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Biophysical Properties of Erbb2 Mutants Positively Selected in the Male Germline

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ErbB2, a critical member of the epidermal growth factor receptor (EGFR) family, plays a role in the facilitation of signaling by heterodimerization. Specific ErbB2 mutations (R143Q, R678Q, V842I) are identified as being positively selected in tumors and are suggested to confer a survival or proliferative benefit. We investigated the biophysical and signaling characteristics of these mutants to ascertain their functional importance. With FRET and FRAP, we determined their dimerization and lateral mobility in CHO cells, and tyrosine phosphorylation assays provided insight into their signaling activity. Our results demonstrate that gain-of-function ErbB2 mutants exhibit increased baseline heterodimerization with EGFR, which surprisingly leads to an attenuated EGF-induced heterodimerization response. Even with this dimerization that is growth factor-dependent and compromised, the EGF stimulation result in phosphorylation of the receptor and diffusion retardation, suggesting that these variants retain signaling competence. These findings suggest that the selected ErbB2 variants exist as preformed non-fully functional heterodimers with EGFR, which upon EGF stimulation convert into fully active signaling dimers. This mechanistic interpretation provides an explanation for the selective advantage in tissues, linking their altered biophysical features to enhanced proliferative ability.