Two Motifs within a Transmembrane Domain, One for Homodimerization and the Other for Heterodimerization*

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Protein assembly is a critical process involved in a wide range of cellular events and occurs through extracellular and/or transmembrane domains (TMs). Previous studies demonstrated that a GXXXG motif is crucial for homodimer formation. Here we selected the TMs of ErbB1 and ErbB2 as a model since these receptors function both as homodimers and as heterodimers. Both TMs contain two GXXXG-like motifs located at the C and N termini. The C-terminal motifs were implicated previously in homodimer formation, but the role of the N-terminal motifs was not clear. We used the ToxR system and expressed the TMs of both ErbB1 and ErbB2 containing only the N-terminal GXXXG motifs. The data revealed that the ErbB2 but not the ErbB1 construct formed homodimers. Importantly, a synthetic ErbB1 TM peptide was able to form a heterodimer with ErbB2, by displacing the ErbB2 TM homodimer. The specificity of the interaction was demonstrated by using three controls: (i) Two single mutations within the GXXXG-like motif of the ErbB1 peptide reduced or preserved its activity, in agreement with similar mutations in glycoporphin A. (ii) A TM peptide of the bacterial Tar receptor did not assemble with the ErbB2 construct. (iii) The ErbB1 peptide had no effect on the dimerization of a construct containing the TM-1 domain of the Tar receptor. Fluorescence microscopy demonstrated that all the peptides localized on the membrane. Furthermore, incubation with the peptides had no effect on bacterial growth and protein expression levels. Our results suggest that the N-terminal GXXXG-like motif of the ErbB1 TM plays a role in heterodimerization with the ErbB2 transmembrane domain. To our knowledge, this is the first demonstration of a transmembrane domain with two distinct recognition motifs, one for homodimerization and the other for heterodimerization.

Protein recognition within the membrane milieu is crucial for a wide range of processes in all organisms. Membrane proteins associate via their extracellular and transmembrane (TM) or solely via their TM domains. Understanding the interactions involved in peptide-peptide recognition within the membrane milieu is therefore an important task. Despite advances, the limited number of studies conducted report mainly on homodimerization and not on heterodimerization of TM segments in vitro and in vivo (1–7). The ability of TM domains to homodimerize in vivo was reported using either the ToxR (2) system or the TOXCAT (8) system. To our knowledge, only a few studies reported on hetero-association of TM domains in vivo. These studies include: (i) introducing exogenous TM peptide mutants of glycoporphin A (GPA) to the ToxR system, which expresses the TM domain of glycoporphin A, and observing a dominant negative effect (9); and (ii) the study of hetero-association of the TM domains α and β integrin subunits, using the GALLEX system (10). Furthermore, a direct identification of two assembly motifs within a single TM domain has not been reported.

For this purpose, we investigated the recognition patterns of the ErbB receptor family TM domains. This single span TM receptor family (type I), which is involved in a variety of cell processes, is also implicated in several types of cancer (11, 12). Homodimerization of these receptors has been known to be a prerequisite for signal transduction for over a decade (13, 14). Cell transformation and cancer can be induced by overexpression of the ErbB receptors (15, 16), as well as by specific mutations that increase the dimerization propensity of the receptor, independent of ligand binding (17). Lately, it was established that the heterodimerization of different ErbB receptors in a ligand-dependant manner is responsible for the proper transmittance of signals into the cell (18–21).

The TM domains are also involved in the dimerization process (16, 17, 22). The TMs of these receptors by themselves were shown to adopt a monomeric form in vitro in some cases (23). In another case, the extracellular domain was demonstrated to be involved in homo- but not heterodimerization of the ErbB receptors (24). Recently, the TM domains of ErbB1–4 were shown to homodimerize in vivo (25). The ErbB1 and ErbB2 TM domains contain two GXXXG-like motifs (Fig. 1). Mutations corresponding to the GPA G83I mutant (the second Gly position was mutated to Ile) suggested that the site II motif is responsible for homodimerization of both ErbB1 and ErbB2 TM segments. On the other hand, the results of mutation within site I are less clear (23). More precisely, the site I motif seems to play a role in homodimerization of ErbB2 but not in that of ErbB1. This is in agreement with studies were a Glu or Gln mutation was introduced into the Val position within the site I motif (25, 26). The mutation did not interfere with ErbB1 proper homodimerization or function.

