

THE ERBB FAMILY OF RECEPTOR TYROSINE KINASES AND TUMOR CELL BIOLOGY

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There are four ErbB receptor family members, ErbB1/EGF receptor, ErbB2, ErbB3 and ErbB4. Under normal physiological conditions, activation of ErbB receptors is controlled by spatial and temporal expression of their ligands, EGF-related peptides. Ligand binding induces the formation of multiple combinations of ErbB receptor homo- and heterodimers, resulting in activation of the cytoplasmic kinase domain. This in turn promotes phosphorylation of specific tyrosine residues, leading to stimulation of multiple signal transduction pathways. ErbB2 is ligand-less; it functions as a co-receptor and is actually the preferred partner for the other ligand-bound ErbB family members (1).

ErbB receptors are important not only because they have essential roles in normal physiological processes occurring during development, but also because of their involvement in numerous types of human tumors. Cancer patients whose tumors have alterations in ErbB1 or ErbB2, tend to have a more aggressive disease, associated with parameters predicting a poor clinical outcome. The receptors have been implicated in the pathology of a broad spectrum of carcinomas, including breast, ovarian, gastric, non-small cell lung carcinoma and bladder. ErbB1 is activated by various mechanisms including gene amplification, autocrine activation and mutations in its extracellular domain or kinase domain. Gene amplification leading to ErbB2 overexpression, which has been proposed to cause spontaneous dimerization and activation in the absence of ligand, is the most common mechanism of ErbB2 activation. Based upon these clinical findings, ErbB receptors have become appealing therapeutic targets. Over the past years, several approaches, including targeting

with antagonistic antibodies or small-molecule tyrosine kinase inhibitors, have been developed (2).

Cancer development is a multistep process starting from a local benign hyperplasia and ending with an invasive tumor able to metastasize to distant organs. During this process cancer cells acquire new properties, which are necessary for the full malignant phenotype. ErbB receptors and their ligands have been shown to play roles in each of these processes. For example, cancer cells must acquire proliferative potential and divide continuously. In order to accomplish this the cells must circumvent contact inhibition and natural checkpoints, which normally would induce apoptosis. The significance of constitutive ErbB receptor activation in driving cancer cells through the cell cycle is evident from results showing that interfering with receptor signaling, either with antagonistic antibodies or with kinase inhibitors, leads to a proliferative block. Furthermore, a main effector of ErbB signaling, the PI-3K/PKB pathway, is particularly important in mediating cell survival since several PKB substrates directly control various apoptotic processes (1).

For growth beyond a certain size, the primary tumor must ameliorate its supply of nutrients and oxygen through new vessel formation or angiogenesis. During the course of tumor-induced neoangiogenesis, endothelial cells (ECs) proliferate and undergo differentiation; the ErbB receptor/ligand network influences these processes. On one hand, ECs express ErbBs; on the other hand, ErbBs have been implicated in the tumor cell production of proangiogenic factors, the most potent being vascular endothelial growth factor (VEGF). It will be important to understand the role of the ErbB receptor/ligand network in the EC/ tumor cell interaction in order to plan therapeutic strategies to block tumor proliferation, survival and neovascularization.

The final steps in the metastatic process involve tumor cells leaving the site of primary growth, which requires that the cells gain several new features including the ability to migrate, invade through their basement membrane and invade and grow at distant sites. The role of ErbB receptors in these processes is only beginning to emerge; nevertheless, it is worth mentioning a few specific findings. Many types of tumor cells migrate due to autocrine receptor activation

or in response to *in vitro* treatment with EGF-related ligands. ErbB2 appears to have a special role, as its functional inactivation blocks ligand-induced breast cancer cell migration. Since ErbB2-containing heterodimers promote strong activation of the MAPK and PI3K pathways, known to have important roles in migration, cells lacking ErbB2 might fail to migrate simply because these pathways are weakly stimulated. However, work from our laboratory has revealed that in addition to activation of these pathways, a novel downstream target of ErbB2, named Memo, has an essential role in the migration process (3).

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