

Conformational Activation in the Human Epidermal Growth Factor Receptor

The epidermal growth factor receptor (EGFR), and its three homologues (ErbB2, ErbB3, ErbB4) represent a family of human receptor tyrosine kinases¹. EGFR family members receive extracellular signals in the form of growth factors and process those signals, via autophosphorylation, by recruiting adapter proteins that transmit signals including cell survival, apoptosis, tissue specialization and cell migration. Dysregulation of this pathway can lead to tumor formation and other human diseases². Two groups of EGFR inhibitors are currently approved for cancer treatment, monoclonal antibodies and tyrosine kinase inhibitors, however both can be rendered ineffective by resistance mutations³. Because of EGFR's significance in human biology and potential in drug design, it is critical to reveal the mechanism for EGFR activation.

Activation of EGFR has long been attributed to intermolecular interactions. Cross-linked EGFR antibodies were observed to stimulate activity⁴. Structural prediction studies describe the formation of three possible dimer interactions. Of those, the asymmetric model is most interesting because it allows the EGFR family member ErbB3, which has a highly distorted N terminal region, to participate in a heterodimer interaction with other family members⁵. From these investigations, it is probable that **formation of an asymmetric dimer is necessary for EGFR activation**.

In order to investigate this hypothesis, a combination of structural and biological evidence is necessary. It is important to confirm the dimerization interaction and then to solve a crystal structure of the EGFR dimer. For the determined dimer, mutational analysis will support biological relevance. To further investigate biological relevance, the determined structure must be compatible with a model for communication of the extracellular domain with the kinase domain through the transmembrane domain.

Isolated kinase domains were found to have activity in correlation with local concentration, confirming an intermolecular interaction⁶. Further, the crystal structure of EGFR was determined to include both an asymmetric and symmetric dimer. Mutational evidence supports a biological role for the asymmetric dimer in which the C terminal region of one monomer interacts with the N-terminal region of the other to impart activation⁶. To determine how the kinase domain functions as a part of the entire receptor, structural and mutational evidence have been combined to build a model in which the juxtamembrane domain of each kinase interacts with the other, with a pair of antiparallel helices closest to the transmembrane domain⁷. This model is consistent with the structure of the isolated transmembrane domain; in the active form the transmembrane domains of two kinases form a parallel α -helical bundle⁸. Also, this model provides a mechanism in which MIG6, a known protein inhibitor of EGFR, competes with the juxtamembrane domain to prevent EGFR activation⁹.

Taken together, current research supports a model of EGFR activation in which ligand binding in the extracellular domain can induce conformational change resulting in activation through asymmetric dimerization of kinase domains. This model describes a complete activation mechanism for EGFR and provides information that will be crucial to designing novel EGFR family therapeutics.

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