The sequential binding of different tetratricopeptide repeat (TPR) proteins to heat shock protein 90 (hsp90) is essential to its chaperone function in vivo. We have previously shown that three basic residues in the TPR domain of PP5 are required for binding to the acidic C-terminal domain of hsp90. We have now tested which acidic residues in this C-terminal domain are required for binding to three different TPR proteins as follows: PP5, FKBP52, and Hop. Mutation of Glu-729, Glu-730, and Asp-732 at the C terminus of hsp90 interfered with binding of all three TPR proteins. Mutation of Glu-720, Asp-722, Asp-723, and Asp-724 inhibited binding of FKBP52 and PP5 but not of Hop. Mutation of Glu-651 and Asp-653 did not affect binding of FKBP52 or PP5 but inhibited both Hop binding and hsp90 chaperone activity. We also found that a conserved Lys residue required for PP5 binding to hsp90 was critical for the binding of FKBP52 but not for the binding of Hop to hsp90. These results suggest distinct but overlapping binding sites on hsp90 for different TPR proteins and indicate that the binding site for Hop, which is associated with hsp90 in intermediate stages of protein folding, overlaps with a site of chaperone activity.

Heat shock protein 90 (hsp90) is a molecular chaperone required for the proper folding of steroid receptors and a growing number of proteins involved in signal transduction (1, 2). Over the past few years, many co-chaperones that play an important role in the folding of different subsets of proteins via the hsp90 pathway have been identified (1, 2). Several of these proteins bind to hsp90 via tetratricopeptide repeat (TPR) domains. The order and specificity with which different TPR proteins bind to hsp90 complexes containing newly synthesized proteins is critical for proper protein folding (3, 4). This pathway has been best characterized in the study of steroid receptors. Newly synthesized receptors are found in complexes with hsp70. Intermediate complexes contain hsp70, hsp90, and Hop, a protein with two separate TPR domains that bind to hsp70 and hsp90. At this stage, receptors acquire the ability to bind hormone. Mature complexes contain either PP5 or one of the large immunophilins (FKBP51, FKBP52, or CyP-40), each of which contains a single hsp90-binding TPR domain (reviewed in Refs. 1–4). At this point, the receptor can bind steroids with high affinity and is fully functional in vivo.

Understanding the structural basis for the interactions between TPR proteins and hsp90 has become an important problem. Not only must specific TPR proteins bind to hsp90 complexes at specific stages of protein folding, but the TPR proteins found in mature hsp90 complexes containing steroid receptors differ according to the identity of the receptor (2). In the case of the glucocorticoid receptor, the identity of the large immunophilin bound can dramatically affect hormone binding affinity (5). Furthermore, PP5 has been shown to modulate glucocorticoid receptor signaling (6, 7). Thus, specificity for the binding of TPR proteins to hsp90 exists and is functionally important, but its structural basis remains unknown. Determining what guides a particular TPR protein to a particular hsp90 complex at a particular time is of interest not only in terms of understanding protein folding but also for potential drug development. Geldanamycin is an antitumor antibiotic that blocks hsp90 function by competing with ATP for a binding site at its N terminus (8, 9). Its biological activity is thought to be due to prevention of proper folding and stabilization of proteins required for cell growth. If it were possible to specifically inhibit the binding to hsp90 of Hop, of PP5, or of particular large immunophilins, it would be possible to target specific subsets of proteins involved in cell signaling.

Hsp90 contains two functional chaperone domains. One domain, at the N terminus, has been extensively characterized, including determination of its three-dimensional structure (8, 9). The structure of the other domain, at the C terminus, is not known. This highly acidic 12-kDa domain contains the binding site for TPR proteins and can promote protein folding in an ATP-independent manner (10–12). Although the structure of this domain has not yet been determined, the structure of the TPR domain of PP5, to which it binds, has been solved (13). The TPR domain of PP5 consists of a series of antiparallel α-helices that form a right-handed superhelix (13) making it similar to the α subunit of farnesyltransferase, which consists largely of a TPR domain (14, 15). Both TPR domains contain a groove involved in protein-protein interactions (13, 14).

We have shown that, for PP5, four basic residues in this groove are involved in binding to the C-terminal domain of hsp90 (16). Several of these basic residues are conserved in Hop and in the large immunophilins. We have now used site-directed mutagenesis to determine the location of both the TPR-binding and chaperone sites within the C-terminal domain of hsp90. Our results indicate that similarities exist between the binding sites for PP5, FKBP52, and Hop, but we also identified interesting differences between these binding sites. Thus, the structural basis for the different biological activities of these different TPR proteins may lie partly in different interactions between their TPR domains and hsp90.

