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S100 proteins regulate the interaction of Hsp90 with Cyclophilin 40 and FKBP52 through their tetratricopeptide repeats

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ABSTRACT

S100 proteins are a subfamily of the EF-hand type calcium sensing proteins, the exact biological functions of which have not been clarified yet. In this work, we have identified Cyclophilin 40 (CyP40) and FKBP52 (called immunophilins) as novel targets of S100 proteins. These immunophilins contain a tetratricopeptide repeat (TPR) domain for Hsp90 binding. Using glutathione-S transferase pull-down assays and immunoprecipitation, we have demonstrated that S100A1 and S100A2 specifically interact with the TPR domains of FKBP52 and CyP40 in a Ca^{2+}-dependent manner, and lead to inhibition of the CyP40–Hsp90 and FKBP52–Hsp90 interactions. These findings have suggested that the Ca^{2+}/S100 proteins are TPR-targeting regulators of the immunophilins–Hsp90 complex formations.

Structured summary:
MINT-7710442: *FKBP52* (uniprotkb:Q02790) *physically interacts* (MI:0915) with *S100A6* (uniprotkb:P06703) by *competition binding* (MI:0405)
MINT-7710192: *Cyp40* (uniprotkb:P26882) *binds* (MI:0407) to *S100A1* (uniprotkb:P35467) by *pull down* (MI:0096)
MINT-7710412: *Cyp40* (uniprotkb:P26882) *physically interacts* (MI:0915) with *S100A2* (uniprotkb:P29034) by *competition binding* (MI:0405)
MINT-7710374: *FKBP52* (uniprotkb:Q02790) *binds* (MI:0407) to *S100A2* (uniprotkb:P29034) by *pull down* (MI:0096)
MINT-7710452: *Cyp40* (uniprotkb:P26882) *physically interacts* (MI:0914) with *S100A2* (uniprotkb:P29034) and *Hsp90* (uniprotkb:P07900) by *anti tag coimmunoprecipitation* (MI:0007)
MINT-7710387: *FKBP52* (uniprotkb:Q02790) *binds* (MI:0407) to *S100A6* (uniprotkb:P06703) by *pull down* (MI:0096)
MINT-7710279: *FKBP52* (uniprotkb:Q02790) *physically interacts* (MI:0915) with *S100A1* (uniprotkb:P35467) by *competition binding* (MI:0405)
MINT-7710224: *FKBP52* (uniprotkb:Q02790) *binds* (MI:0407) to *Hsp90* (uniprotkb:P07900) by *pull down* (MI:0096)
MINT-7710464: *Cyp40* (uniprotkb:P26882) *physically interacts* (MI:0914) with *S100A6* (uniprotkb:P06703) and *Hsp90* (uniprotkb:P07900) by *anti tag coimmunoprecipitation* (MI:0007)
MINT-7710249: *Cyp40* (uniprotkb:P26882) *binds* (MI:0407) to *Hsp90* (uniprotkb:P07900) by *pull down* (MI:0096)
MINT-7710422: *Cyp40* (uniprotkb:P26882) *physically interacts* (MI:0915) with *S100A6* (uniprotkb:P06703) by *competition binding* (MI:0405)
MINT-7710348: *Cyp40* (uniprotkb:P26882) *binds* (MI:0407) to *S100A2* (uniprotkb:P29034) by *pull down* (MI:0096)
MINT-7710208: *FKBP52* (uniprotkb:Q02790) *binds* (MI:0407) to *S100A1* (uniprotkb:P35467) by *pull down* (MI:0096)
MINT-7710265: *Cyp40* (uniprotkb:P26882) *physically interacts* (MI:0915) with *S100A1* (uniprotkb:P35467) by *competition binding* (MI:0405)

Abbreviations: CyP40, Cyclophilin 40; TPR, tetratricopeptide repeat; CaM, calmodulin; Hop, Hsp70/Hsp90-organizing protein; KLC, kinesin light chain; GST, glutathione-S transferase; PPIase, peptidyl-prolyl isomerase; CaMBD, CaM binding domain; SR, steroid receptor

