Studying growth factor receptor proteins in whole cells in liquid using scanning transmission electron microscopy

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Correlative Liquid scanning transmission electron microscopy (STEM) and fluorescence microscopy were used to study the epidermal growth factor receptor HER2 [1] within the intact plasma membrane of whole SKBR3 breast cancer cells in their native liquid environment. The obtained spatial resolution of 3 nm was sufficient to resolve the constituents of individual protein complexes. Contrast was obtained on specific protein labels consisting of fluorescent nanoparticles, so-called quantum dots (QDs) [2]. On account of the atomic number (Z) contrast of the annular dark field detector of STEM, these nanoparticles of high-Z material were detected within the background signal produced by the low-Z material of the cell and surrounding liquid. The particular distribution of monomers, and homodimers (a protein complex consisting of a pair of HER2 proteins) of these receptors is of relevance for understanding cell growth triggering in cancer cells. Data was obtained from several tens of intact cells thus achieving statistics of thousands of protein positions with nanometer resolution. The signaling-active dimerized form of HER2 dimerization was localized in certain functional membrane regions exhibiting membrane ruffles. Larger-order clusters were also present. Membrane areas with homogeneous membrane topography, on the contrary, displayed HER2 in random distribution.

[1] D.B. Peckys, U. Korf, N. de Jonge, Science Advances 1:e1500165 (2015).
[2] D.B. Peckys, N. de Jonge, N., JoVE, e53186 (2015).