EXPERIMENTAL PROCEDURES

Plasmid Construction—Sequences encoding rabbit FKBP52 and murine Hop were amplified by polymerase chain reaction, using plasmids...
and 5.

Dulbecco's modified Eagle's medium containing 10% fetal bovine serum confirm the presence of the desired mutations and the absence of FKBP52 and Lys-429 of Hop to Ala. All mutants were sequenced to as a template to mutate the indicated residues to Ala. The Bluescript instructions. For C90, the previously described pET30a-C90 (16) was used as

Site-directed Mutagenesis—Mutagenesis with the Stratagene QuikChange kit was performed according to the manufacturer's instructions. For C90, the previously described pET30a-C90 (16) was used as

Tissue Culture and Transfections—COS-7 cells were maintained in Dulbecco's modified Eagle's medium containing 10% fetal bovine serum and 5 μg/ml gentamicin. Transfections were performed using Superfect reagent (Qiagen) according to the manufacturer's instructions.

Co-immunoprecipitation of Hsp90 with TPR Proteins—Two days after transfection of COS-7 cells in 60-mm plates with the indicated plasmids, cells were washed on ice with 20 ml Hapes, pH 7.4, 150 mM NaCl, and lysed into 1 ml of Hapes, pH 7.4, 20 mM sodium molybdate, 10 mM MgCl2, 1 mM EDTA containing 10 μg/ml aprotinin and leupeptin. Cells were lysed by passage 10 times through a 26-gauge needle. Lysates were clarified by centrifugation at 4 °C for 20 min at 21,000 × g. To reduce nonspecific binding, supernatants were incubated with end-over-end rotation for 1.5 h at 4 °C with 25 μl of anti-mouse IgG-agarose beads (Sigma). After removing the beads by centrifugation, FLAG-tagged TPR proteins were adsorbed to 25 μl of M2 beads (Sigma) for 1.5 h at 4 °C with end-over-end rotation. After five washes with HBS containing 1% Triton X-100 (HBST), beads were heated in sample buffer, and samples were analyzed by immunoblotting with monoclonal antibodies to hsp90 or to the FLAG epitope as described previously (16).

Purification of C90 Proteins—800-ml cultures of BL21 (DE3) cells containing the various pET30a-C90 constructs were induced with 0.25 mM isopropyl-1-thio-β-D-galactopyranoside for 5 h at 22 °C. Cells were harvested by centrifugation and stored frozen at −20 °C. The following procedures were all performed at 4 °C. Frozen cell pellets were taken up in 30 ml of 20 mM Tris, 5 mM imidazole, 0.5 mM NaCl, pH 8.0, containing 0.5 mg/ml lysozyme, 10 μg/ml aprotinin, 10 μg/ml leupeptin, and 20 mM benzamidine. After stirring for 30 min, and by sonication, lysates were centrifuged for 1 h at 18,000 × g. Streptokinase sulfite (final 2.5%) was added to the clarified lysates, followed by stirring for 30 min. Samples were then centrifuged at 18,000 × g for 30 min, and supernatants were loaded onto a 5-ml Hitrap Chelating column (Amersham Pharmacia Biotech). The His-tagged proteins were eluted using a gradient of 0.06–1 M imidazole in 20 mM Tris, pH 8.0, 500 mM NaCl. Fractions containing pure C90 protein, as assessed by SDS-PAGE, were pooled and dialyzed against 50 mM Hepes, 100 mM NaCl, pH 7.0, at concentrations of 0, 2, 4, and 10 μM. Ten μl of 50 μM rhodanese in 6 M guanidine HCl, 50 mM Hepes, pH 7.0, was then added, and the rate of rhodanase aggregation was determined by measuring the increase in absorbance at 320 nm. Aggregation was essentially complete after 20 min.