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MINT-7710361: *Cyp40* (uniprotkb:P26882) *binds* (MI:0407) to *S100A6* (uniprotkb:P06703) by *pull down* (MI:0096)
MINT-7710476: *FKBP52* (uniprotkb:Q02790) *physically interacts* (MI:0914) with *S100A2* (uniprotkb:P29034) and *Hsp90* (uniprotkb:P07900) by *anti tag coimmunoprecipitation* (MI:0007)
MINT-7710316: *FKBP52* (uniprotkb:Q02790) *physically interacts* (MI:0914) with *S100A1* (uniprotkb:P35467) and *Hsp90* (uniprotkb:P07900) by *anti tag coimmunoprecipitation* (MI:0007)
MINT-7710432: *FKBP52* (uniprotkb:Q02790) *physically interacts* (MI:0915) with *S100A2* (uniprotkb:P29034) by *competition binding* (MI:0405)
MINT-7710488: *FKBP52* (uniprotkb:Q02790) *physically interacts* (MI:0914) with *S100A6* (uniprotkb:P06703) and *Hsp90* (uniprotkb:P07900) by *anti tag coimmunoprecipitation* (MI:0007)
MINT-7710329: *S100A6* (uniprotkb:P14069) *physically interacts* (MI:0914) with *FKBP52* (uniprotkb:P30416) and *Cyp40* (uniprotkb:Q08752) by *anti bait coimmunoprecipitation* (MI:0006)
MINT-7710295: *Cyp40* (uniprotkb:P26882) *physically interacts* (MI:0914) with *Hsp90* (uniprotkb:P07900) and *S100A1* (uniprotkb:P35467) by *anti tag coimmunoprecipitation* (MI:0007)

1. Introduction

S100 proteins are acidic, small molecular weight (10–12 kDa) proteins, and the members have 25–65% similarity at the amino acid level. As in the prototypical EF-hand protein calmodulin (CaM), S100 proteins act as Ca^{2+}-sensors and modulate the target proteins. S100 proteins are thought to have intracellular roles in the regulation of many cellular processes such as muscle contraction, cell motility, and growth, transcription and protein phosphorylation [1,2]. However, the precise intracellular roles of the S100 proteins are not fully understood. Identification of the S100 target proteins is essential to elucidate the biological function of the S100 proteins.

Previously, we demonstrated that S100A2 and S100A6 interacted with the tetratricopeptide repeat (TPR) domains of Hsp70/Hsp90-organizing protein (Hop), kinesin light chain (KLC) and Tom70 in a Ca^{2+}-dependent manner, led to dissociation of the Hsp90–Hop–Hsp70, KLC–JIP1 and Tom70–Hsps interactions both in vitro and in vivo [3]. TPR, degenerate 34-amino acid helix-turn-helix sequences, is a structural module that able to interact with specific partner proteins. This property enables TPR-containing proteins (~30 known so far) to work as scaffold proteins and allows them to be involved in a variety of cellular functions [4–6]. These evidences have prompted us to hypothesize that S100 proteins are Ca^{2+}-dependent regulators for the specific interactions between TPR–proteins and their partner proteins.

Cyclophilin 40 (CyP40) and FKBP52 belong to a subclass of TPR-containing immunophilins. The interactions of Hsp90 with these immunophilins through their TPR domains [7,8] are necessary for steroid hormone receptor signalling [6,9]. In this paper we have examined potential roles of the S100 proteins in the interaction of the immunophilins with Hsp90 and demonstrated that S100A1 and S100A2 regulate the CyP40–Hsp90 and FKBP52–Hsp90 interactions through their TPR domains.

2. Materials and methods

2.1. Plasmids

The plasmids for glutathione-S transferase (GST)–CyP40 and GST–FKBP52 proteins were described [10]. The truncate constructs of GST–CyP40 (amino acid residues 1–225, 185–356 and 344–370) and GST–FKBP52 (residues 1–267, 254–400 and 390–459) were amplified by PCR and subcloned into the pGEX4T2 and pGEX4T1, respectively. For mammalian cell transfections, CyP40 and FKBP52 were amplified by PCR and cloned into pME18S–HA. The plasmids for pET11a–S100s were previously reported [10]. S100s were amplified by PCR from pET11a–S100s template and subcloned into pME18S mammalian expression vector. The pET16b-human Hsp90αfor Hsp90 expression was described [3]. The sequence integrity of the all inserts was confirmed by automated sequence analysis (Applied Biosystems).

2.2. Expression and purification of recombinant proteins

All recombinant S100 proteins were prepared as described previously [10]. The expression and purification of Hsp90 was reported [3]. GST-fusion proteins were expressed in *Escherichia coli* BL21 and purified according to the manufacturer's instructions.