Here we used a ToxR system combined with synthetic TM peptides to shed light on the possible role of the TM domains in the assembly process of the ErbB1 and ErbB2 receptors. Our findings demonstrate a role for the site I motif in the homodimer formation by ErbB2 but not ErbB1 and in the heterodimer assembly of the ErbB1 and ErbB2 receptors.
**EXPERIMENTAL PROCEDURES**

**Peptide Synthesis and Purification**—Three ErbB1 peptides, as well as the aspartate receptor peptide, were synthesized by a standard Fmoc solid-phase method on a Rink methyl benzhydryl amide resin (27, 28). The peptides were cleaved from the resin by trifluoroacetic acid and were purified by RP-HPLC on a C4 reverse phase Bio-Rad semipreparative column (250 × 10 mm, 300-Å pore size, 5-μm particle size). The purified peptides were shown to be homogeneous (>99%) by analytical HPLC. The compositions of the peptides were confirmed by Platform LCZ electrospray mass spectrometry. A guest host system of 4 lysines was used to ensure the solubility of the TM segment (29).

**Fluorescent Labeling of Peptides**—The Fmoc protecting group was removed from the N terminus of the resin-bound peptides by incubation with piperidine for 15 min, whereas all the other reactive amine groups of the attached peptides were kept protected. The resin-bound peptides were washed twice with dimethylformamide and then treated with rhodamine (2 equivalents) in anhydrous dimethylformamide containing 2% N,N-diisopropylethylamine, leading to the formation of a resin-bound N-rhodamine peptide. After 24 h, the resin was washed thoroughly with dimethylformamide and then with methylene chloride. The labeled peptides were cleaved from the resin and purified as described above.

**MalTose Complementation Assay**—Membrane insertion and correct orientation of the various ToxR chimera constructs (GPA, A16, ErbB1, ErbB2, and ΔTM) were examined as described previously (30). Briefly, PD28 cells were transformed with the different plasmids and cultured overnight. The cells were washed twice with 4 ml of phosphate-buffered saline and resuspended in 0.8 ml of phosphate-buffered saline. They were then used to inoculate M9 minimal medium, with 0.4% maltose, at 37 °C. The cultures were then used to inoculate M9 minimal medium, with 0.4% maltose, at 0.4% maltose, at 37 °C. The cultures were then used to inoculate M9 minimal medium, with 0.4% maltose, at 0.4% maltose, at 37 °C. The cultures were then used to inoculate M9 minimal medium, with 0.4% maltose, at 0.4% maltose, at 37 °C.

**In Vivo Detection of Homo- and Heterodimerization of Proteins in the Membrane**—The ToxR transcription activator can be used successfully to assess weak protein-protein interactions within the E. coli membrane. Previously, a TM-encoding DNA cassette was inserted on a plasmid, between the maltose-binding protein and the ToxR transcription activator (2). Dimerization of the TM domains results in association and activation of the ToxR transcription factor, which then becomes active and is able to bind the ctx promoter. Plasmids were transformed into E. coli FH12, which contain β-galactosidase under the control of a ctx promoter. After transforming FH12 cells, 1 ml of cultures were grown in the presence of chloramphenicol and 0.1% isopropyl-1-thio-D-galactopyranoside for 20 h at 37 °C. β-galactosidase activity was quantified in crude cell lysates after the addition of 1 ml of culture. The samples were added to 2× sample buffer and boiled for 5 min. The samples were separated on a 12% SDS-PAGE and then blotted. The primary antibody used was anti-maltose-binding protein. The detection was performed using an Olympus IX70 FV500 confocal laser-scanning microscope. Care was taken that any photobleaching did not compromise the interpretation, and laser irradiation and other illumination were prevented between acquisitions. The confocal images were obtained at 12-bit resolution.

