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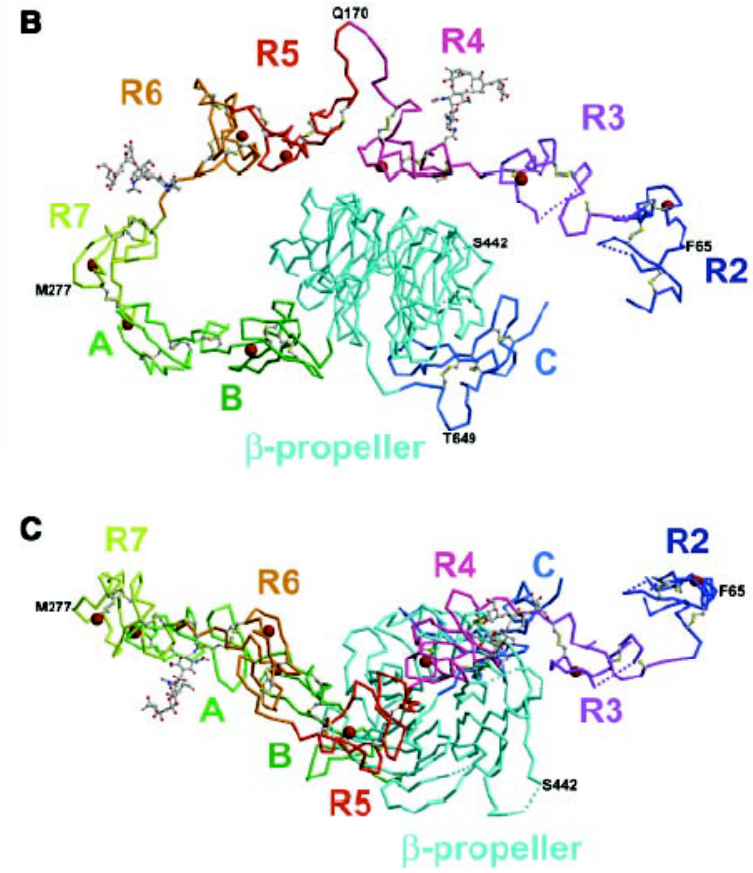
Structure of the LDL Receptor Extracellular Domain at Endosomal pH

Gabby Rudenko,[1] Lisa Henry,[1,3] Keith Henderson,[4]
Konstantin Ichtchenko,[2]* Michael S. Brown,[2]
Joseph L. Goldstein,[2] Johann Deisenhofer[1,3]†

The low-density lipoprotein receptor mediates cholesterol homeostasis through endocytosis of lipoproteins. It discharges its ligand in the endosome at pH _ 6. In the crystal structure at pH _ 5.3, the ligand-binding domain (modules R2 to R7) folds back as an arc over the epidermal growth factor precursor homology domain (the modules A, B, -propeller, and C). The modules R4 and R5, which are critical for lipoprotein binding, associate with the -propeller via their calcium-binding loop. We propose a mechanism for lipoprotein release in the endosome whereby the -propeller functions as an alternate substrate for the ligand-binding domain, binding in a calcium-dependent way and promoting lipoprotein release.



(**B**) C_ trace of LDL-R monomer. Modules are colored according to their boundaries with the ligand-binding domain containing R2 (residues 44 to 85), R3 (85 to 124), R4 (124 to 170), R5 (170 to 212), R6 (212 to 254), R7 (254 to 294), and the EGF precursor homology domain containing A (294 to 332), B (332 to 377), □-propeller (377 to 643), and C(643 to 693). Regions of poor backbone connectivity are dashed. Calcium ions are indicated as red spheres, and disulfide bonds and carbohydrates on Asn135 and Asn251 are shown in gray as ball and stick (sulphur atoms, yellow; oxygen, red; nitrogen, blue; and carbon, gray). (**C**) The view is rotated 90° from that of (B).

Many of the residues that bind the calcium ion in R4 and R5 also form the interface with □-propeller, and these residues (or ones close by) likely bind to apoB and apoE as well. For example, two of these, Trp144 and Trp193, donate only a main-chain carbonyl to calcium coordination; nevertheless their side chains are strictly conserved in 15 sequences.