Crystal structure of mouse CD1d with a phospholipid self ligand: insights in the molecular basis of regulatory NKT cell activation. Massimo Degano[a], Barbara Giabbai[a], Stèphane Sidobre[b], Yovan Sanchez-Ruìz[c], Angela Bachi[c], Mitchell Kronenberg[b].
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NKT cells are immunoregulatory lymphocytes able to modulate the immune response through rapid secretion of cytokines. These cells are known to promote spontaneous rejection of tumors, or control an unwanted immune reaction in several autoimmune pathologies. NKT cells are activated is by the recognition of glycolipid antigens bound to the CD1d molecules by a semi-invariant T cell antigen receptor (TCR). The molecular details of the interactions between CD1d and its ligands, however, are still elusive. Here we present the crystal structure to 2.8Å of mouse CD1d bound to the self ligand phosphatidyl choline. The structure of the CD1d/ligand complex allows the definition of the structural and chemical requirements for the binding of lipids to group II CD1 molecules. The shape and volume of the binding groove limit the pool of CD1d-restricted lipid antigens to compounds with defined acyl chain composition. The orientation of the antigen polar headgroup towards the C-terminus of the α1 helix provides a rationale for the structural basis for the observed Vα chain bias in NKT cells. The contribution of the ligand to the protein surface suggests a likely mode of recognition of lipid antigens by the NKT cell TCR that is distinct from the classic TCR/MHC/peptide interaction. The structure of the CD1d/self antigen complex suggests rational modifications of known antigens that could modulate the activity in vivo of NKT cells.