A Remote Secondary Binding Pocket Promotes Heteromultivalent Targeting of DC-SIGN.

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Dendritic cells (DC) are antigen-presenting cells coordinating the interplay of the innate and the adaptive immune response. The endocytic C-type lectin receptors DC-SIGN and Langerin display expression profiles restricted to distinct DC subtypes and have emerged as prime targets for next-generation immunotherapies and anti-infectives. Using heteromultivalent liposomes copresenting mannosides bearing aromatic aglycones with natural glycan ligands, we serendipitously discovered striking cooperativity effects for DC-SIGN; +; but not for Langerin; +; cell lines. Mechanistic investigations combining NMR spectroscopy with molecular docking and molecular dynamics simulations led to the identification of a secondary binding pocket for the glycomimetics. This pocket, located remotely of DC-SIGN's carbohydrate bindings site, can be leveraged by heteromultivalent avidity enhancement. We further present preliminary evidence that the aglycone allosterically activates glycan recognition and thereby contributes to DC-SIGN-specific cell targeting. Our findings have important implications for both translational and basic glycoscience, showcasing heteromultivalent targeting of DCs to improve specificity and supporting potential allosteric regulation of DC-SIGN and CLRs in general.

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