FEBS Letters 584 (2010) 3269–3274

FEBS Letters

journal homepage: www.FEBSLetters.org

S100 proteins interact with the N-terminal domain of MDM2

Jan van Dieck [1], Jenifer K. Lum [1], Daniel P. Teufel, Alan R. Fersht *

MRC Centre for Protein Engineering, Hills Road, Cambridge CB2 0QH, UK

ARTICLE INFO

Article history:
Received 16 April 2010
Revised 1 June 2010
Accepted 14 June 2010
Available online 19 June 2010

Edited by Gianni Cesareni

Keywords:
S100
p53
MDM2
Ternary complex
Protein–protein interaction

ABSTRACT

S100 proteins interact with the transactivation domain and the C-terminus of p53. Further, S100B has been shown to interact with MDM2, a central negative regulator of p53. Here, we show that S100B bound directly to the folded N-terminal domain of MDM2 (residues 2-125) by size exclusion chromatography and surface plasmon resonance experiments. This interaction with MDM2 (2-125) is a general feature of S100 proteins; S100A1, S100A2, S100A4 and S100A6 also interact with MDM2 (2-125). These interactions with S100 proteins do not result in a ternary complex with MDM2 (2-125) and p53. Instead, we observe the ability of a subset of S100 proteins to disrupt the extent of MDM2-mediated p53 ubiquitylation in vitro.

Structured summary:
MINT-7905256: *MDM2* (uniprotkb:Q00987) *binds* (MI:0407) to *s100A6* (uniprotkb:P06703) by *surface plasmon resonance* (MI:0107)
MINT-7905063: *MDM2* (uniprotkb:Q00987) and *s100A1* (uniprotkb:P23297) *bind* (MI:0407) by *molecular sieving* (MI:0071)
MINT-7905376: *s100A4* (uniprotkb:P26447) and *MDM2* (uniprotkb:Q00987) *physically interact* (MI:0915) by *competition binding* (MI:0405)
MINT-7905130: *s100A6* (uniprotkb:P06703) and *MDM2* (uniprotkb:Q00987) *bind* (MI:0407) by *molecular sieving* (MI:0071)
MINT-7905207: *s100A6* (uniprotkb:P06703) and *p53* (uniprotkb:P04637) *bind* (MI:0407) by *molecular sieving* (MI:0071)
MINT-7905043: *s100B* (uniprotkb:P04271) and *MDM2* (uniprotkb:Q00987) *bind* (MI:0407) by *molecular sieving* (MI:0071)
MINT-7905196: *p53* (uniprotkb:P04637) and *s100A4* (uniprotkb:P26447) *bind* (MI:0407) by *molecular sieving* (MI:0071)
MINT-7905358: *p53* (uniprotkb:P04637) and *s100A4* (uniprotkb:P26447) *physically interact* (MI:0915) by *fluorescence polarization spectroscopy* (MI:0053)
MINT-7905220: *MDM2* (uniprotkb:Q00987) *binds* (MI:0407) to *s100B* (uniprotkb:P04271) by *surface plasmon resonance* (MI:0107)
MINT-7905104: *s100A4* (uniprotkb:P26447) and *MDM2* (uniprotkb:Q00987) *bind* (MI:0407) by *molecular sieving* (MI:0071)
MINT-7905229: *MDM2* (uniprotkb:Q00987) *binds* (MI:0407) to *s100A1* (uniprotkb:P23297) by *surface plasmon resonance* (MI:0107)
MINT-7905317, MINT-7905162: *s100B* (uniprotkb:P04271) and *p53* (uniprotkb:P04637) *bind* (MI:0407) by *molecular sieving* (MI:0071)
MINT-7905238: *MDM2* (uniprotkb:Q00987) *binds* (MI:0407) to *s100A2* (uniprotkb:P29034) by *surface plasmon resonance* (MI:0107)
MINT-7905174, MINT-7905308: *s100A1* (uniprotkb:P23297) and *p53* (uniprotkb:P04637) *bind* (MI:0407) by *molecular sieving* (MI:0071)
MINT-7905247: *MDM2* (uniprotkb:Q00987) *binds* (MI:0407) to *s100A4* (uniprotkb:P26447) by *surface plasmon resonance* (MI:0107)

Abbreviations: SEC–MALS, size exclusion chromatography and multi-angle light scattering; PIS, physiological ionic strength; M_W, weight-average molar mass; K_d, dissociation constant; t_r, retention time

* Corresponding author. Fax: +44 1223 402 140.
E-mail address: arf25@cam.ac.uk (A.R. Fersht).

