Predominance of activated EGFR higher-order oligomers on the cell surface

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The Epidermal Growth Factor Receptor (EGFR) kinase is generally considered to be activated by either ligand-induced dimerisation or a ligand-induced conformational change within pre-formed dimers. We report the relationship between ligand-induced higher-order EGFR oligomerization and EGFR phosphorylation on the surface of intact cells. We have combined lifetime-detected Förster resonance energy transfer (FRET-FLIM), as a probe of the receptor phosphorylation state and Image Correlation Spectroscopy (ICS), to extract the relative association state of activated versus unactivated EGFR. There are at least 4-times as many receptors in the ligand-induced active clusters than inactive clusters. Contrary to the prevailing view that the EGFR dimer is the predominant, active form, our data determine that higher-order EGFR oligomers are the dominant species associated with the ligand activated EGFR tyrosine kinase.

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