RESULTS

Similarities and Differences between TPR-binding Sites for Hsp90—We have previously shown that four basic residues (Lys-32, Arg-74, Lys-97, and Arg-101) located in a groove in the TPR domain of PP5 are important for binding to the acidic C terminus of hsp90 (16). Since these residues are conserved in the TPR domains of FKBP52 and Hop (Fig. 1), we hypothesized that they would also be important for the binding of these proteins to hsp90. The sequences of the TPR domains of PP5, FKBP52, and Hop, all of which bind to hsp90, are aligned in Fig. 1, with the residues important for PP5 binding to hsp90 highlighted. Lys-97 of PP5 is absolutely required for binding of the TPR domain of PP5 to hsp90 (16), but the role of homologous residues in the binding of other TPR proteins to hsp90 had not previously been tested. We therefore mutated the corresponding residue in FKBP52 and in Hop. A co-immunoprecipitation assay was then used to test the ability of the wild-type and mutant TPR proteins to bind to hsp90 in transfected COS cells.

As shown in Fig. 2, hsp90 co-immunoprecipitated as expected with FLAG-tagged PP5, FKBP52, or Hop from lysates of transfected COS-7 cells. When Lys-97 in PP5, or the corresponding Lys-354 in FKBP52 was mutated to Ala, the interaction with hsp90 was abolished (Fig. 2). Mutation of the corresponding Lys-429 in Hop, however, did not reduce binding to hsp90 (Fig. 2). These results suggested both similarities and differences between the hsp90-binding determinants for FKBP52, PP5, and Hop. Alternatively, it is possible that the sequence alignments are misleading and that Lys-429 in Hop may prove not to correspond to Lys-97 of PP5 when the structure of the Hop TPR domain has been determined.

If different residues in different TPR proteins are involved in binding to hsp90, however, it stands to reason that different residues in hsp90 may be involved in binding to different TPR proteins.
proteins. We therefore compared which hsp90 residues were involved in binding to PP5, FKBP52, and Hop.

Identification of Acidic Residues in Hsp90 Required for Binding of TPR Proteins—We and others (10, 16, 22) have shown that the C-terminal 12-kDa fragment of hsp90, designated C90, contains the binding site for the TPR domains of PP5, FKBP52, CyF-40, and Hop. Acidic residues, in particular the EEEVD sequence at the C terminus of hsp90, have been implicated in these interactions (16, 22, 23). In order to identify which of the 25 acidic residues in C90 are required for interaction with TPR proteins, we mutated each of these residues to Ala, either singly or in groups, in a series of 13 mutations (Fig. 3). The ability of each mutant C90 protein to bind to PP5, FKBP52, and Hop was then examined.

FLAG-tagged TPR proteins were overexpressed in COS-7 cells and purified from lysates by adsorption to anti-FLAG beads. The beads, with bound TPR proteins, were then incubated with purified wild-type C90 or C90 mutants. After washing the beads to remove unbound material, samples were analyzed by SDS-PAGE and blotting with S-protein, to detect the S-tagged C90 proteins. As a control, parallel blots were developed using the M2 anti-FLAG antibody to determine the level of the bound TPR proteins.

As shown in Fig. 4 (top), the only mutation that significantly affected the binding of C90 to immobilized full-length PP5 was mutant 13, in which the C-terminal EEVD sequence was mutated to AAVA. This mutation completely blocked binding. Each of the binding assays presented here was performed at least twice, and other small quantitative differences in binding were not reproducible. As expected based on sequence homology to the TPR domain of PP5, and on a known interaction with the MEEVD sequence of hsp90 (23), results were similar with FKBP52 (Fig. 4, middle). In this case, both mutation 12 and mutation 13 inhibited C90 binding. These mutations, however, resulted in only partial inhibition of binding to FKBP52, unlike the complete elimination of binding to PP5 observed with mutant 13. In both cases, however, the critical binding determinants were at the very C terminus of hsp90. This was consistent with previous studies suggesting a role for the C-terminal MEEVD sequence in binding several different TPR proteins, and with this sequence being somewhat less important for the binding of FKBP52 binding than for that of other proteins (23).

Quite different results were obtained when we examined the ability of the panel of C90 mutants to bind to immobilized Hop (Fig. 4, bottom). In this case, the only mutation that blocked binding was mutant 4, located toward the amino end of C90.

The binding of mutant 2 to Hop was also somewhat less than that of wild-type C90 (Fig. 4, bottom), and this decreased binding was seen in two separate experiments (data not shown). Mutations at the C terminus had no obvious effect on binding to Hop. Thus, different determinants on hsp90 seemed to be involved in binding to different TPR proteins.

