# Structural Analysis of Virus-Receptor Interactions

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My laboratory studies the interactions between viruses and receptors, in order to describe mechanisms of viral attachment to target cells and to provide a basis for vaccine and drug design. I will present our recent progress on work with adenoviruses, reoviruses, and Simian Virus 40. In each case, structural and functional analyses of virus-receptor-complexes provide insights into ligand specificity, tropism, and disease outcomes, while also guiding strategies for interfering with binding. Adenoviruses are human pathogens as well as highly useful vehicles for gene delivery. Vectors based on group B adenoviruses are especially attractive tools for use in human gene therapy because this subgroup exhibits low seroprevalence and efficient transduction capacity. The latter is linked to the usage of the ubiquitously expressed complement regulatory protein CD46 as a cellular receptor. The crystal structure of the group B adenovirus type 11 knob in complex with CD46 reveals a profound alteration of a cellular receptor structure by its viral ligand. This alteration of a cellular receptor structure by its viral ligand represents a new mechanism of interaction that is likely to be conserved among many pathogens that use CD46 or related proteins as receptors. Mammalian reoviruses are highly tractable experimental models for studies of double-stranded RNA virus replication and pathogenesis. I will describe the recently-determined structure of the reovirus attachment protein in complex with its receptor junctional adhesion molecule-A, a critical component of intercellular tight junctions. The structure reveals an unusual contact surface and provides a molecular framework for understanding reovirus cell attachment. We engineered structure-guided mutations in the reovirus attachment protein to identify residues required for reovirus binding and infection. Given the use of reovirus as an oncolytic agent, this work establishes a platform for manipulation of reovirus tropism for improved vector targeting. Simian virus 40 (SV40) has been a paradigm for understanding attachment and entry of non-enveloped viruses, viral DNA replication, and virus assembly, as well as for endocytosis pathways associated with caveolin and cholesterol. The high-resolution crystal structure of recombinantly produced SV40 capsid protein, VP1, in complex with the carbohydrate portion of its receptor GM1 reveals that the receptor is bound in a shallow, solvent-exposed groove at the outer surface of the capsid. Through a complex network of interactions, VP1 recognizes a conformation of GM1 that is the dominant one in solution. Analysis of contacts provides a structural basis for the observed specificity and suggests binding mechanisms for additional, physiologically relevant GM1 variants. Comparison with murine polyomavirus receptor complexes reveals that SV40 uses a different mechanism of sialic acid binding, which has implications for receptor binding of human polyomaviruses.