2.3. GST pull-down assay

The GST-fusion proteins (25 μg) and Ca^{2+}-binding proteins (25 μg) were mixed in buffer A (20 mM Tris–HCl and 0.1 M KCl, pH 7.5) with 1 mM $CaCl_2$ or EGTA. To investigate the effect of S100 proteins on the immunophilins–Hsp90 interactions, the GST-fusion proteins (20 μg), Hsp90 (20 μg) and S100 proteins (0–50 μg) were mixed simultaneously in buffer A with 1 mM $CaCl_2$. The reaction mixtures (200 μl) were incubated with 30 μl of glutathione–Sepharose. The beads were subjected to replicate washes, boiled in SDS–sample buffer and analyzed by Tricine–SDS–PAGE.

2.4. Cell culture, transfection and immunoprecipitation

Cos-7 were cultured as described previously [10] and transiently transfected using Lipofectamine (Invitrogen) according to the manufacturer's instructions. The expression plasmid pME18S–S100s (4 μg) and pME18SHA–CyP40 or pME18SHA–FKBP52 (2 μg) were introduced into Cos-7 and cultured for 2 days. HA–CyP40 or HA–FKBP52 was immunoprecipitated from cell lysates with anti-HA antibody–agarose (Sigma) in the presence of 1 mM $CaCl_2$ or EGTA. Antibodies used for Western blottings were: anti-Hsp90 AC88; anti-FKBP59 KN382/EC1 (Stressgen); anti-Cyclophilin D H-185 (Santa Cruz); anti-S100A1 (Novus Biologicals); anti-S100A2 (Abnova); anti-S100A6 (Proteintech Group, Inc).

3. Results and discussion

3.1. Interaction of FKBP52 and CyP40 with the members of the S100 protein family

Previously, we demonstrated that S100A2 and S100A6 interacted with TPR-containing proteins (Hop, Tom 70 and KLC) in a Ca^{2+}-dependent manner [3]. Therefore, we hypothesized that Ca^{2+} regulates the TPR protein–partner protein interactions through S100 proteins. To establish this hypothesis, we examined

the interaction of S100 proteins with the TPR-containing immunophilins, CyP40 and FKBP52.

To study the interaction of S100 proteins with FKBP52 and CyP40, we performed GST-pull down assay using GST–CyP40 and GST–FKBP52 (Fig. 1A and B) in the presence of 1 mM $CaCl_2$ or EGTA. The bound proteins were analyzed by Tricine–SDS–PAGE. S100A2 and S100A6, but not CaM or the other S100 proteins, strongly bound to GST–CyP40 or GST–FKBP52. S100A1 was also bound weakly to GST–CyP40 or GST–FKBP52 in the presence of Ca^{2+}. These results show that S100A1, S100A2 and S100A6 bind to both CyP40 and FKBP52 in a Ca^{2+}-dependent manner. Despite the presence of the putative CaM binding domain (CaMBD) in CyP40 and FKBP52, an interaction with CaM was not observed (Fig. 1A and B, Ref. [10]).

3.2. The interaction sites for S100A1, S100A2 and S100A6 are located in the immunophilin TPR domains

The domain structures of CyP40 and FKBP52 are shown in Fig. 2A and C, respectively. CyP40 and FKBP52 exhibit sequence homology and similar structural organization [11]. These immunophilins consist of peptidyl-prolyl isomerase (PPIase) domain, TPR domain, and CaMBD. CaM and S100 proteins shared conserved structural features and a common mechanism of the interaction with target proteins [2]. Previous studies have indicated that the binding properties of CaM and S100 proteins often overlap [12–15]. Contrary to the above evidence, we have found that S100A2 and S100A6 interact with the TPR domains of Hop, KLC and Tom 70 [3]. These reports prompted us to identify the S100 binding domains of FKBP52 and CyP40.

To determine the S100 binding site of CyP40 and FKBP52, three truncation mutants (PPIase, TPR and CaMBD) of CyP40 and FKBP52 were prepared and assessed for the interaction with the S100 proteins. S100A1, S100A2 and S100A6 bound to TPR domain of CyP40, but not to PPIase domain and CaMBD (Fig. 2B). Similarly, these S100 proteins specifically bound to the TPR domain of FKBP52 (Fig. 2D).

3.3. The effects of S100A1, S100A2 and S100A6 on the CyP40–Hsp90 and FKBP52–Hsp90 interactions in vitro

Both of CyP40 and FKBP52 possess TPR domains that mediate their association with the C-terminal EEVD residues of Hsp90 through electrostatic and hydrophobic interactions [16,17]. We showed that S100A1, S100A2 and S100A6 bound to the identical structural elements (i.e., TPR domain) within CyP40 and FKBP52.

