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# Combinatorial signal transduction by ErbB tyr kinases: generation of diversity and its opportunistic exploitation in oncogenesis

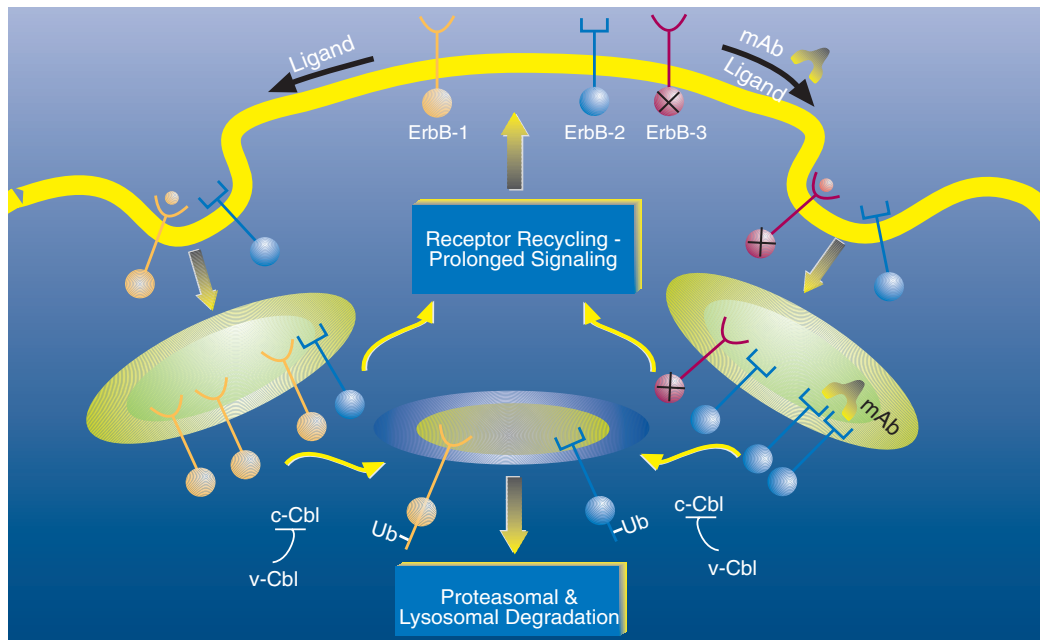
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An epidermal growth factor (EGF) motif is shared by a few dozen neuregulin growth factors, whose signals are transmitted to cells by a group of transmembrane tyrosine kinases of the ErbB family. Uniquely, the evolutionary path of the ErbB signaling module over the last billion years is well characterized: Whereas in worms only a single receptor and one ligand exist, in mammals the module is expanded to include four receptors and multiple families of ligands. Two aspects of the module have attracted our attention as they could not be explained in terms of the accepted linear structure of signaling cascades: First, ErbB-2 binds no known ligand, and second, ErbB-3 is devoid of catalytic activity. In addition, by capturing specific components, several oncogenic agents exploit the ErbB signaling module to transform normal cells. Thus, autocrine loops, mutated receptor versions, and activated forms of the effectors, were identified in spontaneous or virally promoted cancers.

Most relevant to human cancer, however, is the frequent amplification of the *erbB-2* gene, which was identified as a predictor of poor prognosis and resistance to chemotherapy.

Over the last four years we studied the mechanisms underlying oncogenesis by ErbB proteins and the potential of immunotherapy (together with the group of Michael Sela of the Department of Immunology). As an alternative to the prevailing linear view, we presented the concept that signaling by ErbB proteins may be considered in terms of a network, whose function has been perfected throughout evolution. Accordingly, the network is comprised of three layers (ligands, 10 dimeric receptors and multiple downstream effectors), and has a large potential of signal diversification by means of combinatorial interactions. In terms of a signaling network, ErbB-2 acts as a shared low affinity subunit of the three other receptors, which amplifies all growth factor



**Fig. 1.** The alternative routes of ligand- and antibody-induced endocytosis of ErbB homo- and heterodimers are schematically depicted. Note that homodimers of ErbB-1 and ErbB-2 are destined to proteasomal and lysosomal degradation through the action of c-Cbl. On the other hand, heterodimers are targeted to recycling and therefore their signaling is prolonged and more potent

signals by prolonging their action. Most potent is the combination of ErbB-2, the ligand-less receptor, with ErbB-3, the kinase-defective receptor. Another unexplained observation was the more potent signaling of heterodimeric receptors, relative to the corresponding homodimers. We attributed the mechanism to the process of ligand-induced endocytosis of activated ErbBs and differential recruitment of an effector, c-Cbl, which we identified as a ubiquitin ligase (see Fig.).

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