[1] These authors contributed equally to the work.

doi:10.1016/j.febslet.2010.06.024

MINT-7905090: *s100A2* (uniprotkb:P29034) and *MDM2* (uniprotkb:Q00987) *bind* (MI:0407) by *molecular sieving* (MI:0071)
MINT-7905142, MINT-7905326: *MDM2* (uniprotkb:Q00987) and *p53* (uniprotkb:P04637) *bind* (MI:0407) by *molecular sieving* (MI:0071)
MINT-7905185, MINT-7905347: *s100A2* (uniprotkb:P29034) and *p53* (uniprotkb:P04637) *bind* (MI:0407) by *molecular sieving* (MI:0071)

1. Introduction

S100 proteins are small acidic calcium-binding proteins. The protein family consists of more than 25 members with intracellular and extracellular functions [1]. The proteins usually form dimers. Each monomer of S100 is composed of two EF-hand, Ca^{2+}-binding domains which are connected by a central hinge region. The high-affinity binding to calcium of the C-terminal classical EF-hand induces a conformational change in the S100 proteins to expose a hydrophobic binding site for target proteins. More than 50 target proteins have been identified to interact with various S100 proteins, including transcription factors, metabolic enzymes, kinases, annexins or contractile proteins [2]. In general, most of these interactions are dependent on calcium signalling, but a subset of interactions is independent of Ca^{2+} activation [3].

S100 proteins are normally expressed in a tissue specific manner and their up- or down-regulation has been associated with numerous diseases including several types of cancer [4]. For example, elevated serum levels of S100B have been found in melanoma patients and have been associated with metastasis and a poor therapy prognosis [4,5]. Animal studies showed that S100A4 is involved in the development of metastasis [6,7] and overexpression of S100A4 has been detected in various types of cancer, including breast, pancreatic, colorectal, ovarian, prostate and lung cancer. However, despite inferences to an important role in cancer development, the mode of action of S100 proteins still remains unclear.

Since there is an obvious link between cancer and S100 proteins, the interaction of S100 family members with target proteins also involved in cancer may help to understand the mode of action of S100 proteins and their relevance in tumour development. Among other targets, S100A1, S100A2, S100A4, S100A6 and S100B interact with p53, one of the most important tumour suppressors of the cell [8,9]. The interaction has been mapped to the p53 (1-57) transactivation domain and the p53 (293-393) C-terminus, which includes the tetramerisation domain [8–11]. However, the effect of S100 proteins on p53 activity is not fully understood. On the one hand, there are studies showing that S100B contributes to nuclear accumulation and activation of p53 [12,13], on the other hand, S100B is reported to inhibit p53 activity in transactivation assays [14]. Further, S100A2 and S100A6 stimulate p53 activity in transactivation assays [15,16].

One of the main negative regulators of p53 is the ubiquitin E3 ligase MDM2, which interacts with the N-terminal transactivation domain of p53 and covalently links the proteasomal degradation signal protein, ubiquitin, to lysine residues of p53 [17]. A GST-pull down experiment shows that S100B interacts with MDM2 [18]. Isothermal titration calorimetry studies also show that S100B interacts with a peptide derived from the N-terminal domain of MDM2. Yet it remains unclear if S100 proteins can also bind in the context of the full N-terminal domain of MDM2 [18].

Here, we investigated whether S100B and other S100 proteins have the ability to interact with the full N-terminal domain of MDM2. We found that S100A1, S100A2, S100A4, S100A6 and S100B interacted with MDM2 (2-125) in size exclusion chromatography and multi-angle light scattering (SEC–MALS) and surface plasmon resonance experiments but did not form a ternary complex with MDM2 (2-125) and p53 (1-93). A ternary complex was also absent between the tetramerization domain of p53, MDM2 and S100 proteins, S100B, S100A1, S100A2 and S100A4. When evaluated in ubiquitylation assays, S100A2, S100A4 and S100A6 showed moderate levels of inhibition of MDM2 activity, providing a possible mechanism for the stimulating effect of these S100 proteins on p53 in vivo.

