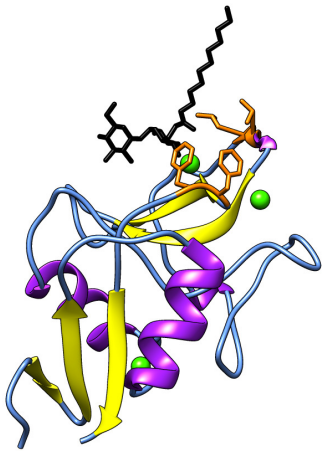
Binding of Glycolipids to the Macrophage Surface Receptor Mincle

Christian A. Söldner, Anselm H. C. Horn, Heinrich Sticht

Macrophage inducible Ca^{2+} dependent lectin (mincle) is a receptor expressed on macrophages that is involved in the recognition of the mycobacterial cord factor trehalose dimycolate thus leading to an immune response against *Mycobacterium tuberculosis*. Recent findings show that mincle is also activated by synthetic glycolipids such as trehalose acyl esters, which could be used as adjuvants for vaccination [1].

Complex structures of mincle and trehalose have been solved by X-ray crystallography and show that the sugar forms stable contacts with a conserved carbohydrate recognition domain and a Ca^{2+} ion [2, 3]. Hydrophobic residues on the surface of mincle form a groove that is likely to interact with the fatty acid of the trehalose acyl esters. However, the interaction between mincle and the acyl chains is difficult to characterize in detail: From an X-ray structure published for a complex of mincle and trehalose monobutyrate, only the first two carbon atoms of the fatty acid could be determined from the electron density map suggesting that the remainder might be flexible [3]. Although only linear acyl chains up to eight carbon atoms fit into the groove, esters with longer fatty acids have been shown to bind and activate mincle with even higher affinity [1, 3].



Trehalose acyl ester bound to mincle (black sticks: trehalose dodecyl ester, orange sticks: hydrophobic groove, green spheres: Ca^{2+} ions)

To investigate the interaction between fatty acids of different lengths and the protein, we performed all atom molecular dynamics (MD) simulations of trehalose acyl esters bound to mincle in explicit water. In our calculations, the acyl chains remain indeed very flexible and sample both linear and globular conformations during simulation. Frequent transient contacts occur predominantly with the hydrophobic residues of the protein groove. Longer acyl chains, however, contact also distant residues on the protein surface. Thus, the additional CH_2 groups confer an enhanced stabilization of the protein ligand complex due to an increased Van-der-Waals energy.

References

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