The structure of the complex of the cytoplasmic guanine nucleotide exchange factor Ric-8A with Gαi1

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The alpha subunits (Gα) of heterotrimeric G proteins are activated by guanine nucleotide exchange factors (GEFs) that catalyze the release of GDP from the Gα nucleotide binding site and subsequent loading of GTP into that site1. Plasma membrane-bound, agonist-stimulated G protein-coupled receptors (GPCRs) are the best characterized heterotrimeric G protein GEFs, but cytoplasmic GEFs have also been discovered. Of these, the 530-residue Ric-8A protein has been identified as both a GEF and a folding chaperone for the i, q, and 12/13 classes of Gα2. Here we present the X-ray crystallographic and cryo-EM structures of the complex of Ric-8A (residues 1-491) bound Gαi1 stabilized by three camelid nanobodies at 3.5-4.5Å resolution. The N-terminal 430 residues of Ric-8A adopt a mixed Armadillo/HEAT repeat fold and the disordered segment that follows includes two highly conserved serine and threonine residues that, when phosphorylated, stimulate the GEF activity of Ric-8A3. Ric-8A interacts with the Ras-like domain of Gαi1 at two major interfaces: with the two beta strands in the C-terminal half of the Ras domain opposite to the nucleotide binding site, and through extensive contact surface with the C-terminal alpha helix. The latter interaction is analogous to, but structurally different from, that observed in G protein complexes with with G protein-coupled receptors (GPCRs). The former has no parallel in G-protein:GPCR interactions. Together, the contacts between Ric-8A and Gα induce allosteric changes that result in the expulsion of GDP from the nucleotide binding site.