2. Methods

2.1. Plasmids, protein expression and purification

Plasmids used for the expression of untagged recombinant human S100A1, S100A2, S100A6 and S100B were as described [8,9]. The proteins were purified by ammonium sulphate precipitation, hydrophobic interaction chromatography and gel filtration. S100A4 was expressed and purified via a His_6-Tag and metal affinity chromatography and gel filtration as described [9]. Human MDM2 (2-125) was expressed as a GST-fusion protein and purified as described [19]. The expression and purification of human p53 (1-93) and p53 (1-393) has also been described elsewhere [20,21]. p53 (313-393) L344P was constructed by PCR and cloned into a pRSET vector. The protein was expressed as described [9].

2.2. Analytical size exclusion chromatography

Analytical gel filtrations were performed using a GE Healthcare Superdex™ 75 analytical gel filtration column as described [10]. Hundred microliters of 25–100 μM proteins in physiological ionic strength-buffer [9] (PIS-buffer) were injected. Multi-angle light scattering (MALS) was detected on-line using a DAWN HELEOS™ (Wyatt Technology) and an Optilab™ rEX (Wyatt Technology). The data were analysed using ASTRA™ software.

2.3. Surface plasmon resonance

Steady-state equilibrium experiments were performed with a Biacore™ 2000 (GE Healthcare). A streptavidin-coated sensor Chip SA (Ge Healthcare) was loaded with 100 ng biotinylated MDM2 (2-125). The chip was then tested with different concentrations of S100 proteins, 20 μl injections at a flow rate of 5 μl/min. The binding experiments were performed in PIS-buffer and the bound S100 protein was washed off with 20 mM Tris pH 7.4, 200 mM NaCl and 1 mM EDTA. The binding was quantified using a two-site binding model as described [9].

2.4. Biotinylation of MDM2 (2-125), fluorescence anisotropy titrations and ubiquitylation assay

See Supplementary data.

3. Results

3.1. S100 proteins interact with the N-terminal p53-binding domain of MDM2

Previous studies indicated an interaction between S100B and a peptide derived from the N-terminal domain of MDM2 [18]. Here we investigated, whether S100B as well as other S100 proteins also interact with the full N-terminal domain of MDM2. We initially investigated the interaction by SEC–MALS, which has been shown to be a powerful tool to study protein–protein interactions without the use of a label or immobilization of one of the binding partners. The elution profiles of S100 proteins together with MDM2 (2-125) displayed peaks significantly different in retention time (t_r) and weight-average molar mass (M_w) from the individual components alone, indicating the presence of protein–protein interactions between S100 proteins and MDM2 (Fig. 1). The M_w of ~31–35 kDa across the peaks corresponded to a complex of one dimer of S100 (~20 kDa) and a monomer of MDM2 (2-125) (~14.3 kDa) for S100A1, S100A2, S100A4 and S100A6 (Table 1). For S100B, a small shift in t_r was observed corresponding to a M_w smaller than calculated for the theoretical complex of a dimer of S100B and a monomer MDM2 (2-125) (Table 1, Fig. 1B), indicating that the interaction between S100B and MDM2 (2-125) was weaker than that with the other S100 proteins (Fig. 1C). As a control, we showed that MDM2 (2-125) interacts with p53 (1-93) in SEC–MALS, indi-