This last result was surprising in that, using different materials and methods, two other groups have reported that the MEEVD sequence was required for Hop binding (22, 23). It was difficult to compare our data with those of Chen et al. (23) due to numerous differences in experimental design. The only major difference between the methods of Carello et al. (22) and ours, however, seemed to be that their binding assays were performed with immobilized C90 proteins and soluble Hop, whereas we had examined the binding of soluble C90 mutants to immobilized Hop. We wondered whether this simple difference in assay protocols might explain the divergent results.

We therefore used the methods described in Ref. 22 to examine the ability of soluble FLAG-tagged PP5, FKBP52, and Hop, from COS cell extracts, to bind to C90 proteins immobilized via their His tags (Fig. 5). By using this assay we obtained similar results to those described above for PP5 and for FKBP52 (Fig. 5, top and middle), except that binding was even more sensitive to the two C-terminal mutations. Mutant 13 did not bind at all to either protein, and binding of mutant 12 was barely detectable. Thus, using either binding assay, it is clear that critical binding determinants for FKBP52 and for PP5 reside primarily at the C terminus of the C90 protein. The situation was more complex for Hop; soluble Hop bound only weakly to immobilized mutant 4, consistent with the results shown above. It did not bind at all, however, to immobilized mutant 13 (Fig. 5, bottom). Thus, conformational changes or steric hindrances, resulting from protein immobilization in the binding assay, are probably responsible for the observed differences in C90 residues required for Hop binding. We suggest that Hop interacts with determinants altered in mutants 2, 4, and 13. We further conclude that when Hop is immobilized, some binding determi-
nants become inaccessible, making the residues altered in mutants 2 and 4 more important for binding. Similarly, when C90 is immobilized, we speculate that other C90 residues become inaccessible to Hop, making the residues altered in mutant 13 critical for binding. Under ordinary circumstances, multiple sites of interaction may make any single determinant dispensable.

For all three immobilized TPR proteins we also observed enhanced binding of mutants 6 and 7 relative to the wild-type C90 (Fig. 4). Unlike mutants 8 and 9, this did not appear to be due to nonspecific binding to the beads (data not shown) but was not seen in assays using immobilized C90 (Fig. 5). The significance of this observation is thus unclear. The effects of all of the hsp90 mutations are summarized in Table I.

**DISCUSSION**

We have previously identified a groove in the TPR domain of PP5 that contains several basic residues critical for the binding of hsp90, and we hypothesized that these basic residues interacted with the abundant acidic residues in the 12-kDa C-terminal domain of hsp90 (16), designated C90. It has been speculated that this groove could bind an amphipathic α-helix (13), a structure predicted to be found in C90. We have now determined which of the 25 acidic residues in this 105-amino acid region are required for binding to the TPR domains of PP5, FKBP52, and Hop; all three proteins bind to C90 and contain the same conserved basic residues. Our results confirm and extend previous data suggesting that the MEEVD sequence at the C terminus of hsp90 was important for binding TPR proteins and that different TPR proteins competed for binding to the same site (22, 23). The data presented here, however, suggest a more complex picture. Although it seems clear that the MEEVD sequence is involved in binding to all three TPR proteins, there are also differences in their binding determinants. A cluster of four acidic amino acids adjacent to the MEEVD sequence (Glu-720, Asp-722, Asp-723, and Asp-724) is involved in binding to FKBP52 and PP5, proteins that are found in mature hsp90 complexes. Its mutation does not affect the binding of Hop, however, which is found in intermediate complexes. Mutation of either of these C-terminal sequences, while inhibiting TPR binding, does not affect the chaperone activity of C90, suggesting that the site of chaperone activity is located more toward the N terminus of this domain. Mutation of Glu-651 and Asp-653 decreases not only chaperone activity but Hop binding. Thus, the site of Hop binding, but not that of FKBP52 or PP5 binding, appears to overlap with the site of chaperone activity. One might speculate that Hop enters the hsp90 complex at an intermediate stage of protein folding because it is recognized by hsp90 as a misfolded protein, binding to one of the two available chaperone sites. Hop differs from FKBP52 and PP5 in another respect; a Lys residue conserved...
The data presented in the figures regarding the effects of C90 mutations on the binding of TPR proteins and on chaperone activity are summarized here.

