(초청강연)

Structure of the Extracellular Region of HER2 Both Alone and Complexed with the Herceptin Fab

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HER2 (Neu, erbB2) is a member of the epidermal growth factor receptor (EGFR or erbB) family of receptor tyrosine kinases, which in humans includes HER1 (EGFR, erbB1), HER2, HER3 (erbB3), and HER4 (erbB4). ErbB receptors are essential mediators of cell proliferation and differentiation in both the developing embryo and adult, and their inappropriate activation is associated with the development and severity of many cancers. In particular, overexpression of HER2 is found in 20-30% of human breast cancers and correlates with more aggressive tumors and a poorer prognosis. Anticancer therapies targeting erbB receptors have shown promise, and a monoclonal antibody against HER2, Trastuzumab (Herceptin), is currently used to treat breast cancer. We report here crystal structures of the entire extracellular regions of rat HER2 at 2.4 Å and human HER2 complexed with the Herceptin Fab fragment at 2.5 Å. These structures reveal a fixed conformation for HER2 that resembles a ligand-activated state and show HER2 poised to interact with other erbB receptors in the absence of direct ligand binding. Herceptin binds to the juxtamembrane region of HER2, identifying this site as a target for anticancer therapies.