Ligand Discrimination in Signaling through an ErbB4 Receptor Homodimer*

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The epidermal growth factor (EGF)-like family of growth factors elicits cellular responses by stimulating the dimerization, autophosphorylation, and tyrosine kinase activities of the ErbB family of receptor tyrosine kinases. Although several different EGF-like ligands are capable of binding to a single ErbB family member, it is generally thought that the biological and biochemical responses of a single receptor dimer to different ligands are indistinguishable. To test whether an ErbB receptor dimer is capable of discriminating among ligands we have examined the effect of four EGF-like growth factors on signaling through the ErbB4 receptor homodimer in CEM/HER4 cells, a transfected human T cell line ectopically expressing ErbB4 in an ErbB-null background. Despite stimulating similar levels of gross receptor tyrosine phosphorylation, the EGF-like growth factors betacellulin, neuregulin-1β, neuregulin-2β, and neuregulin-3 exhibited different biological potencies in a cellular growth assay. Moreover, the different ligands induced different patterns of recruitment of intracellular signaling proteins to the activated receptor and induced differential usage of intracellular kinase signaling cascades. Finally, two-dimensional phosphopeptide mapping of ligand-stimulated ErbB4 revealed that the different growth factors induce different patterns of receptor tyrosine phosphorylation. These results indicate that ErbB4 activation by growth factors is not generic and suggest that individual ErbB receptors can discriminate between different EGF-like ligands within the context of a single receptor dimer. More generally, our observations significantly modify our understanding of signaling through receptor tyrosine kinases and point to a number of possible models for ligand-mediated signal diversification.

The accurate interpretation of growth factor-encoded signals by cell surface receptor tyrosine kinases (RTKs)† is critical to the cellular growth regulatory processes that underlie tissue development. The mammalian ErbB signaling network, consisting of four known receptor tyrosine kinases and more than ten epidermal growth factor (EGF)-like growth factor ligands, serves as a model for understanding how RTKs translate ligand binding into cellular response (1). Numerous studies point to a role for receptor dimerization in the stimulation of receptor tyrosine kinase activity by growth factors (2). Moreover, because the ten different ErbB receptor homo- and heterodimeric pairs are capable of mediating different cellular responses, dimerization also appears to be involved in signal specification (3, 4). Specification is thought to arise from differences in the intrinsic abilities of each of the different tyrosine phosphorylated ErbB receptors to recruit and activate specific src homology-2 (SH2) and phosphotyrosine binding (PTB) domain-containing intracellular signaling proteins (4, 5).

The ErbB signaling network model emphasizes that it is the identity of the receptor dimer that dictates the ultimate cellular response and makes no provisions for a single receptor dimer to discriminate among ligands. In this study we examine the effects of several different ligands on cellular growth signaling in a cell line expressing a single member of the ErbB family. We observed that different ligands are capable of inducing different biological and biochemical responses, indicating that an ErbB receptor homodimer is capable of discriminating among its binding ligands.

EXPERIMENTAL PROCEDURES

Materials—CEM/HER4 cells were from Bristol-Myers Squibb Co., Seattle, WA. Recombinant human betacellulin was purchased from R & D Systems. GST fusion proteins of the EGF-like domains of mouse NRG1β and NRG2β were produced, purified, and handled as described previously (6, 7). GST-NRG-3 was produced by first amplifying the region corresponding to the EGF-like domain from a full-length NRG-3 cDNA clone obtained by screening a mouse C57Bl/6 IZAP cDNA library.‡ The region selected includes the 10 amino acids amino-terminal to the first cysteine residue of the NRG-3 EGF-like domain (primer sequence corresponds to the amino acid sequence STERSEHF) and ends with the sequence ESEDVQR, which immediately precedes the predicted transmembrane domain. The resulting fragment was subcloned into the EcoRI/BamHI sites of pAcSecGST (PharMingen). Subsequent steps were identical to those used in the preparation of GST-NRG-1β and GST-NRG-2β, as described previously (6).

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† The abbreviations used are: RTK(s), receptor tyrosine kinases(s); EGF, epidermal growth factor; SH2, src homology-2; PTB, phosphotyrosine binding; FBS, heat-inactivated fetal bovine serum; PAGE, polyacrylamide gel electrophoresis; BTC, betacellulin; NRG, neuregulin; the cellular growth regulatory processes that underlie tissue development. The mammalian ErbB signaling network, consisting of four known receptor tyrosine kinases and more than ten epidermal growth factor (EGF)-like growth factor ligands, serves as a model for understanding how RTKs translate ligand binding into cellular response (1). Numerous studies point to a role for receptor dimerization in the stimulation of receptor tyrosine kinase activity by growth factors (2). Moreover, because the ten different ErbB receptor homo- and heterodimeric pairs are capable of mediating different cellular responses, dimerization also appears to be involved in signal specification (3, 4). Specification is thought to arise from differences in the intrinsic abilities of each of the different tyrosine phosphorylated ErbB receptors to recruit and activate specific src homology-2 (SH2) and phosphotyrosine binding (PTB) domain-containing intracellular signaling proteins (4, 5).

