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## Molecular Recognition and Adhesion in Innate Immunity

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Innate immunity is the first line of defense against pathogen infection prior to the slower response of the adaptive immune system. DC-SIGN is a member of a class of C-type lectins that recognizes high mannose sugars on pathogen surfaces. It mediates cell-pathogen adhesion and subsequent pathogen internalization and processing for antigen presentation. It is also the primary target for HIV binding to and subsequent internalization by oligodendrocytes in the immune system. A structurally related protein, DC-SIGNR is also a target of viral infections, and structural variants correlate with different viral infection rates. These investigations used molecular force measurements to establish how protein architecture and ligand presentation contributes to high avidity pathogen binding by dendritic cells in the immune system.

Surface force apparatus and surface plasmon resonance measurements were used to investigate how ligand presentation and protein architecture affects the capacity for DC-SIGN (and DC-SIGNR) to recognize glycan structures on cell surfaces. Surface force apparatus measurements directly quantified both the range and magnitude of the forces between membrane-bound, oriented DC-SIGN (or DC-SIGNR) and glycan presenting bilayer membranes. The distance resolution achieved in surface force apparatus revealed that ligand docking induces a conformational change that enhances pathogen adhesion. Measurements also demonstrated that adhesion depends on both the distribution of carbohydrate ligands on the target surface and the ligand mobility. Finally, we determined how naturally occurring variations in the length of the DC-SIGNR neck region impacts recognition. These molecular level measurements thus defined key mechanisms governing pathogen recognition in innate immunity and established design rules for therapeutic agents to block viral infectivity.