Therefore, we next tested the influence of the S100 proteins on the FKBP52–Hsp90 and CyP40–Hsp90 interactions by a GST-pull down approach. To estimate the displacement effect of the S100 proteins, the various amounts of the S100 proteins were used (0, 20 and 50 μg). Quantitative analyses of all gels were performed using the Quantity One software (BioRad) (Fig. 3A). S100A1,

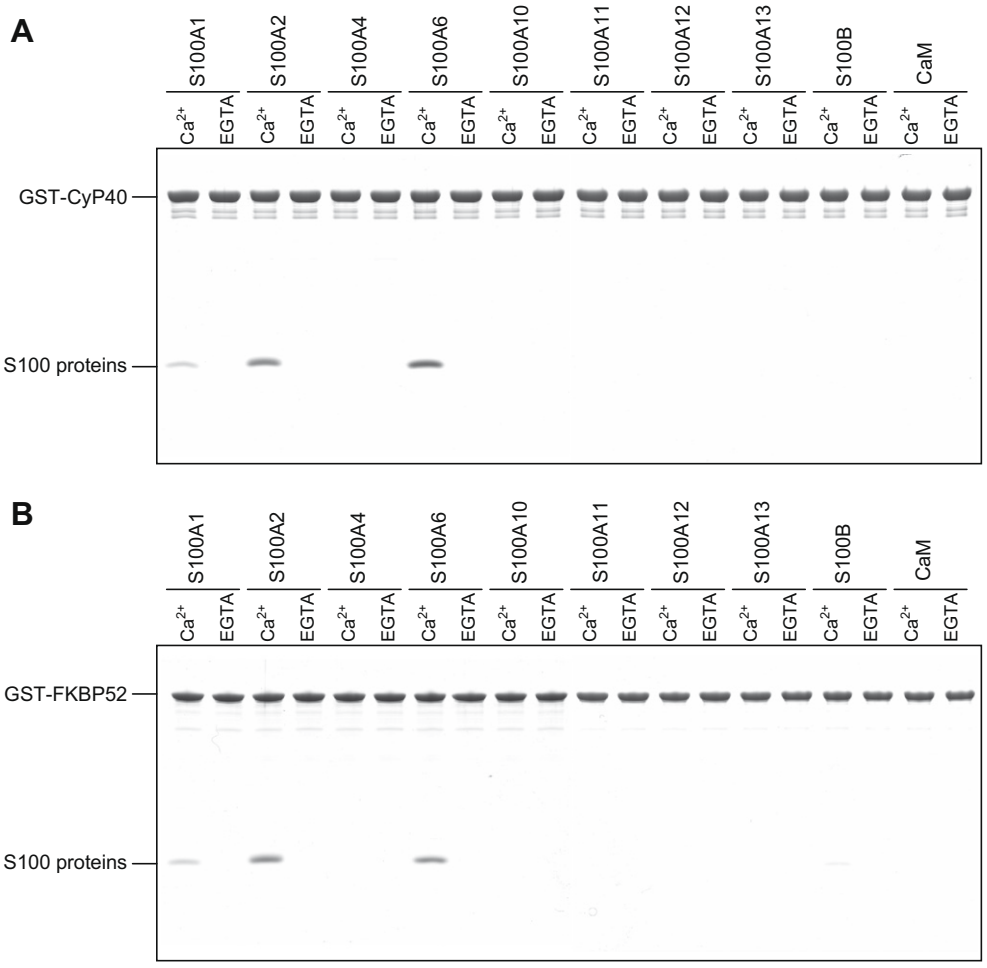

Fig. 1. Binding properties of S100 proteins to CyP40 and FKBP52. Ca^{2+}-binding proteins and GST–CyP40 (A) or GST–FKBP52 (B) were incubated with glutathione–Sepharose in the presence of 1 mM $CaCl_2$ or EGTA. After the beads were washed, the eluted samples were resolved on SDS–PAGE and visualized by Coomassie Brilliant Blue.