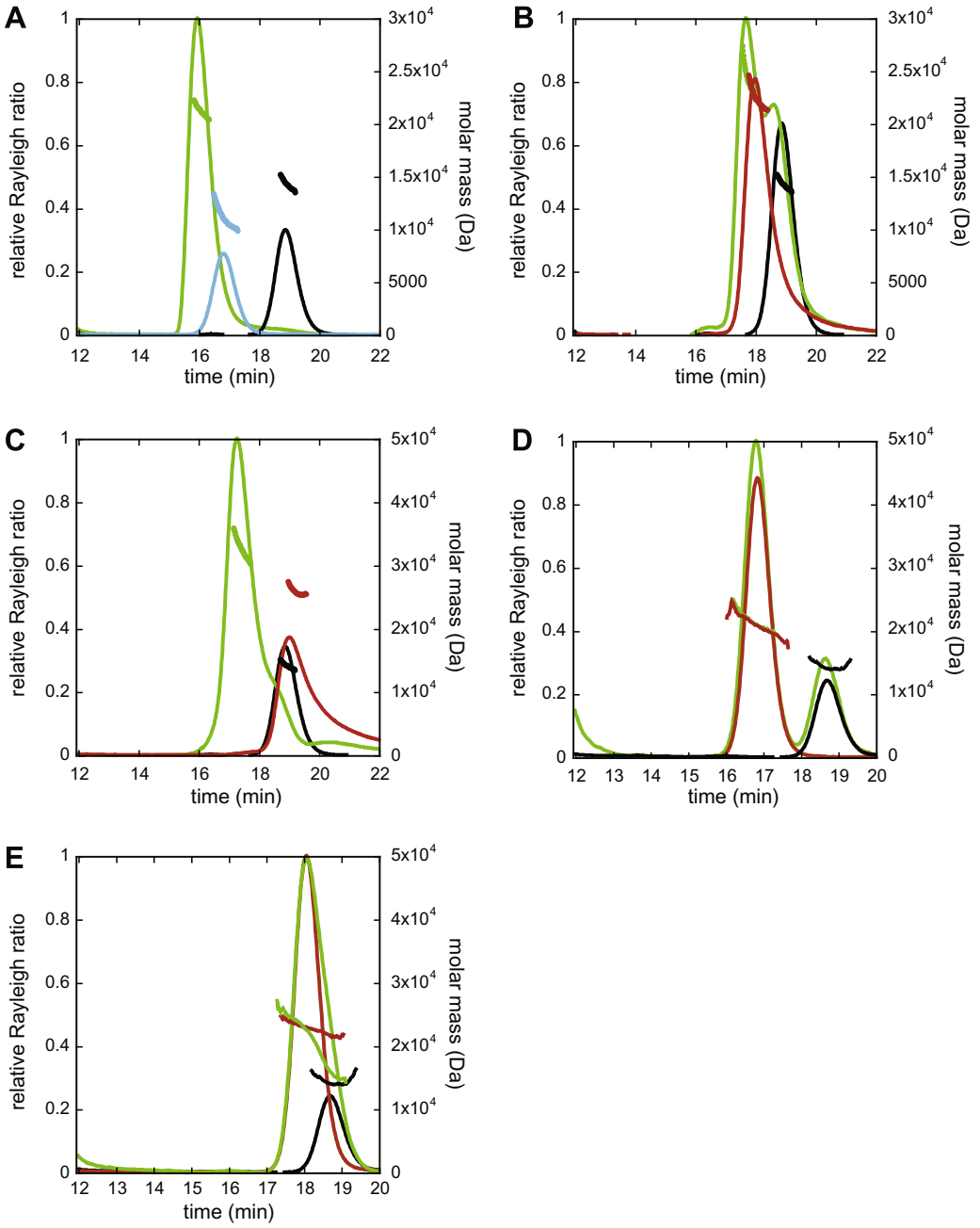

Fig. 1. S100 proteins interact with MDM2 (2-125) in SEC–MALS. Hundred microliters of 25 μM MDM2 (black), 25 μM p53 (1-93) (blue) and 50 μM S100 proteins (red) were injected. When a mixture of proteins was injected (green), protein–protein interactions resulted in shifts in t_r and M_w (horizontal line across the peak) from the individual components. The experiments were performed in PIS-buffer (A–C) or a calcium-free buffer (D and E). (A) MDM2 (2-125) + p53 (1-93), (B) S100B + MDM2 (2-125), (C) S100A4 + MDM2 (2-125), similar elution profiles were obtained with S100A1, S100A2 and S100A6, (D) S100B + MDM2 (2-125), (E) S100A4 + MDM2 (2-125).

Table 1
M_w of the dominant peak in the elution profiles of S100 proteins in complex with MDM2 as determined by MALS.