**RESULTS**

We investigated the ErbB TM domains as a model for a TM with two recognition motifs. Our objective was to find out whether the two motifs have a distinct role in the homodimerization or heterodimerization. For this purpose, we have prepared 16-amino-acid long ToxR constructs of the ErbB1 and ErbB2 TM domains (Table I). These two constructs contain the Site I motif but not the Site II motif. The latter was previously demonstrated to control homodimerization of ErbB1 and ErbB2 TMs (23). Thus, we could use the ErbB1 and ErbB2 constructs to investigate the Site I motif for both its homodimerization and its heterodimerization propensities in our modified ToxR system (9, 32) (Fig. 2).

**Proper Insertion and Growth of the Chimeric Proteins**—We have transformed PD28 bacteria that lack the endogenous MalE gene with the various ToxR constructs under investigation. These bacteria are unable to grow on minimal M9 medium containing maltose without the presence of a properly inserted ToxR-TM-MalE chimera protein on the inner membrane. We followed the PD28 growth curve for 60 h, and the results are shown in Fig. 3. The PD28 bacteria survived and proliferated ever when transformed with the ToxR constructs containing the following TM domains: ErbB1 and ErbB2, GPA, and A16. However, there was no significant growth when transformed with a
Fig. 2. Homodimerization and heterodimerization of TM domains in vitro. A schematic illustration of the ToxR system is shown. The functional organization (heterodimer) of the ToxR chimera in FHK13 cells (kindly provided by Dr. Langosch, Heidelberg University, Germany) (2) activates the ctx promoter, initiating lacZ transcription. Thus, the measured signal of β-galactosidase activity is proportional to the amount of homodimers formed. Heterodimerization of an exogenous TM peptide with the ToxR TM domain inhibits transcription by forming an inactive complex. As a result, a lower lacZ signal is detected. The decrease is proportional to the amount of heterodimers. The inserted TM domain (e.g. ErbB1, or ErbB2) is illustrated as a light gray cylinder, and the exogenously added TM peptide (e.g. ErbB1) is illustrated as a black helix.

Table II

| Designation and sequence of the TM peptides investigated | Amino acid sequence* |
|--------------------------------------------------------|----------------------|
| Wild type ErbB1                                         | KK-SIATGMVGALLLLVV-KK* |
| M650V                                                  | KK-SIATGVRGALLLVLV-KK |
| G652I                                                  | KK-SIATGMVALLLLLVV-KK |
| Tar-FG                                                 | KKK-MVLGVFALLFLIGGSL-KK |

* Mutated amino acids are marked in bold and underlined letters.

Fig. 3. Determining the proper insertion and orientation of the various ToxR constructs. The correct integration of the ToxR-TM-MalE chimera proteins into the inner membrane was examined by their ability to functionally complement the MalE deficiency of PD28 bacteria. PD28 cells transformed with the different plasmids were grown in minimal medium containing maltose. Only cells that expressed periplasmic MalE were able to grow with maltose as the only carbon source. All constructs showed similar growth curves (GPA (filled squares); A16 (open squares); ErbB1 (filled diamonds); and ErbB2 (open diamonds)), except for the negative control with the deleted TM domain (ΔTM, filled triangles), indicating proper membrane integration.

construct lacking a TM domain. Thus, we concluded that all the constructs used in this study are expressed and inserted in the correct orientation into the inner membrane.