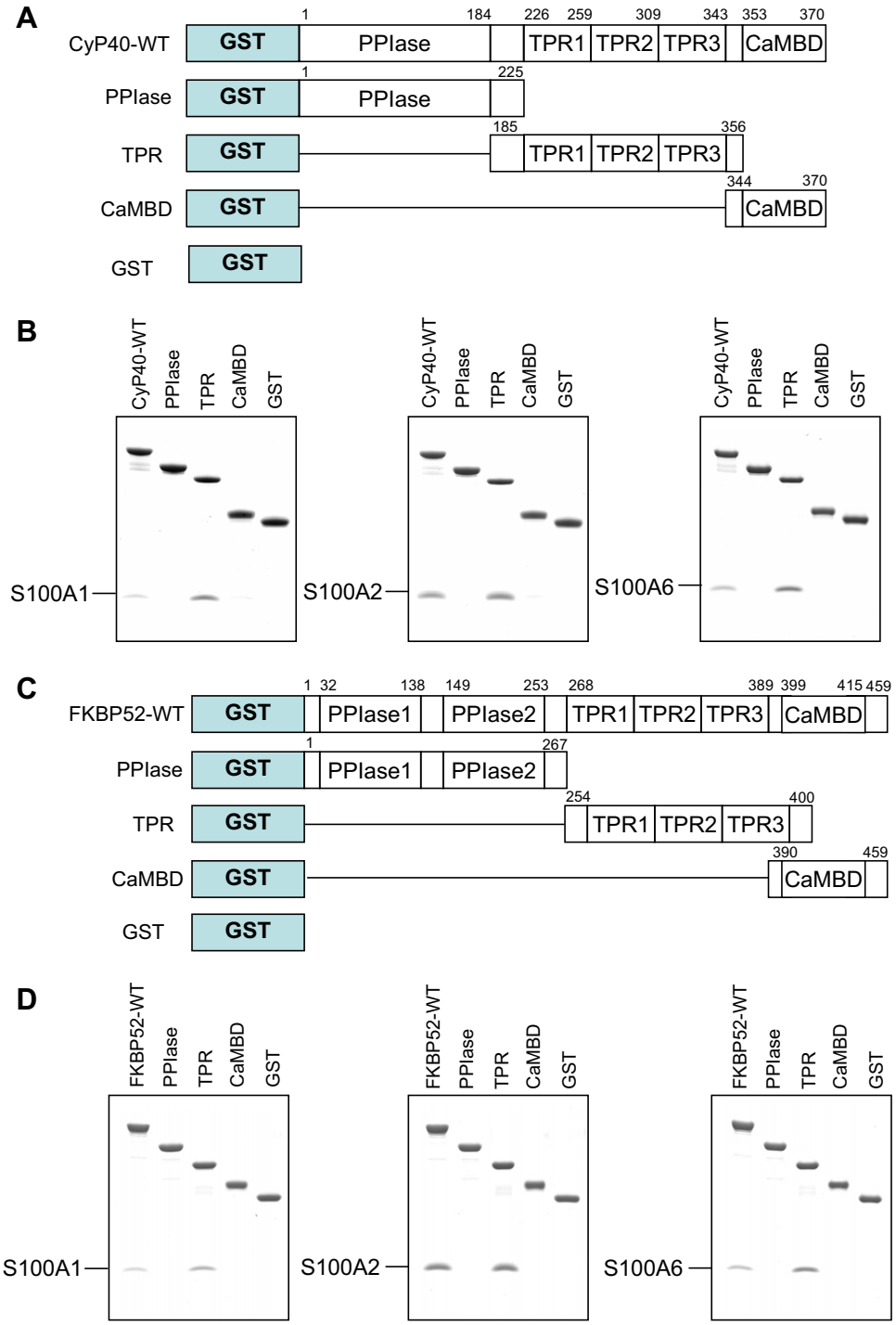

Fig. 2. S100 proteins specifically interact with the TPR domains of CyP40 or FKBP52. (A) The schematic diagrams of CyP40 and its truncation construct. The numbering refers to amino acid positions in CyP40. (B) GST–CyP40, its truncation constructs and GST alone (control) were assayed for S100 proteins binding in the presence of 1 mM $CaCl_2$ as described in Fig. 1. (C) The schematic diagrams of FKBP52 and its truncation construct. The numbering refers to amino acid positions in FKBP52. (D) GST–FKBP52, its truncation constructs and GST alone (control) were assayed for S100 proteins binding in the presence of 1 mM $CaCl_2$.

