Several unrelated proteins are known that specifically interact with members of the mammalian hsp70 chaperone protein family independent of the hsp70 substrate-binding site. One of these is Hap46, also called BAG-1, which binds to the ATP-binding domain of hsp70 and its constitutively expressed, highly homologous counterpart hsc70, thereby affecting nucleotide binding, as well as protein folding properties, of these molecular chaperones. In an attempt to delineate the potential contact sites on hsp70/hsc70 involved in this interaction we made use of the following two independent approaches: (i) screening of membrane-bound peptide libraries based on the sequence of the ATP-binding domain and (ii) the phage-display technique with random dodecapeptides. These approaches yielded partially overlapping results and identified several possible contact regions. On the space-filling model of hsc70, the two major contact areas for Hap46 delineated in the present study are located on the same side of the molecule on either subdomain that border the central cleft harboring the nucleotide-binding site. We suggest that this bridging affects the conformation of the ATP-binding domain in a way similar to the opening of the nucleotide-binding cleft produced in the bacterial hsp70 homologue DnaK upon binding its regulatory protein GrpE.

Members of the hsp70 (70-kDa heat shock protein) family are among the most abundant soluble proteins in mammalian cells, most notably the constitutively expressed form, hsc70 (for reviews see Refs. 1–3). They are involved in a great variety of functions, i.e. they prevent hydrophobic areas of proteins from aggregating, function in the folding and unfolding of protein structures, participate in transport into cellular organelles (4, 5), deliver proteins for intracellular degradation (6), and play a role in the survival of cancer cells (7). Often the activities of hsp70s, for example in protein folding reactions, are stimulated by hsp40 or other members of the DnaJ-like protein family (8). Common to all hsp70 proteins is a highly conserved domain structure; the 44-kDa ATP-binding domain occupies more than the amino-terminal half of the molecule and is made up of two subdomains of about equal size and similar three-dimensional structure (9–11). Substrate binding employs the carboxyl-terminal part of the molecule that is composed of two very differently structured subdomains (12). One of the most interesting open questions at present is how these major hsp70 domains interact with each other to bring about the biological effects of hsp70 chaperones. Such interdomain interactions appear particularly relevant in situations when various accessory proteins are present that upon association modulate the functions of hsp70 molecular chaperones.

In addition to cochaperones of the DnaJ/hsp40 family, several unrelated protein factors have been identified that specifically bind to mammalian hsp70s. The hsc70-interacting protein Hip, also called p48, was the first (13, 14). The hsp70/hsc70-associating protein Hap46, also known as BAG-1, has originally been detected by interaction screening approaches using as bait a nuclear receptor, the anti-apoptotic protein Bcl-2, or a membrane receptor of the tyrosine kinase family (15–17) but was subsequently found to directly interact with members of the hsp70 family (18–21). Third is the hsp70-interacting protein HspBP1 (22, 23). All these factors are known to interact with the ATP-binding domain of hsp70 chaperones and have been found to affect their biochemical activities, albeit in different ways. By contrast, the carboxyl-terminal domain of hsp70s is involved in interactions with the hsp70/hsp90-organizing protein Hop/p60 (18, 24, 25) and the carboxyl terminus of Hsc70-interacting protein CHIP (26). Nevertheless, DnaJ/hsp40 and CHIP affect the ATPase activity of hsp70s even though they bind to the distally located carboxyl-terminal part (18, 25, 26). Moreover, the interaction of Hop/p60 is inhibited when Hap46 binds to the amino-terminal domain of hsc70 (24). These observations suggest that there are intricate interrelationships between hsp70 domains and the proteins associating with them.

In an attempt to achieve a better understanding of the molecular interactions between hsp70s and their accessory proteins we investigated the ATP-binding domain of mammalian hsc70 for contact sites with Hap46. To this end, we employed as complementary approaches (i) screening of membrane-bound peptides covering the sequence of the ATP-binding domain of hsc70 and (ii) the phage-display technique using random peptide libraries. Several potential contact sites were detected by these independent techniques. Our data suggest that Hap46 binds to hsc70 from one side of the ATP-binding domain by making use of two major contact areas.

