

Signal transduction at the single-molecule level

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Transmembrane receptor proteins regulate basic cellular processes by transducing extracellular signals across the plasma membrane. In mammalian cells, the epidermal growth factor receptor (EGFR) controls healthy cell proliferation and differentiation as well as disorders such as cancer. While the structures of the extracellular and intracellular domains of EGFR have been individually resolved, the transmembrane structural signaling responsible for their connection has remained elusive. To identify this connection, we isolate the full-length receptor in membrane nanodiscs and probe the ligand-induced conformational response with single-molecule Förster energy transfer (smFRET). We discover a lipid and ligand dependent transmembrane conformational coupling between the extracellular and intracellular domains. The conformational coupling was blocked by mutations and therapeutics that lower phosphorylation levels in cells, suggesting that the conformational coupling actively mediates signaling. 47% of membrane proteins, including EGFR, contain a single transmembrane α -helix. How, or even whether, a single α -helix propagates regulatory signals was undetermined. These observations provide the first evidence, to our knowledge, of signal transduction via a single α -helix, introducing a minimal system for transmembrane communication. The observed transmembrane conformational coupling could be a feature common to many single-pass membrane proteins.