Epigen, the last ligand of ErbB receptors, reveals intricate relationships between affinity and mitogenicity

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Abstract:

Four ErbB receptors and multiple growth factors sharing an epidermal growth factor (EGF) motif underlie transmembrane signaling by the ErbB family in development and cancer. Unlike other ErbB proteins, ErbB-2 binds no known EGF-like ligand. To address the existence of a direct ligand for ErbB-2, we applied algorithms based on genomic and cDNA structures to search sequence data bases. These searches reidentified all known EGF-like growth factors including Epigen (EPG), the least characterized ligand, but failed to identify novel factors. The precursor of EPG is a widely expressed transmembrane glycoprotein that undergoes cleavage at two sites to release a soluble EGF-like domain. A recombinant EPG cannot stimulate cells singly expressing ErbB-2, but it acts as a mitogen for cells expressing ErbB-1 and co-expressing ErbB-2 in combination with the other ErbBs. Interestingly, soluble EPG is more mitogenic than EGF, although its binding affinity is 100-fold lower. Our results attribute the anomalous mitogenic power of EPG to evasion of receptor-mediated depletion of ligand molecules, as well as to inefficient receptor ubiquitylation and down-regulation. In conclusion, EPG might represent the last EGF-like growth factor and define a category of low affinity ligands, whose bioactivity differs from the more extensively studied high affinity ligands.

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