Understanding the molecular recognition of Bacteroides fragilis glycosphingolipids by Natural Killer T-cell receptor

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The human gut microbiota comprises more than 50% of Bacteroides species that produce small diffusible molecules like sphingolipids that play a key role in modulating the host’s immune responses. In particular, Bacteroides fragilis produces glycosphingolipids similar to α-galactosylceramides termed as ‘BfaGCs’ that can activate type I Natural Killer T (NKT) cells when presented by the antigen-presenting molecule CD1d. While they share key chemical similarities with the type I NKT cell marker antigen, α-galactosylceramide (KRN7000), they possess distinctive structural features including short sphinganine chains, branching and functional groups, implying a basis for their unique immunomodulatory properties. Our X-ray crystallographic studies on two such CD1d-presented BfaGCs in complex with the type I NKT TCR revealed the TCR adopted a parallel docking topology atop the F'-pocket of CD1d in recognising the presented BfaGCs [1]. Interestingly, the terminal sphinganine branching of the BfaGCs mediated unique interactions within the F'-pocket of CD1d providing a mechanism for their differing agonistic properties. The NKT TCR recognised the CD1d presented stimulatory and non-stimulatory BfaGCs with nanomolar affinities. Thus, BfaGCs were demonstrated to be bonafide CD1d ligands that function as immunomodulatory mediators influencing the host’s defence in the context of NKT cells. Together, this study sheds light on a better understanding of the existing symbiotic relationship between the microbes producing these endogenous lipids and the host.