**EXPERIMENTAL PROCEDURES**

Expression of Recombinant Hap46—The fusion protein of glutathione S-transferase with Hap46 was expressed in Escherichia coli JM109 and purified on GSH-Sepharose as described earlier (15). Cleavage was with thrombin (27).

Synthesis of Immobilized Peptides and Immunodetection—Peptides were synthesized on activated membranes containing a polyethylene glycol 600 amino spacer (Abimed) using Fmoc chemistry (28). After completion of the synthesis, membranes were washed three times with phosphate-buffered saline and blocked overnight in saline containing 5% dried milk powder. Following a wash with saline containing 0.2% Tween 20, membranes were allowed to react overnight with 1–2 μg/ml of antibody.
Hap46 in saline containing milk powder. Unbound Hap46 was removed by three washes in saline containing 0.2% Tween 20 whereupon membranes were incubated for 4 h with appropriate dilutions of monoclonal antibodies CC9E8 (29) and 3.10G3E2 (30). Bound Hap46-antibody complexes were visualized using a 1:5000 dilution of horseradish peroxidase-coupled goat anti-mouse antibody (Dianova) in saline containing milk powder for 1 h, followed by detection via enhanced chemiluminescence (ECL; Amersham Pharmacia Biotech).

In an attempt to reuse membranes pre-exposed to Hap46 and antibodies, the membranes were stripped by 3 washes each in the following solutions: (i) dimethylformamide, (ii) 8 M urea, 10% SDS, 1% β-mercaptoethanol, and (iii) 50% ethanol, 10% acetic acid. Upon incubation with antibodies alone, the very same regions lighted up (data not shown), demonstrating that Hap46 had not been removed from the membranes. In independent sets of experiments with membrane-bound peptides used for epitope mapping of monoclonal antibodies,1 it was observed that, when blocking as above, the interacting protein was not removed by guest on July 25, 2018http://www.jbc.org/Downloaded from

**FIG. 1.** Membrane-bound peptide scans. Decapeptides covering amino acids 1 to 383 of the hsc70 ATP-binding domain were synthesized in arrays as described under “Experimental Procedures.” The very last 4 amino acids (residues 380 to 383) showed no interaction, and the respective peptides are left out from the presentation. The left column of peptide spots presents staining with antibody CC9E8, and the right column shows staining with antibody 3.10G3E2. Peptides of strong interaction with Hap46 are marked in blue, and these regions are labeled with roman numerals according to their occurrence within the sequence of hsc70.

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1 M. Blüthner and G. Petersen, unpublished results.
Peptide synthesis and antibody reactions were performed as described before (33, 34) with 15–20 residues of human Hap46 (15), staggered by two amino acids. Pentadecapeptides encompassing the complete amino acid sequence of Hap46 were synthesized and antibody CC9E8 reacted with amino acids 151–161, encompassing the sequence NSPQEEVELKK. Whereas antibody 3.10G3E2 recognized the amino acid sequence RSEEVTREEMA, corresponding to amino acids 59–69 of Hap46, the antibody CC9E8 reacted with amino acids 151–161, encompassing the sequence NSPQEEVELKK.

