Structure-function relationships and supra-molecular organisation of the Epidermal Growth Factor Receptor (EGFR) on the cell surface

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The human epidermal growth factor receptor (HER1/EGFR) is the founding member of the HER family (HER1-4) of receptor tyrosine kinases, which are initiators of signals for cell proliferation, differentiation, survival, and transformation. These receptors have an extracellular growth factor-binding domain (ECD), a single-pass transmembrane region, and an intracellular domain (ICD), that in HER1, HER2 and HER4 has tyrosine kinase activity. HER1 activation is triggered by the binding of epidermal growth factor (EGF) and involves the formation of back-to-back receptor dimers. HER1 activation may also be mediated by ECD/ICD conformational changes and by clustering within plasma membrane domains, both of which remain poorly understood. This is largely attributable to the lack of methods with sufficient resolution to report in cells changes in receptor structure and/or distinguish HER dimers from HER confinement within lipid rafts and/or membrane skeleton fences.

We used fluorescence lifetime imaging, resonance energy transfer, single molecule nanoscale localisation, and super-resolution microscopy to investigate the conformation and supra-molecular organisation of wild-type HER1 and a range of HER1 mutants permanently expressed in mammalian cells. By using antagonist and agonist ligands to label the ECD in conjunction with fluorescence tyrosine kinase inhibitors to label the ICD, we have determined EGFR conformational changes and interactions that regulate EGFR signal transduction across the plasma membrane. The data are beginning to reveal the molecular details of the complex mechanisms regulating the onset of HER1 signalling.