Interaction of Glycolipids with the Macrophage Surface Receptor Mincle

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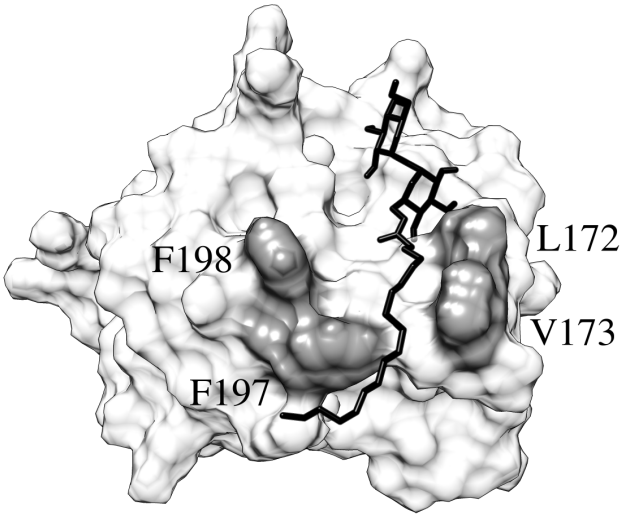
Synthetic analogues of mycobacterial trehalose-dimycolate such as trehalose acyl esters have been proposed as novel adjuvants for vaccination. They induce an immune response by binding to the macrophage C-type lectin receptor Mincle [1]. The binding site of trehalose is known [2], but there is yet only very limited structural information about the binding mode of the acyl esters.



Trehaloseoctadecanoate (black sticks) bound to Mincle (white surface representation). Key interacting residues, which form a hydrophobic groove on the surface, are colored in gray.

Here, we performed a systematic molecular dynamics study of trehalose mono- and diesters with different chain lengths. All acyl chains investigated exhibited a high flexibility and interacted almost exclusively with a hydrophobic groove on Mincle. Despite the limited length of this hydrophobic groove, the distal parts of the longer monoesters can still form additional interactions with this surface region due to their conformational flexibility. In diesters, a certain length of the second acyl chain is required to contact the hydrophobic groove. However, a stable concomitant accommodation of both acyl chains in the groove is hampered by the conformational rigidity of Mincle. Instead multiple dynamic interaction modes are observed, in which the second acyl chain contributes to binding. This detailed structural information is considered helpful for the future design of more affine ligands that may foster the development of novel adjuvants.

References

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