**RESULTS**

**Screening of Membrane-bound Peptides with Hap46**—To investigate the interaction of the molecular chaperones hsp70 and hsc70 with the accessory protein Hap46 we used membrane-bound decapeptides deduced from the amino acid sequence of the human hsc70 ATP-binding domain. These peptides were arranged in scans staggered by one amino acid, beginning at the amino-terminal end and resulting in a total of 370 peptides covering amino acids 1 to 379. For screening we used recombinant Hap46 and visualized the complexes with monoclonal antibodies CC9E8 or 3.10G3E2 specific for Hap46/hsc70. For the above reasons we only used newly synthesized peptide arrays for our interaction studies. Epitopes on Hap46 Recognized by Monoclonal Antibodies CC9E8 and 3.10G3E2—Epitopes were mapped by screening of membrane-bound pentadecapeptides encompassing the complete amino acid sequence of 274 residues of human Hap46 (15), staggered by two amino acids. Peptide synthesis and antibody reactions were performed as described above. Antibody 3.10G3E2 recognized the amino acid sequence RSEEVTREEMA, corresponding to amino acids 59–69 of Hap46, whereas antibody CC9E8 reacted with amino acids 151–161, encompassing the sequence NSPQEEVELKK.

Phage Display—Pannings were carried out essentially as described before (33, 34) with 15 to 20 µg of recombinant Hap46 immobilized on Petri dishes (3.5-cm diameter; Greiner), blocked, and incubated with 5 × 10⁶ phage particles from a 12-mer random peptide phage-display library (PhD library; New England Biolabs), following the manufacturer’s protocol. To eliminate enrichment of phage clones interacting with the plastic surface or the blocking agent, the following two strategies were employed: (i) diluted and amplified material from the first panning was either subjected to a preadsorption step on bovine serum albumin-coated Petri dishes prior to subsequent pannings, or (ii) bovine serum albumin as blocking agent was alternated with casein in the form of dried milk powder. After the second and third round of panning, phage clones were picked at random and amplified individually. Following standard procedures, DNA was purified and subjected to cycle sequencing and was analyzed on an ABI Prism 310 sequencer (Big Dye; PerkinElmer Life Sciences).

Computer-assisted Analysis of Hsc70—The three-dimensional models of hsc70 and DnaK were visualized and processed from the PDB files 1BUP and 1DKG, respectively, using the program RASMOL (Version 2.6).

### TABLE I

| Region | Amino acid positions | Sequence |
|--------|----------------------|----------|
| I      | 17–25                | CVGVFQHKG |
| II     | 87–98                | MKHWPPMVYND |
| III    | 121–131              | SMVLTKKEIA |
| IV     | 134–142              | YLGKTVTNA |
| V      | 266–274              | ACERAKRTL |
| VI     | 281–289              | SIEIDSLYE |
| VII    | 354–360              | NGRELNKK |

from the contact spot if concentrations above 100 ng/ml had been used. Although the complex Hap46/hsc70 has an equilibrium dissociation constant in the order of 1 to 100 nM (31, 32) and is readily formed in the presence of 1 M urea (19), we expected lower affinities of Hap46 to peptides derived from hsc70. For the above reasons we only used newly synthesized peptide arrays for our interaction studies.

Interestingly, peptides covering positions 281 to 289 (Fig. 1, region VI) lighted up strongly with only one of the monoclonal antibodies, 3.10G3E2, used in the present study (Fig. 1, right row). This suggests that the epitope specific for the other antibody, CC9E8, is not readily accessible once Hap46 is bound to this peptide sequence. We also need to draw attention to the set of peptides that constitute region II (cf. Fig. 1 and Table I). They differ from all the others in that they include a Trp residue and cover the region of hsc70 containing the only Trp present in the ATP-binding domain. In control experiments we observed that peptides containing one or several Trp residues reacted very strongly in our peptide screening assays, almost independent of the other amino acids and the sequence (data not shown).
not shown). This coincides with the experience of others who found that Trp-containing peptides used in the phage-display approach resulted in exceedingly strong interactions, easily leading to misinterpretations (35).