	M_w (kDa)					
	–	S100A1	S100A2	S100A4	S100A6	S100B
–		21.2 ± 1.0	22.8 ± 0.4	24.8 ± 0.1	20.5 ± 0.8	21.8 ± 0.7
MDM2 (2-125)	13.8 ± 0.1	31.0 ± 3.0	34.8 ± 1.0	33.0 ± 1.5	34.3 ± 4.0	24.0 ± 0.3

cating that MDM2 (2-125) is in its native conformation (Fig. 1A). Further, the interaction of MDM2 (2-125) and S100 proteins was dependent on calcium and no interaction could be detected in a calcium-free buffer (Fig. 1D and 1E).

The interaction between S100 proteins and MDM2 (2-125) was further analysed by surface plasmon resonance steady-state experiments with immobilized biotinylated MDM2 (2-125). The binding data fitted best to a two-site binding model with a high-affinity binding site with dissociation constants (K_d) in the low μM range and a low-affinity binding site with dissociation constants >100 μM (Table 2 and Fig. 2).

3.2. Interplay between p53, MDM2 and S100

S100 proteins not only bind to MDM2, but also interact with the N-terminal transactivation domain and the C-terminus of p53 [10,11]. Here, we investigated whether S100, p53 and MDM2 can form a ternary complex. The formation of such a ternary complex with MDM2 and p53 has been suggested to be of physiological relevance in the case of the histone acetyltransferase p300 [22]. We initially studied the complex formation of p53 (1-93) and MDM2 (2-125) in the presence of S100 proteins by SEC–MALS, comparing the elution profiles of the complexes S100/p53 (1-93), S100/MDM2 (2-125) and MDM2 (2-125)/p53 (1-93) with the elution profiles of a mixture of S100, MDM2 and p53 (1-93). The t_r and the M_w across the peaks did not correspond to a tight ternary complex of S100 proteins with p53 (1-93) and MDM2 (2-125), possessing M_w values much lower than theoretical mass of ~45 kDa. The retention times were more similar to the ones observed for the isolated complexes, indicating that no ternary complex was formed for any of the S100 proteins tested (Fig. 3). A potential ternary complex was also evaluated with the C-terminus of p53 (313-393). The tetramerisation domain of p53, especially in its monomeric form, has previously been described as a binding site for S100B, S100A1 and S100A2 proteins [9]. To evaluate if MDM2 (2-125) and S100 proteins form a ternary complex with p53 (313-393), the elution profiles of mixtures of S100 proteins, MDM2 (2-125) and a monomeric mutant of p53, p53 (313-393) L344P were compared with the complexes of p53 (313-393) L344P/MDM2 (2-125), S100/p53 (313-393) L344P and S100/MDM2 (2-125) (Fig. 4 and Supplementary Figs. 1 and 2). The t_r and M_w values were similar to the isolated complexes, indicating no ternary complex formation between MDM2 (2-125), p53 (313-393) L344P and S100 proteins S100B, S100A1 and S100A2. Interestingly, according to the elution profiles of the complexes, S100B formed a complex with p53 (313-393) L344P in the presence of MDM2 (2-125) whereas S100A1 and S100A2 formed a complex with MDM2 (2-125) in the presence of p53 (313-393) L344P.

We also studied the interplay between S100A4, MDM2 (2-125) and the C-terminus of p53 by fluorescence anisotropy, using the fluorescein-labelled monomeric mutant L344P of the tetramerisation domain p53 (325-355) L344P [9]. When a complex of S100A4 and p53 (325-355) L344P peptide was titrated with MDM2 (2-125) a decrease in anisotropy was observed, indicating competition between MDM2 (2-125) and the p53-tetramerization domain for the interaction with S100A4 and no ternary complex formation (Supplementary Fig. 3).

3.3. S100 proteins inhibit MDM2-mediated ubiquitylation of p53

Given that S100 proteins make direct contacts with p53 and MDM2, we examined the effect of S100 proteins on MDM2 ubiquitylation of p53 in vitro. S100 proteins had a moderate effect on p53 oligo-ubiquitylation, with the largest inhibition of the extent of ubiquitylation observed with S100A4 and S100A6 (Supplementary Fig. 4 and Supplementary Table 1). A mild effect on ubiquitylation was observed for S100A2. No changes in the extent of ubiquitylation were observed for S100B and S100A1. Inhibition of ubiquitylation was also calcium dependent (data not shown).