| Mutant | Residues mutated | Inhibition of binding | Changes in chaperone activity |
|--------|------------------|----------------------|-------------------------------|
| 1      | E635A            |                     |                               |
| 2      | D639A            |                     |                               |
| 3      | E644A            |                     |                               |
| 4      | E651A, E652A     | ±                    | Increased                     |
| 5      | D656A            |                     | Decreased                     |
| 6      | D661A            |                     |                               |
| 7      | E668A            |                     |                               |
| 8      | E679A, D680A     |                     | Proteins folded improperly, not characterized |
| 9      | D699A, E700A, D701A, D702A | +                  |                               |
| 10     | D706A, D707A     |                     |                               |
| 11     | E714A, E715A     |                     |                               |
| 12     | E720A, D722A, D723A, D724A | +                  |                               |
| 13     | E729A, E730A, D732A | +                |                               |

among these three proteins is absolutely required for binding of PP5 or FKBP52 to hsp90 but not for binding of Hop. This suggests that there are differences between the interactions between Hop and hsp90 and those between FKBP52 or PP5 and hsp90. This could either involve a difference in the binding of the TPR domain of Hop itself or simply the presence of additional binding determinants outside the TPR domain. With the exception of Hop, the conserved Lys residue may be of general importance in the binding of TPR proteins to hsp90. Recently, several investigators have found that its mutation prevents binding of hsp90 to CyP-402, FKBP51, and CNS1.

At least two caveats apply to these data. First, as always, there is the possibility that site-directed mutagenesis can have global effects on protein folding, i.e., that particular mutants may result in altered folding of either C90 or of the TPR proteins. Although determination of the three-dimensional structure of hsp90 complexes with these proteins will be required to address fully this question, it is clear that whether due to loss of charged residues or whether to altered folding TPR proteins do not bind to hsp90 in an identical fashion. Similarly, homologous mutations in three TPR proteins differentially affect their binding to hsp90. We are, therefore, confident in drawing the general conclusion that the interactions between hsp90 and Hop are substantially different than those between hsp90 and PP5 or FKBP52. A second concern in interpreting the binding data has to do with the effects of experimental conditions on the results. Carello et al. (22) have previously shown that deletion of the MEEVD sequence results in a loss of binding of Hop to the immobilized C-terminal domain of hsp90. Chen et al. (23) have previously demonstrated that mutation of this sequence to MAADV in chicken hsp90 resulted in a complete loss of binding of Hop immobilized on an antibody resin and in a modest decrease in binding to FKBP52. We obtained results identical to those of Carello et al. (22), but when we performed the assay slightly differently, immobilizing Hop by an N-terminal FLAG tag rather than immobilizing C90, we found that mutating MEEVD to MAAVA had no effect on Hop binding. We also found that this mutation inhibited binding to FKBP52 as well as to PP5, no matter which protein was immobilized. We interpret these results to indicate that the MEEVD sequence is involved in binding to all three TPR proteins but that multiple binding determinants exist for Hop. Only under some experimental conditions does a single mutation result in a complete loss of Hop binding.

The observation that there appear to be different binding determinants for different TPR proteins, both within the TPR domain and within hsp90, is somewhat surprising. It has been assumed that all TPR proteins bind to the identical site on hsp90, and competition binding studies have reinforced this notion (22, 24, 25). Such studies, however, have also shown that bound TPR proteins can block the interaction of hsp90 with cdc37, which presumably binds to a separate nearby site (26, 27). If the TPR domains all bound to hsp90 in an identical fashion, then biological differences between hsp90-binding TPR proteins would reside outside their TPR domains. This hypothesis is consistent with the observations that only Hop contains an hsp70-binding domain, only FKBP52 contains a peptidylprolyl isomerase domain, and only PP5 contains a phosphatase domain. However, the situation may not be so simple. First, the TPR domains diverge considerably in sequence. Second, the TPR domain of a large immunophilin has the same biological activity as the full-length protein in yeast, and inhibition of the peptidylprolyl isomerase activity of a large immunophilin does not block its chaperone activity in vitro (28–30). Thus, TPR domains may function as more than simple targeting or docking domains. Even if the biological differences between these TPR proteins prove to be mainly due to interactions taking place outside their TPR domains, differences in binding determinants may be exploited pharmacologically. Our results suggest that there are structural differences between the binding sites on hsp90 for PP5, FKBP52, and Hop. This, in turn, suggests that it should be possible to develop inhibitors of...
specific TPR complexes. These would have potential uses both as
drugs and in the study of proteins whose folding, processing, and
subcellular trafficking is dependent on particular TPR proteins.

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Note Added in Proof—It has now been shown that sequence align-
ments were indeed misleading and that Lys-301 rather than Lys-429 of
Hop corresponds to Lys-97 of PP5 (Scheufler, C., Brinker, A., Bouren-
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