Homodimerization of the ErbB1 and ErbB2 TM Domains—Our hypothesis that the site I motif plays a role in the heterodimerization of ErbB1 and ErbB2 is based on the propensity of each of them to form homodimers. The ToxR plasmid construct is a simple and robust method for detecting homodimerization of TM domains in vitro (2). The detection is done through the signal of a β-galactosidase reporter gene. We tested the propensity of the ErbB1 and ErbB2 constructs to form homodimers. The ErbB1 construct displayed a signal corresponding to a monomeric TM domain, whereas the ErbB2 construct demonstrated homodimerization propensity (Fig. 4). We used the GPA TM as a positive control for homodimerization and a construct with 16 alanines (A16) as a monomer control (33, 34). These results fit the current model, in which only the site II motif is involved in homodimerization of the ErbB1, whereas both the site I and the site II motifs are involved in the homodimerization of ErbB2 TM domain (23).

Heterodimerization of the ErbB1 and ErbB2 TM Domains—Heterodimerization can be detected through the addition of an exogenous peptide to the ToxR system (9, 32). Interaction of this peptide with a ToxR receptor within the membrane will form a heterodimer, thus inactivating the ToxR transcription factor. In our case, the exogenous addition of an ErbB1 synthetic peptide to the ErbB2 construct resulted in a dose-dependent reduction of the β-galactosidase reporter gene signal (Fig. 5). We normalized this inhibition to the homodimer signal of the ErbB2 construct in the absence of peptide and the monomeric signal of the A16 construct. These signals correspond to 0% heterodimerization and 100% heterodimerization, respectively (Fig. 5). The extrapolated IC50 was found to be 0.63 μM with R² of 0.96 for the heterodimerization between the ErbB1 peptide and the ErbB2 construct by fitting to the model described under “Experimental Procedures.” The scaling constant was set to 0.65 by the non-linear least square fitting.

To verify the specificity of the heterodimerization, three controls were used: (i) We introduced two mutations that correspond to significantly inactive and active mutations within the corollary GXXXG motif of GPA. The G83I mutation in the GPA TM domain significantly reduced the homodimerization propensity, whereas the mutation M81V did not interfere much with the homodimerization of GPA (1). Here an ErbB1 G652I mutant peptide had a significantly reduced affinity to the ErbB2 TM domain. The extrapolated IC50 of the interaction with the homodimerization of GPA (1). Here an ErbB1 G652I mutant peptide had a significantly reduced affinity to the ErbB2 TM domain. The extrapolated IC50 of the interaction was 4.1 μM with R² of 0.91. The scaling constant was set to 0.7 by the non-linear least square fitting. In contrast, an M650V mutant peptide preserved the ErbB1 affinity to ErbB2. (ii) We used a peptide corresponding to the TM domain of the bacterial aspartate receptor that is practically a monomer in the membrane (similarly to ErbB1) and inserts properly into the membrane (35). This peptide demonstrated virtually no propensity to assemble with the ErbB2 construct, as illustrated in Fig. 5. (iii) To verify that the ErbB1 peptide could not interact non-
specifically with different homodimer-forming ToxR chimeras, we used a construct containing the TM-1 domain from the bacterial aspartate receptor, which forms homodimers in the membrane (35). The data reveal no interaction between the ErbB1 peptide and the TM-1 construct (Fig. 5).

Membrane Localization of the ErbB1 Peptide Analogues—The binding of ErbB1 peptides to the membrane of the FHK12 bacteria is a prerequisite for the interaction between the peptide and the ErbB2 ToxR construct. To verify that the ErbB1 peptides bind to FHK12 membranes, the bacteria were observed under a confocal microscope in the absence and presence of a rhodamine-labeled ErbB1 peptide at a 0.5 μM concentration. The results confirmed that the ErbB1 peptides are mainly localized to the bacterial membrane. The binding of ErbB1 as a representative example is given in Fig. 6. It is clear that the peptides bind the membrane of the bacteria, although it is impossible to distinguish between the inner and outer membranes. Nevertheless, we observed localized concentrations within the bacteria. We believe that these are invaginations of the inner membrane into the cytoplasm. Regardless, it clearly demonstrates that the peptides can enter through the outer membrane.