**Screening of Phage-displayed Random Peptide Libraries with Hap46**—In an alternative approach we used a peptide library expressed in fusion with the pIII protein of a derivative of the filamentous phage M13 (33). This commercially available library had a complexity of $10^9$ primary transformants presenting random dodecapeptides. Selection of interacting phage particles was performed with bacterially expressed Hap46 immobilized on plastic Petri dishes. Recombinant phage particles retained on this matrix were then amplified in *E. coli* and used for further biopanning with Hap46, carried out in parallel using alternating block and preclearing conditions to eliminate plastic and block binders. After two and three rounds of panning, respectively, clones were isolated, and the inserted DNAs were analyzed. As shown in Table II, the 12-mer peptide sequence QHFNNSVNLGFT was greatly enriched, representing roughly 70% of the inserts after the second and third panning rounds. Other sequences, however, were not significantly enriched.

Upon checking the published amino acid sequences of hsp70 (36) and hsc70 (37) we did not find the above dodecapeptide QHFNNSVNLGFT linearly represented in the primary amino acid sequence. We then searched for homologies within the published three-dimensional structure of hsc70 (9, 11) and indeed detected an almost linear area on the surface with striking similarities to the respective phage-displayed peptide. Peptide QHFNLGFT is thus reduced to residues QHFVLGT, corresponding to positions Gln22–His23–Phe21–Val20 and Leu135–Gly136–Thr138 in a split sequence with opposing polarities in the polypeptide. This in fact shows that only about half of the amino acid residues of the dodecapeptide contribute to the molecular interaction on the surface of the hsc70 molecule. Depicted in red in the model of Fig. 2H, the QHFVLGFT area (region A) is located on subdomain I of the ATP-binding domain of hsc70 and partially overlaps with region I (amino acids Gln22, His23, Phe21, and Val20) and region IV (amino acids Leu135, Gly136, and Thr138) disclosed by the peptide scans (Table I).

When we compared the amino acid sequences of hsc70 and hsp70 within the potential Hap46 interaction sites identified by both approaches we detected only some minor differences. Conservatively substituted residues include Val95 → Ile,

### Table II

| Peptide          | Frequency |
|------------------|-----------|
| After 2nd round of panning (15 inserts sequenced) |           |
| QHFNNSVNLGFT     | 11        |
| SPERHLHDLRPY     | 1         |
| NKLQPDAYFNPG     | 1         |
| GGNWTAATASWA     | 1         |
| RICMLVIRSNAA     | 1         |
| After 3rd round of panning (29 inserts sequenced) |           |
| QHFNNSVNLGFT     | 20        |
| SPERHLHDLRPY     | 3         |
| AILLISMLGFT      | 1         |
| APTVKNCPSPCP     | 1         |
| YTTTWBRQPPSH    | 1         |
| YWKIIQYTTTF      | 1         |
| TLATVPSSLFLV     | 1         |
| LVDHHQTYTFPP     | 1         |

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**Fig. 3. Three-dimensional model of the ATP-binding domain of hsc70 showing combined results.** Potential Hap46 interacting regions identified from membrane-bound peptide scans (regions I—VII; in blue) and by the phage-display technique (region A) are presented. The overlap of region A with regions I and IV is shown in purple. Coloring of hsc70 subdomains is as in Fig. 2. A, front view. B, model turned by roughly 90°.

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**Fig. 4. Comparison of binding areas on DnaK and hsc70.** The three-dimensional model of the ATP-binding domain of DnaK in the open configuration (49) is used throughout. A, interaction sites for GrpE (49) shown in ochre. B, contact areas for Hap46 projected onto DnaK shown in blue. C, combined interaction areas for GrpE and Hap46 with topological overlaps shown in red.
Interaction of Hap46 with hsc70

Alanine \( \rightarrow \) Gly, Ile \( \rightarrow \) Leu, Tyr \( \rightarrow \) Phe, and Lys \( \rightarrow \) Arg and are expected not to influence interactions with Hap46. Less conservative is the Lys \( \rightarrow \) Tyr exchange in region IV, indicating that these residues may not significantly contribute to the interaction with Hap46. Similarly, amino acids Cys \( \rightarrow \) Ala, Val \( \rightarrow \) Leu, Gly \( \rightarrow \) Ala, Ile \( \rightarrow \) Leu, Met \( \rightarrow \) Ala, and Ala \( \rightarrow \) Val (region III), Ala \( \rightarrow \) Leu, and Cys \( \rightarrow \) Gly, which are present in the interacting membrane bound peptides but buried inside the hsc70 molecule, will probably not participate in the interaction. However, these residues may stabilize structures required for interaction.

