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CD1d lipid-antigen recognition by the γδ TCR

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The T lymphocytes repertoire is divided into two major lineages, αβ and γδ T cells, which are defined by their T cell receptor (TCR) gene-segment usage. To date, the key discoveries on human CD1d restricted T cells have focussed on the type I Natural Killer T cells (NKT) subset that express an invariant TCR α chain (Vα24Jα18) which pairs with a β chain (Vβ11). The structural basis for the recognition of CD1d-lipid antigen by type I NKT cells is also now well established [1, 2]. However, there are other subsets of NKT cells that exhibit reactivity towards lipid-antigen presenting molecules (CD1d) but that do no express the typical Vα24Jα18 TCR. We identify human NKT cell subsets that express Vδ1+ γδ TCRs that recognize CD1d presenting the lipid-antigen α-galactosylceramide (α-Galcer). Here, we describe the first crystal structure of a CD1d/γδ TCR ternary complex [3] and provide structural insights into the binding mode of a γδ TCR with CD1d-αGalcer. The γδ TCR binds orthogonally over the A' pocket of CD1d, that is in clear contrast with the typical type I parallel docking mode in which the αβ TCR is perched over the F' pocket of CD1d. The germ line-encoded CDR1δ loop dominates the contacts with the CD1d molecule while the CDR3γ loop represents the main structural determinant for the antigen specificity. These findings highlight the emergence of diverse populations of NKT TCRs that exhibit different binding mode and lipid antigen specificity.

[1] *NA. Borg, KS. Wun, L. Kjer-Nielsen et al. Nature, 2007, 448, 1137-1145.,* ***[2]*** *KS. Wun, NA. Borg, L. Kjer-Nielsen et al. J. Exp. Med., 2008, 205, 939-949.,* ***[3]*** *AP. Uldrich, J. Le Nours, DG. Pellicci et al. Nature Immunology, 2013, 14, 44-49.*

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