S100A2 and S100A6 effectively inhibited the Hsp90 binding to GST–CyP40 in a dose-dependent fashion. S100B did not stably bind to GST–CyP40 (Fig. 1A) and was not an effective competitor for the Hsp90 binding. S100A1 and S100A2 effectively dissociate the FKBP52–Hsp90 interaction. However, S100A6 mildly affected the FKBP52–Hsp90 interaction. S100B did not bind to FKBP52 (Fig. 1B), and did not affect the FKBP52–Hsp90 interaction either (Fig. 3B). These results suggest that S100A1 and S100A2 bind to the immunophilins, and lead to inhibition of the immunophilins–Hsp90 interaction, in vitro.

3.4. Interaction of S100 proteins with the immunophilins in intact cells

Cos-7 cells were doubly transfected with the plasmid expressing HA–CyP40 (A) or HA–FKBP52 (B) and the S100 proteins. To clarify whether the S100 proteins bind to the immunophilins and

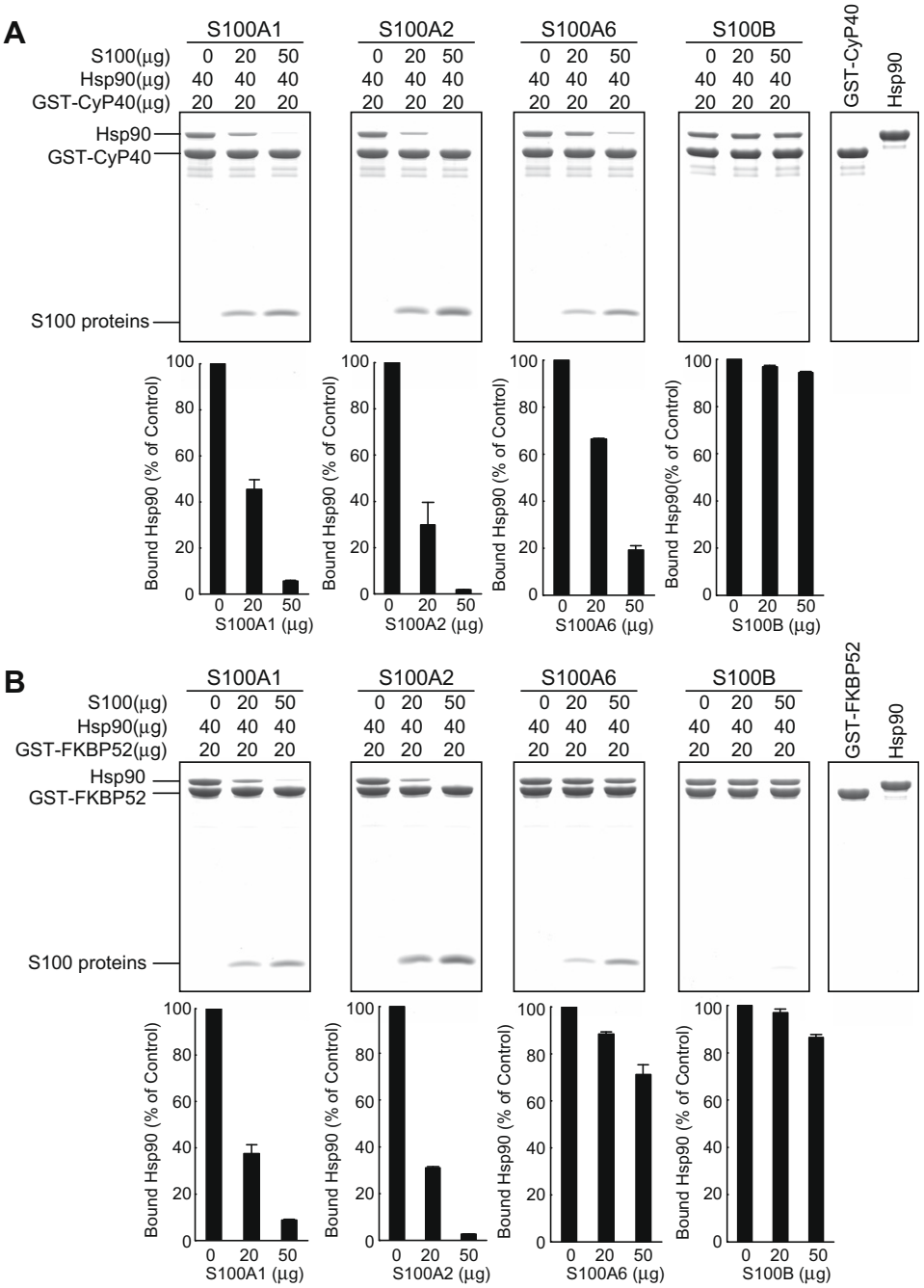

Fig. 3. Effects of the S100 proteins on the CyP40–Hsp90 and FKBP52–Hsp90 interactions in vitro. A and B (upper), GST–CyP40 (A) or GST–FKBP52 (B), Hsp90 and S100 proteins were mixed with glutathione–Sepharose as described in the Section 2. The protein amounts of each reaction are indicated on the top of the panels. Authentic GST–CyP40, GST–FKBP52 and Hsp90 (2.5 μg) were shown on the right lane. A and B (lower), The Coomassie-stained gels were scanned, and arbitrary densitometric values were obtained for Hsp90. The binding level of Hsp90 to the immunophilins in the absence of the S100 proteins was designated as 100%, and the subsequent levels of Hsp90 were measured as relative amounts. The *error bars* indicate the S.E. with $n = 3$.

lead to the regulation of the immunophilins–Hsp90 interaction in intact cells, the immunoprecipitates with the anti-HA antibody were analyzed by Western-blotting (upper, A and B). The results of densitometry and statistical analyses were shown in the lower panels. When HA–CyP40 and the S100 proteins were doubly transfected, HA–CyP40 was co-precipitated with anti-HA antibody in the presence or absence Ca^{2+} (Fig. 4A, *top panel*). The overexpressed-S100A1, S100A2 and S100A6 bound to HA–CyP40 in the presence of Ca^{2+}, no interaction was observed without Ca^{2+} (Fig. 4A, *low panel*). Inversely, the amount of Hsp90 bound to HA–CyP40 was decreased in cells co-expressing S100A1 or S100A2. Overexpression of S100A6 did not influence the amount of co-precipitated Hsp90 with HA–CyP40 (Fig. 4A, *middle panel*).