4. Discussion

The results presented here show that S100B interacts directly with the p53-binding domain of MDM2 (2-125) in a calcium dependent manner. Moreover, S100A1, S100A2, S100A4 and S100A6 also interact with MDM2 (2-125), making the binding to

Table 2
Affinity of S100 proteins in a two-site binding model to biotinylated MDM2 (2-125) in surface plasmon resonance.

	K_d1 (μM)	K_d2 (μM)
S100A1	3.8 ± 0.4	129 ± 16
S100A2	2.2 ± 0.4	>200
S100A4	2.5 ± 0.6	>200
S100A6	6.6 ± 0.7	>200
S100B	5.0 ± 1.6	240 ± 62

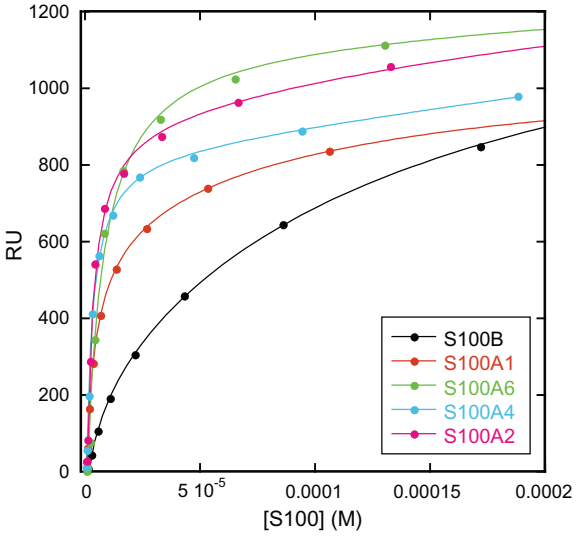

Fig. 2. S100 proteins interact with biotinylated MDM2 (2-125) in surface plasmon resonance steady-state experiments. Immobilized biotinylated MDM2 (2-125) was probed with S100A1 (orange) S100A2 (red) S100A4 (blue), S100A6 (green) and S100B (black) at different concentrations and the resulting change in response units were fitted to a two-site binding model. The experiments were carried out in PIS-buffer.

