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Crystal Structure of a LDLR/RAP Complex: Insights into Ligand Binding and Intracellular Trafficking of the LDLR Family Proteins. Natalia Beglova, Carl Fisher, Stephen C. Blacklow, Dept. of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115.

Proteins of the LDLR family bind a diverse range of ligands, yet the basis for ligand recognition is poorly understood. We solved the 1.3 Å X-ray structure of a complex between a two-module region of the ligand-binding domain of the LDLR and the third domain of RAP, an escort protein for LDLR family members. Each LA module combines four residues to create a virtually identical binding pocket for a lysine side-chain protruding from the second helix of RAP. All four LA residues that form the binding pocket participate in calcium coordination and, as a consequence, the relative positions of their side chains are constrained. This calcium-dependent mode of electrostatic recognition, together with avidity effects resulting from the use of multiple sites, represents a general binding strategy likely to apply in the binding of other basic ligands to LDLR family proteins. Complexes dissociate, when the pH drops below 6.5. Titration of histidine residues oriented toward the interior of the helical hairpin of RAP-D3 results in unfolding of the helix bundle and release of the receptor.

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