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MTT, thiazolyl blue; GST, glutathione S-transferase; JNK, c-Jun NH₂-terminal kinase; ERK, extracellular signal-regulated kinase; TPCK, t-1-tosylamido-2-phenylethyl chloromethyl ketone; EPO, erythropoietin.

‡ C. Lai, unpublished observation.
Anti-ErbB4 antibodies Ab-1 and Ab-2 were from NeoMarkers; RC20, anti-SHP1, and anti-Shc polyclonal antibodies were from Transduction Laboratories; anti-SHP2, anti-Shc monoclonal, anti-Grb2 polyclonal, and immobilized anti-phosphotyrosines PY20 and PY99 antibodies were from Santa Cruz Biotechnologies. Production, characterization, and use of rabbit anti-p85 has been described previously (8). Antibodies to phosphorylated and non-phosphorylated forms of p38, JNK, ERK1/2, and Akt were from New England Biolabs. MTT, soybean trypsin inhibitor immobilized on Sepharose, and TPKC-treated trypsin were from Sigma.

**RESULTS AND DISCUSSION**

To test whether a single ErbB receptor dimer is capable of distinguishing between different EGF-like growth factors, we examined the response of ErbB4 in CEM/HER4 cells to treatment with different ligands. CEM/HER4 is a human T cell line lacking endogenous ErbB receptor expression, as assessed by reverse transcriptase polymerase chain reaction, that has been stably transfected with the cDNA encoding human ErbB4 (10). In the absence of other ErbB family members the only signaling receptor species in these cells is an ErbB4 homodimer. We assessed the biological and biochemical outcomes of treating these cells with the following four EGF-like ligands known to bind to and stimulate ErbB4: betacellulin (BTC), neuregulin-1β (NRG1β), neuregulin-2β (NRG2β), and neuregulin-3 (NRG3). All experiments were carried out using saturating levels of purified growth factors (50 nM) to overcome any differences in receptor binding affinity and to fully activate the ErbB4 receptor.

We observed that the four growth factors examined stimulated similar levels of ErbB4 receptor tyrosine phosphorylation, as determined by immunoblotting anti-ErbB4 immunoprecipitates with anti-phosphotyrosine antibodies (Fig. 1A). No ErbB4 tyrosine phosphorylation was observed prior to growth factor treatment. Re-probing with an anti-ErbB4 antibody revealed similar levels of receptor in all five precipitates. In addition, covalent cross-linking experiments revealed that each growth factor induced similar levels of ErbB4 dimer (not shown).

Despite their abilities to induce similar levels of gross receptor tyrosine phosphorylation, the four growth factors exhibited different biological potencies in the MTT colorimetric assay (Fig. 1B). Because the MTT assay measures mitochondrial activity, differences relative to untreated cells reflect both cell growth induced by growth factors and cell survival following serum starvation. Although none of the growth factors stimulated a response as robust as serum, probably because of the relatively low ErbB4 receptor content of the CEM/HER4 cells,
NRG1β reproducibly exhibited a higher activity in the MTT assay than did the other factors. NRG1β was followed by BTC, NRG2β, and then NRG3. These observations indicate that gross receptor tyrosine phosphorylation as detected by anti-phosphotyrosine blotting does not closely correlate with biological activity, and suggest that an ErbB4 homodimer is capable of discriminating between its binding ligands in mediating biological activity.

To address the biochemical mechanisms underlying the observed differences in biological potencies of the activating ligands we first examined the activation of intracellular kinase cascades associated with receptor stimulation. By immunoblotting with antibodies specific for activated (phosphorylated) forms of the indicated kinases (upper panels) and then re-probed with antibodies recognizing total protein (middle panels). Bands were quantified and normalized (lower panels) by dividing the signal intensity obtained with the phospho-specific antibody by that obtained with the total protein antibody. Shown are the results at the times of peak kinase activation; 5 min for Akt and 10 min for ERK1/2. Results are representative of at least two independent experiments.

**Results**

**A**. Stimulation of signaling kinases. Cells were treated with 50 nM growth factor, and lysates were blotted with antibodies recognizing phosphorylated forms of the indicated kinases (upper panels) and then re-probed with antibodies recognizing total protein (middle panels). Results are representative of at least three independent experiments.