**DISCUSSION**

Over the past few years, Hap46/BAG-1 proteins have been described to associate with an enormous variety of completely unrelated mammalian proteins, like nuclear receptors and other transcription factors (15, 19, 38–41), as well as many other proteins (16, 17, 42–46). However, the majority of these interactions appear to be mediated by molecular chaperones of the hsp70 type, which have the ability to promiscuously associate with all kinds of proteins, in particular if these are partially misfolded and/or contain hydrophobic areas exposed at the surface. On the other hand, Hap46 has also been established as a DNA-binding protein that has the potential to stimulate transcription (47). The amino-terminal end of Hap46, which contains clusters of positively charged amino acids, is involved in this activity (47). By contrast, the carboxyl-terminal portion of Hap46/BAG-1 has been shown to be required for the interaction with hsp70s (20, 32). However, on the part of hsp70s, the interaction sites are rather ill-defined. In Far-Western blots both subdomains I and II of the ATP-binding domain of human hsp70 reacted with Hap46, but in the yeast two-hybrid system only one of these subdomains gave a positive result (18). We therefore now turned to alternative and more sensitive methods with the aim of obtaining more detailed information about the contact areas within the ATP-binding domain of hsp70/hsc70.

Membrane-bound peptide libraries designed according to the amino acid sequence of the ATP-binding domain of human hsc70 were screened with Hap46 and specific monoclonal antibodies. This resulted in detection of several potential regions of strong interactions (cf. Table I). All of these potential contact regions, depicted in blue in Fig. 2, are located on one side of the ATP-binding domain, except for region II, which is on the other side of the molecule (Fig. 2, panel B). We consider the latter region as unlikely to be of any significance for binding of Hap46 because of the fact that it contains a Trp residue and that tryptophanes were found to trigger artifactual protein-protein interaction, as described above. In any event, the peptide-scanning method is able to detect clusters of amino acids, probably because of the fact that a large number of peptide molecules is present in a single spot on the membrane in a densely packed array. Indeed, some of the potential contact regions obtained by peptide scanning look like patches on the surface of hsc70 (cf. Fig. 2).

In a complementary approach, we used the phage-display technique with a random dodecapeptide library. In contrast to peptide scanning, phage M13 presents only a maximum of five peptide copies on the tip of each particle. Furthermore, detection of interaction sites is restricted by the limited complexity of the phage library itself, in particular if rather long polypeptide stretches are inserted, as in our study. In addition, a multitude of parameters (e.g. target concentration, phage valency, degree of background binding, and selection stringency) are known to greatly influence the panning procedure such that eventually only one binder may dominate the population of enriched phages (48). On the other hand, the phage-display technique may uncover rather complex interaction areas that would never show up as such in the peptide-scanning approach. This was indeed the case with region A (cf. Fig. 2H). It is a split epitope in that it is not contiguous within the amino acid sequence of hsp70 or hsc70, and the two polypeptide segments comprising it are of opposite polarity. On the surface of hsc70, region A represents an elongated array of amino acid residues (cf. Fig. 2H).

In the model of Fig. 3, we combined the results obtained with the membrane-bound peptide-scanning and phage-display techniques and show the ATP-binding domain of hsc70 in a front view (A) and turned around by roughly 90° (B). This presentation clearly shows that all interaction regions are on one side of the molecule, except for region II, which remains questionable (see above). The fact that the other side is void of interaction sites suggests specificity. Interestingly, region A identified by phage display overlaps on either end with regions I and IV obtained by peptide scanning (cf. Fig. 3, A and B). Regions A, I, and IV, together with neighboring region III, form a distinct structure including a prominent protuberance, best seen in Fig. 3B. We think that this area on the surface of hsc70 within subdomain I is very well suited for protein-protein interactions as it represents a remarkable structural feature and thus stands out as a major site of contact with Hap46.

