. Aberrant expression of a soluble splice variant of VEGFR-1, encompassing only the extracellular domain (ECD) and acting as a ligand trap, is associated with vascular defects such as the placental deficiency preeclampsia, or corneal avascularity. This variant is thus a potentially interesting target for drug development. A low resolution structure of the full-length VEGFR-2 ECD/VEGF-A complex based on single particle electron microscopy and small angle X-ray scattering data revealed the location of VEGF binding and domain arrangement of the membrane proximal part of the receptor. Here we describe the structure of the full-length VEGFR-1 ECD in complex with VEGF-A at 4 Å resolution. We combined X-ray crystallography, single particle electron microscopy, and molecular modeling for structure determination and validation. The structure reveals the molecular details of ligand-induced receptor dimerization, in particular of homotypic receptor interactions in Ig-domains 4, 5, and 7. Thermodynamic and mutational analyses of ligand binding and receptor activation confirm the functional relevance of these homotypic contacts and identify them as potential therapeutic sites to allosterically inhibit VEGFR-1 activity. This structural and functional information will be central for developing novel, highly specific VEGFR inhibitors.

Keywords: low resolution X-ray crystallography, negative staining EM, SAXS, native-SAD, modeling, receptor tyrosine kinases