Intracellular kinase cascades are triggered in response to the binding of specific SH2 and PTB domain-containing proteins to specific phosphorylated tyrosine residues in tail regions of activated ErbB receptors (4, 5). To determine whether the differential recruitment of signaling proteins might account for the observed differences in signaling kinase activation we examined the association of five representative signaling molecules with ErbB4 in response to growth factor treatment. The signaling proteins examined were the adapter proteins Grb2 and Shc, the tyrosine phosphatases SHP1 and SHP2, and the p85 subunit of phosphatidylinositol 3-kinase. In these experiments cells were treated with growth factors, signaling proteins were immunoprecipitated with their respective antibodies, and the receptor region of the gel was probed with anti-phosphotyrosine antibodies. Because the different ligands stimulated similar extents of total receptor tyrosine phosphorylation (Fig. 2) and Akt and ERK1/2 appeared to be the most potent in stimulating Akt, whereas BTC appeared to be the most potent in stimulating ERK1/2. Differences were due to the overall extent of kinase activation in response to the growth factors rather than to differences in the kinetics of activation (data not shown).

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No evidence for ligand-stimulated association of either of the phosphotyrosine phosphatases with ErbB4 was observed (not shown). However, whereas all four growth factors stimulated the recruitment of Grb2 to ErbB4 to similar extents, BTC and NRG1β preferentially stimulated the recruitment of Shc, and NRG1β and NRG2β preferentially stimulated the association of p85 (Fig. 2B). Taken together, the results of Fig. 2 indicate that ligand discrimination by the ErbB4 receptor results in the differential stimulation of intracellular signaling cascades, possibly through the differential recruitment of intracellular SH2 and PTB domain-containing signaling proteins.

Signaling proteins are thought to become recruited to phosphorylated tyrosine residues of activated receptor tyrosine kinases in a sequence-specific manner (11, 12). For example, the SH2 domain of p85 binds to sites containing a methionine three residues carboxyl-terminal to the phosphorylated tyrosine, whereas the SH2 domain of Grb2 selects sites that have an asparagine two residues carboxyl-terminal to the phosphorylated residue. The PTB domain of Shc selects motifs containing the sequence NPXY, where X is any amino acid and Y is the phosphorylated tyrosine residue.

The selectivity patterns of SH2 and PTB domains suggest that the observed differential recruitment of intracellular signaling proteins may result from the differential phosphorylation of specific ErbB4 tyrosine residues in response to growth factor binding. To test this possibility we metabolically labeled CEM/HER4 cells with [32P]-orthophosphate and examined ErbB4 phosphorylation by two-dimensional tryptic phosphopeptide mapping. Our current (not shown) and previous studies4 indicate that ErbB receptors are very highly constitutively phosphorylated on numerous serine and threonine residues. This yields very complicated phosphopeptide maps that can mask ligand-stimulated differences in receptor tyrosine phosphorylation. For this reason we developed a method for enriching in the phosphotyrosine-containing tryptic peptides by affinity for two anti-phosphotyrosine antibodies prior to mapping (see “Experimental Procedures”).

We observed that the different ligands induced different tyrosine-containing phosphopeptide patterns in ErbB4 (Fig. 3). No phosphopeptides were observed after anti-phosphotyrosine purification when cells were not treated with growth factor. This is consistent with our observation that ErbB4 is not constitutively tyrosine phosphorylated (Fig. 1A) and highlights the utility of the anti-phosphotyrosine peptide purification method.

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NRG1 orthophosphate and treated with 50 nM of the indicated growth factor for 2 min at 37 °C. ErbB4 was immunoprecipitated, purified by SDS-PAGE, and trypsinized. Tyrosine-containing tryptic peptides were recovered with anti-phosphotyrosine and analyzed by two-dimensional phosphopeptide mapping. The far left panel depicts the observed peptides. Results are representative of two independent experiments.

Our previous and unpublished results suggest that ligand-induced differential ErbB receptor phosphorylation is not unique to ErbB4. Using human mammary tumor cells that express different ErbB receptors, we have obtained evidence that EGF and BTC induce the differential phosphorylation of ErbB receptor homodimers and that NRG1

\[ \text{NRG1} \]

induced differential ErbB receptor phosphorylation is not generic; several states of an activated receptor signaling is not reflected in different potencies of growth factor-stimulated cellular growth properties. However, in the normal context of fetal cardiac myocytes or mammary epithelial cells, differential ligand stimulation of ErbB4 could influence diverse cellular activities such as survival, differentiation, or fate (13, 14).