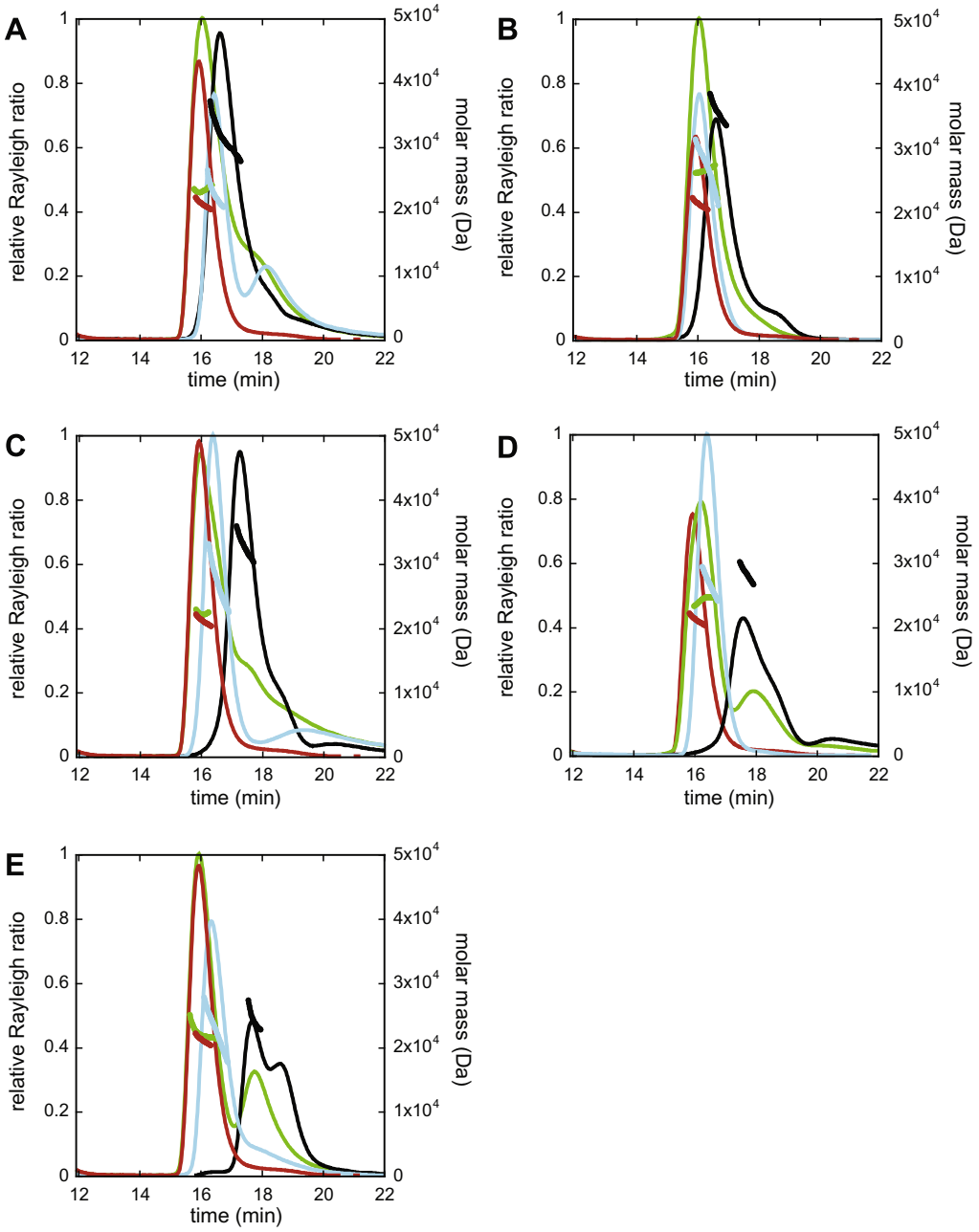

Fig. 3. S100 proteins, p53 (1-93) and MDM2 (2-125) do not form a ternary complex in SEC–MALS. Hundred microliters of 50 μM S100 protein in the presence or absence of 25 μM MDM2 (2-125) and 25 μM p53 (1-93) in PIS were injected. The formation of a ternary complex was judged by differences in t_r and M_w in the elution profile of a mixture of S100/MDM2 (2-125)/p53 (1-93) (green) and the elution profiles of the protein complexes of S100/MDM2 (2-125) (black), S100/p53 (1-93) (blue) and MDM2 (2-125)/p53 (1-93) (red). (A) S100A1, (B) S100A2, (C) S100A4, (D) S100A6, (E) S100B.

MDM2 a general feature of S100 proteins. Additional structural studies will be necessary to evaluate if the interaction is accompanied by a conformational change within MDM2 (2-125) that liberates the hypothesized target site (residues 25–43) within MDM2 required for S100 protein binding.

It is striking that we found here that S100 proteins interact with MDM2 (2-125) since we have previously shown by various methods that S100 proteins also interact with the p53 transactivation domain, which is the binding partner of MDM2 (2-125) [10,11]. It would be interesting to perform structural studies of the complexes between S100 proteins, MDM2 (2-125) and the transactivation and tetramerization domains of p53 to compare binding modes of the two substrates for S100 proteins. As these proteins do not form a ternary complex, it is likely that S100 proteins have the ability to interfere with the interaction between MDM2 and p53.

The potential relevance of these interactions is supported by the observed inhibition of the extent of MDM2 ubiquitylation by S100A2, S100A4 and S100A6 in vitro. Given that interactions exist between multiple domains of p53, MDM2 and S100 proteins, several sites may be simultaneously targeted during inhibition of MDM2 function. Interestingly, the inhibition profile correlates well with the binding affinities of S100 proteins for the p53 N-terminus, suggesting that the interaction with p53 dominates the network of interactions between these partners, as inferred by the observed binding affinities [10]. The influence of these S100 protein interac-

