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Receptor tyrosine kinase signalling in the absence of kinase activity and cancer of non-genetic origin

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Cancer cells which express FGFR2 and have low concentrations of the adaptor protein Grb2 show high prevalence for metastatic outcome. In non-stimulated cells the SH3 domain (and not the SH2 domain(s)) of Plcγ1 directly competes for a proline-rich binding site at the very C-terminus of FGFR2 with the C-terminal SH3 domain of Grb2. Reduction of Grb2 concentration permits access of Plcγ1 to the receptor. Recruitment of Plcγ1 in this way is sufficient to up-regulate phospholipase activity. This results in increased cell motility and promotion of cell invasive behavior in the absence of extracellular receptor stimulation. Therefore metastatic outcome can be dictated by the constitutive competition between Grb2 and Plcγ1 for the phosphorylation-independent binding site on FGFR2. Since the majority of receptor tyrosine kinases have proline-rich sequences in their C-termini, the possibility of a second tier of signal transduction in the absence of growth factor stimulation, or kinase-activating mutations emerges – leading to cancer of non-genetic origin.