Our observations suggest that the different EGF-like ligands are capable of influencing phosphorylation site usage in the ErbB4 homodimer, thereby dictating which intracellular signaling proteins become efficiently recruited and activated, and hence determining which kinase signaling cascades are efficiently triggered. In the heterologous context of the transfected T cell ligand discrimination is reflected in different potencies of growth factor-stimulated cellular growth properties. However, in the normal context of fetal cardiac myocytes or mammary epithelial cells, differential ligand stimulation of ErbB4 could influence diverse cellular activities such as survival, differentiation, or fate (13, 14).

Our previous and unpublished results suggest that ligand-induced differential ErbB receptor phosphorylation is not unique to ErbB4. Using human mammary tumor cells that express different ErbB receptors, we have obtained evidence that EGF and BTC induce the differential phosphorylation of ErbB receptor homodimers and that NRG1 and NRG2 induce the differential phosphorylation of ErbB receptor homodimers. Taken together, our observations suggest that the stimulation of ErbB receptor signaling is not generic; several states of an activated receptor complex may exist depending on the identity of the growth factor bound to the dimeric receptor complex. Different activation (phosphorylation) states could then influence the usage of intracellular signaling pathways, which in turn could dictate cellular response (Fig. 4A).

The physical mechanism by which ligands differentially influence ErbB receptor tyrosine phosphorylation remains a very interesting question. It has been previously suggested that tyrosine phosphorylation site usage within ErbB2 may be dictated by its dimerizing ErbB receptor partner (15). Hence, differences in the intrinsic abilities of different ligands to induce different receptor heterodimers could result in differential receptor phosphorylation and signaling. However, because the CEM/HER4 cells lack other ErbB receptors and an ErbB4 homodimer is the only signaling entity, differential receptor heterodimerization cannot account for the observed differential signaling. A number of studies have ascribed differences in the biological activities of EGF-like ligands to differences in the stability of the ligand-receptor complex during internalization and routing (16–18). In our studies we examined ErbB4 phosphorylation at 2 min, and we have observed differential phosphorylation of ErbB2 30 s after ligand treatment. Because differential phosphorylation appears to precede significant receptor internalization, receptor-ligand complex stability is also an unlikely explanation.

Fig. 4B illustrates three possible mechanisms for differential signaling through a single ErbB receptor dimer. One possibility (depicted by ligand 2) is that growth factors differentially promote the association of the active receptor complex with other cellular components that in turn modulate the receptor phosphorylation state. Candidates for such components are other kinases, phosphatases, or scaffolding proteins involved in the assembly of signaling complexes (19). Interestingly, our recent work has uncovered evidence for a class of cell surface proteins called modulators that directly interact with ErbB receptors to...
regulate their response to EGF-like ligands. The kekkon-1 protein from Drosophila melanogaster appears to interact directly with Drosophila EGF receptor to suppress its activity (20), whereas the membrane-bound ASGP2 component of the rat mucin MUC4 interacts directly with ErbB2 to potentiate its response to NRG1β (21). These or other cell surface modulator components may also affect autophosphorylation site usage in activated ErbB receptors.

Alternatively, ligand discrimination may be a property intrinsic to ErbB receptors, so that other cellular components are not required to mediate differential phosphorylation and signaling. One possibility, depicted by ligand 3 in Fig. 4B, is that the different ligands might induce different oligomeric states of the receptor, which in turn influences phosphorylation site selection. Biochemical (22) and molecular modeling (23) studies have pointed to a potential role for higher order oligomers of ErbB receptors in signaling. It has also been reported that differential oligomerization of the ephrins induces differential signaling through the eph family growth factor RTKs (24). Finally, the tyrosine kinase domain of the fibroblast growth factor receptor crystallized as a dimer with the catalytic sites oriented away from each other (25). Because intermolecular cross-phosphorylation of the kinase domain subunits in this conformation would be difficult, it has been speculated that higher-order aggregates may be involved in RTK tyrosine phosphorylation.

Another very intriguing hypothesis is that the different ligands could induce different conformations within the context of a receptor dimer (ligand 4 in Fig. 4B; reviewed in Ref. 26). Indeed, crystal structures suggest that erythropoietin (EPO) receptor ligands that exhibit different potencies induce different conformations within EPO receptor dimers (27, 28). Moreover, Burke and Stern (29) have suggested that the rotational orientation of ErbB2 subunits within a receptor homodimer may be a critical determinant in the transforming activity of this receptor.

Studies are currently underway to determine whether ligand discrimination is a property intrinsic to the ErbB receptors themselves or whether other cellular components may contribute to differential ErbB receptor tyrosine phosphorylation.

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