In the doubly transfected cells with HA–FKBP52 and the S100 proteins, S100A1 and S100A2 were co-immunoprecipitated with HA–FKBP52, and the amount of Hsp90 bound to HA–FKBP52 was decreased. S100A6 did not affect the amount of Hsp90 bound to HA–FKBP52, although the protein co-precipitated with HA–FKBP52 in the presence of Ca^{2+} (Fig. 4B, *middle panel* and *low panel*). These data suggest that S100A1 and S100A2 interact with the immuno-

philins, and lead to dissociation the immunophilins–Hsp90 complex in a Ca^{2+} dependent manner. S100A6 physically interact with both of the immunophilins in a Ca^{2+} dependent manner, however, this interaction does not regulate the immunophilins–Hsp90 interaction. To further confirm the in vivo interaction of S100 proteins with the immunophilins, we carried out co-immunoprecipitation assays using anti-S100A6 antibody. S100A6, but not S100A1 and S100A2, is enriched in Cos-7 cells [3]. In the presence of Ca^{2+}, endogenous S100A6 co-precipitated with endogenous CyP40 and FKBP52 (Fig. 4C). These results suggest that S100A6 interacts with the immunophilins in intact cells in a Ca^{2+}-dependent manner.

To clarify the cellular function of the S100-dependent Ca^{2+}-signalling pathway, identification of the S100 target proteins and analyses of biological actions of the target proteins are essential. In this paper, we have identified CyP40 and FKBP52 as novel targets of S100A1 and S100A2. In vitro and in vivo, we have revealed that these S100 proteins inhibit the CyP40–Hsp90 and FKBP52–Hsp90 interactions in a Ca^{2+}-dependent manner. It is well known that the interactions of CyP40 and FKBP52 with Hsp90 are necessary for the cytoplasmic-nuclear movement of steroid receptor (SR) along the microtubule network [18]. CyP40 and FKBP52 link between the Hsp90–SR complexes and the dynein–dynactin movement machinery through their TPR and PPIase domains [19,20].