![Alignment of sequences within the ATP-binding domains of hsc70 and DnaK](http://www.jbc.org/)

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area of significant interaction is defined by regions V and VI located on subdomain II, i.e., on the other side of the central cleft of the ATP-binding domain. Located in between these major areas of contact but positioned somehow to the lower portion of subdomain II is region VII (Fig. 3A), which possibly contributes to a much lesser degree to the interaction with Hap46. Nevertheless, it is astonishing at first glance that interaction with Hap46 should involve such large surface areas of hsp70/hsc70, as outlined in Fig. 3, located on the same side of the molecule.

The above considerations lead us to compare the potential contact areas on mammalian hsc70 for the associating protein Hap46 with the interaction sites on the ATP-binding domain of the bacterial hsp70 counterpart DnaK for its respective regulatory factor GrpE. These were established by x-ray structural analysis of the complex and showed several areas of close contact (49) covering a significant surface area on one side of the molecule. The two largest of them are on the upper portions of subdomains I and II, respectively, on each side of the central cleft of the ATP-binding domain. Binding of GrpE was thus shown to produce a torsion of subdomain II with a relative opening of the cleft that harbors the ATP-binding site (49). This readily explained the large stimulation of the ADP/ATP exchange on DnaK upon association with GrpE (49, 50). The experiments described in the present study disclosed two major contact areas on hsc70 for the associating factor Hap46, located on the same side of the ATP-binding domain. One of these (combined regions A, I, and IV) corresponds in parts to some of the contact areas on DnaK for binding of GrpE (49), as depicted in the side by side views of Fig. 4. Most of the amino acid residues exposed to the respective surfaces are different with the exception of the peptide sequence Tyr-Leu-Gly within region IV, as highlighted in Fig. 5. The second contact area on hsc70 (regions V and VI) shows a limited degree of topological overlap with DnaK on the space-filling model (Fig. 4) but no similarities within the respective polypeptide sequences (Fig. 5). As the comparison of Fig. 4 shows, Hap46 and GrpE touch hsc70 and DnaK, respectively, at somewhat different areas on subdomain II. These differences are consistent with the fact that GrpE and Hap46 have no significant homologies in sequence and hsc70 does not bind to DnaK (19), whereas GrpE is unable to interact with hsc70, just as antibiotic insect peptides bind to DnaK but not to eukaryotic hsp70 (51). Nevertheless, we expect that Hap46 binding produces a similar opening of the central cleft in the ATP-binding domain of mammalian hsp70/hsc70, probably by grasping it on either subdomain, as GrpE does. In fact, the region of position V (Fig. 4B) suggests that Hap46 partially reaches into the central cleft for binding. Recently, an alternative three-dimensional structure of the hsp70 ATP-binding domain has been identified that shows a distinct outward shift of the upper part of subdomain II (52). Binding of Hap46 to the hsp70/hsc70 molecular chaperone may then favor this more open conformation, which, however, can only be proven by a detailed analysis of crystals of the hsp70-Hap46 complex. Hap46 has been shown to enhance the nucleotide exchange reaction of hsc70 (21, 24), and in this respect it resembles GrpE. However, GrpE and Hap46 are certainly not equivalent regulators of hsp70 chaperones, as the former greatly stimulates protein refolding reactions involving DnaK in combination with DnaJ (49, 53) whereas the latter inhibits the respective activity of hsc70 (18–20, 54).

Hap46 and Hip/p48 very differently affect the nucleotide binding and chaperoning activities of hsp70s. Thus Hip/p48 was found to stabilize the ADP-bound state and to increase the

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Dissection of the ATP-binding Domain of the Chaperone hsc70 for Interaction with the Cofactor Hap46
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