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The Liganding of Glycolipid Transfer Protein is Controlled by Glycolipid Acyl Structure. Lucy Malinina[1#], Margarita L. Malakhova[2#], Alex T. Kanack[2], Ruben Abagyan[3], Rhoderick E. Brown[2*], Dinshaw J. Patel[1], [1]Structural Biology Program, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, [2]Hormel Inst., Univ. of Minnesota, Austin, MN 55912, [3]Dept. of Molecular Biology, The Scripps Research Institute La Jolla, CA, 92037.

Glycosphingolipids (GSLs) play major roles in cellular growth and development. Mammalian glycolipid transfer proteins (GLTPs) are potential regulators of cell processes mediated by GSLs and display a unique architecture among lipid binding/transfer proteins. We determined crystal structures of human GLTP bound to GSLs of diverse acyl chain length, unsaturation and sugar composition. Structural comparisons show a highly conserved anchoring of galactosyl- and lactosyl-amide headgroups by the GLTP recognition center. By contrast, acyl chain structure dictates partitioning between sphingosine-in and sphingosine-out ligand-binding modes. In the sphingosine-out mode, the sphingosine chain is directed outwards and enters the hydrophobic tunnel of a partner complex, whereas the sphingosine-in mode is achieved through encapsulation of both ceramide chains within a hydrophobic tunnel of a single GLTP molecule. The structural insights, combined with computed interaction propensity distributions, suggest a concerted sequence of events mediated by GLTP conformational changes during GSL transfer to/from membranes or presentation/transfer to other proteins.