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Heterodimerization of wild-type and mutant fibroblast growth factor receptors in cell-derived vesicles. KALINA HRISTOVA, NUALA DEL PICCOLO, SARVENAZ SARABIPOUR, Johns Hopkins University — The activity of receptor tyrosine kinases (RTKs) is controlled through their lateral dimerization in the plasma membrane. RTKs are believed to form both homodimers and heterodimers, and the different dimers are believed to play unique roles in cell signaling. However, RTK heterodimers remain poorly characterized, as compared to homodimers, due to limitations in current experimental methods. Here, we develop a Förster Resonance Energy Transfer (FRET)-based methodology to assess the thermodynamics of hetero-interactions in the plasma membrane. To demonstrate the utility of the methodology, we use it to study the hetero-interactions between three Fibroblast Growth Factor Receptors – FGFR1, FGFR2, and FGFR3 – in the absence of ligand. Our results show that all possible FGFR heterodimers form, suggesting that the biological roles of FGFR heterodimers may be as significant as the homodimer roles. We further investigate the effect of two pathogenic point mutations in FGFR3 (A391E and G380R) on heterodimerization. We show that each of these mutations stabilize most of the heterodimers, with the largest effects observed for FGFR3 wild-type/mutant heterodimers. We thus demonstrate that the methodology presented here can yield new knowledge about RTK interactions and can further our understanding of signal transduction across the plasma membrane..

Kalina Hristova
Johns Hopkins University

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