Effects of the Exogenous Peptides on Protein Expression—We have used Western blot analysis to detect the effect of the ErbB1 peptide, its mutants, and the Tar-FG peptide on the expression level of the ToxR system. As expected, similar expression patterns of the ErbB2 and Tar-1 constructs were observed both in the presence and in the absence of the corresponding exogenous peptides (Fig. 7). Thus, the reduction in β-galactosidase signal, observed in the presence of the ErbB1 peptide, is due to the interaction with the ErbB2 TM and not due to variation of protein expression levels. It is worth noting that slight variations in lane intensities are mainly due to differences in loading of the gel. Less than 10% differences were measured when comparing the ratios of ErbB2 or Tar-1 chimera expression with respect to endogenous MalE expression (data not shown).

DISCUSSION

The main finding in this study is that a single TM domain contains two GXXXG-like motifs (site I and site II), each with a separate function in TM domain assembly. The site I motif is implicated in heterodimer formation, and the site II motif is implicated with homodimer formation. Previously, it was demonstrated, through mutational analysis, that the site II motif plays an important role in the homodimerization of both ErbB1 and ErbB2 receptors. However, the data with regard to the site I motif of ErbB1 and ErbB2 do not suggest a uniform role for the motif (23). Mutations within the site I motif of ErbB2 suggest that it is involved in homodimerization, whereas mutations within the site I motif of ErbB1 had negligible effect on assembly. Our data demonstrate that the ErbB1 site I motif is not sufficient for formation of homodimers. This complements the data obtained previously by point mutations in this region that demonstrated only a small effect on homodimerization of the ErbB1 TM domain (23, 25, 26). On the other hand, the ErbB2 site I motif has sufficient propensity to form homodimers. The latter result fits well with existing data (23).
For example, the most infamous point mutation in the ErbB2 receptor (neu) involves a Val to Glu change within the site I motif of the TM domain (17). The neu mutation is believed to increase the propensity of the TM domain to form homodimers (22). However, in some cases, cell transformation by the ErbB2 receptor is dependent on EGF, through the formation of heterodimers with ErbB1 (21, 22). Furthermore, point mutations within the ErbB2 TM domain pinpointed the interaction surface of the ErbB2 homodimer to its two GXXXG-like motifs (23).

We hypothesized that the site I motif, present in the ErbB1 and ErbB2 TM domains, plays a role in heterodimerization. To validate this model, we utilized a synthetic peptide corresponding to the ErbB1 truncated TM domain (containing only the site I motif) and two of its analogues. This wild-type peptide demonstrated a significant propensity to generate heterodimers with the ErbB2 TM construct. By displacing the ErbB2 TM domain, it created a dose-dependent dominant negative effect that we could quantify. The specificity of this interaction was demonstrated by three controls: (i) Two ErbB1 peptide analogues, the first of which, a Gly652 to Ile, showed a significant reduction in heterodimer formation, and the second of which, a Met650 to Val analogue, was active similarly to wild-type peptide. These results correlate with the role of these residues in the GXXXG motif shown in the GPA TM (1). (ii) A non-related monomeric TM peptide could not interact with the ErbB2 ToxR construct, and (iii) the ErbB1 peptide could not interact with a non-related ToxR construct. To our knowledge, these results demonstrate the first example of a single TM domain (ErbB1) containing two distinct recognition motifs, with each specific for a different interaction; the site I motif is necessary for heterodimerization, whereas the site II motif is needed for homodimerization.

The involvement of the ErbB receptor family in the signal transduction of cells is immense. They play a key role in proliferation as well as differentiation. They are implicated in several types of cancer, such as breast cancer, lung cancer, and pancreatic cancer. In each case, different complexes of the ErbB receptors are considered to be the dominant species in conferring the tumorigenic effects. Understanding the biophysical mode of action of these receptors will bring us a step closer to developing effective therapeutics. Furthermore, understanding the mechanism of ErbB assembly in the membrane can shed light on the nature of protein-protein recognition within membranes and their assembly mechanism in general. The additional benefit of using the peptide displacement strategy is that such an approach can provide leads for drugs designed to inhibit specific ErbB homodimer or heterodimer complexes.

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