Quantitative Study of Heterogeneity in Membrane Protein Interaction in Cancer Cells using Liquid-Phase Electron Microscopy

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We developed a new method for the parallel detection of single molecules of two membrane proteins from the same family of the human epidermal growth factor receptors (EGFR also named HER1), and its protein family member, HER2. In several types of cancer, such as breast cancer, these receptors are overexpressed, and thereby trigger uncontrolled cell growth and cancer cell spreading through homo- and heterodimerization. We here demonstrate how the dimerization of both receptors can be studied at the single-molecule, subcellular, and single-cell level, and up to surface densities of >2.000 receptors/μm^2 [1]. Applying labels consisting of small, specific binding proteins, and two types of quantum dots, a total of 41 breast cancer cells were studied, yielding data of >200.000 of receptor positions. Statistical analysis with the pair correlation function *g(r)* disclosed significant differences in the dimerization behavior of both receptors, depending on the dynamics of the local environment of the plasma membrane. In addition, different receptor interaction profiles were found in small cellular subpopulations [2]. These new possibilities of quantitative analysis of receptor interactions offer a deeper understanding of cancer cell heterogeneity, which is a major cause for drug resistance and disease progression. In addition, by using other binding proteins this method can be tailored to study the interaction of other membrane proteins as well.

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