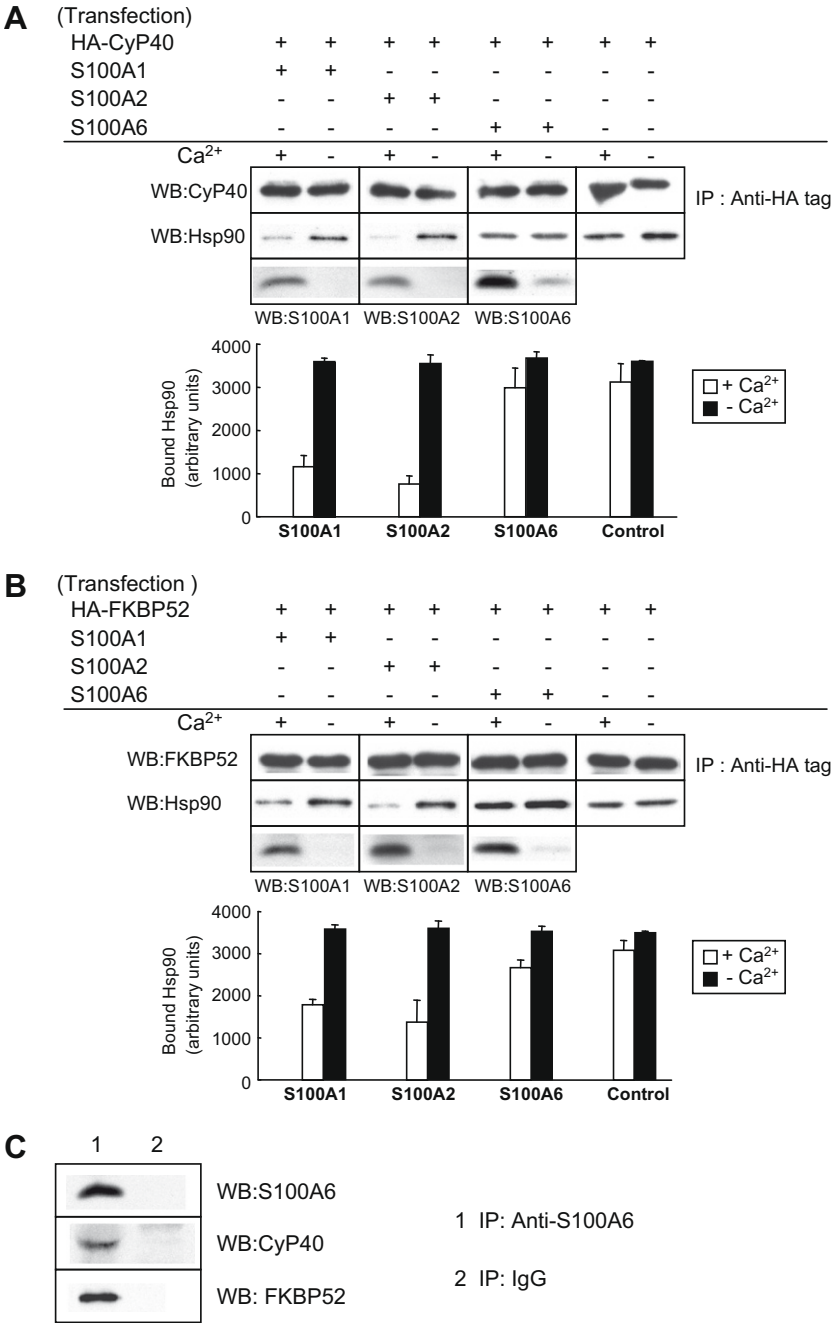

Fig. 4. The S100 proteins inhibit CyP40–Hsp90 and FKBP52–Hsp90 interactions in cultured cells. (A and B, *upper*) Cos-7 cells were doubly transfected with the S100 proteins and HA–CyP40 (A) or HA–FKBP52 (B). The transfected components of each dish are indicated on the top panels. Cell lysates were immunoprecipitated with anti-HA antibody–agarose in the presence of $CaCl_2$ (+) or EGTA (−). The HA–CyP40 or HA–FKBP52 interacting proteins were analyzed by Western blotting (WB). (A and B, *lower*) arbitrary densitometry units were plotted to designate the amount of Hsp90 bind to the immunophilins. The *error bars* indicate the S.E. with $n = 3$. (C) association of endogenous S100A6 with endogenous immunophilins in Cos-7 cells. Cell lysates were subjected to immunoprecipitation with either mouse antibodies to S100A6 or control mouse immunogrobulin (IgG) in the presence of Ca^{2+}. The precipitates were analyzed by Western Blotting.

Our data may suggest the possibility that some S100 proteins can confer Ca^{2+} sensitivity on the SR–Hsp90 heterocomplex retrograde movement. In conclusion, we have focused on the TPR-containing immunophilins CyP40 and FKBP52, and confirmed that Ca^{2+}/S100 proteins inhibit the CyP40–Hsp90 and FKBP52–Hsp90 interactions through their TPR domains. These findings support our hypothesis that Ca^{2+}/S100 proteins regulate the interactions between TPR–proteins and their target proteins.

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