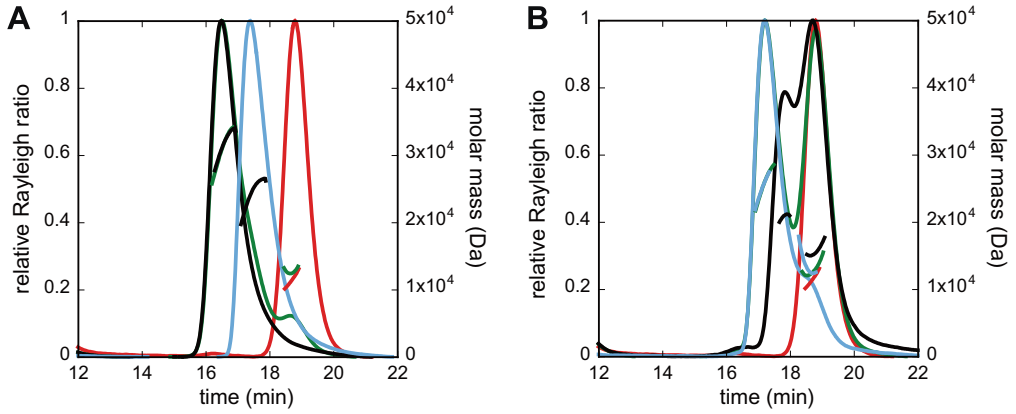

Fig. 4. S100 proteins, p53 monomer (313-393) L344P and MDM2 (2-125) do not form a ternary complex in SEC–MALS. Ternary complex formation was determined by examining differences between t_r and M_w in the elution profiles of S100/MDM2 (2-125)/p53 (313-393) L344P (green) and the elution profiles of the protein mixtures S100/MDM2 (2-125) (black), S100/p53 (313-393) L344P (blue) and MDM2 (2-125)/p53 (313-393) L344P (red). (A) S100A1, (B) S100B; 100 μl injections of 30 μM p53 (313-393) L344P, 30 μM MDM2 (2-125) and/or 60 μM S100 protein were used in each experiment.

tions on p53 activity in vivo will be highly dependent on the concentrations of each partner, calcium and which S100 protein is present. However, the interplay between S100 proteins, MDM2 and p53 may be physiologically relevant because S100 proteins and MDM2 are often overexpressed in cancer [4,23]. The inhibition of MDM2 activity could also explain the activating effects of S100A2 and S100A6 on p53-mediated transcription in cellular assays [15,16]. Overall, we have identified an interaction between S100 proteins and the N-terminal domain of MDM2 that does not permit a ternary complex with p53 (1-93) or p53 (313-393) L344P. Further, moderate inhibition of the extent of MDM2-mediated ubiquitylation of p53 by S100A2, S100A4 and S100A6 may occur via several mechanisms that partially contribute to the stimulatory effects of S100 proteins on p53 activity.

Acknowledgements

We thank Andreas C. Joerger and Maria R. Fernandez-Fernandez for critical reading of the manuscript and Chris M. Johnson for technical assistance.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.febslet.2010.06.024.

References

[1] Donato, R. (2003) Intracellular and extracellular roles of S100 proteins. Microsc. Res. Tech. 60, 540–551.
[2] Leclerc, E., Fritz, G., Vetter, S.W. and Heizmann, C.W. (2009) Binding of S100 proteins to RAGE: an update. Biochim. Biophys. Acta 1793, 993–1007.
[3] Santamaria-Kisiel, L., Rintala-Dempsey, A.C. and Shaw, G.S. (2006) Calcium-dependent and -independent interactions of the S100 protein family. Biochem. J. 396, 201–214.
[4] Salama, I., Malone, P.S., Mihaimeed, F. and Jones, J.L. (2008) A review of the S100 proteins in cancer. Eur. J. Surg. Oncol. 34, 357–364.
[5] Bonfrer, J.M., Korse, C.M., Nieweg, O.E. and Rankin, E.M. (1998) The luminescence immunoassay S-100: a sensitive test to measure circulating S-100B: its prognostic value in malignant melanoma. Br. J. Cancer 77, 2210–2214.
[6] Davies, M.P., Rudland, P.S., Robertson, L., Parry, E.W., Jolicoeur, P. and Barraclough, R. (1996) Expression of the calcium-binding protein S100A4 (p9Ka) in MMTV-neu transgenic mice induces metastasis of mammary tumours. Oncogene 13, 1631–1637.
[7] Ambartsumian, N.S., Grigorian, M.S., Larsen, I.F., Karlstrom, O., Sidenius, N., Rygaard, J., Georgiev, G. and Lukanidin, E. (1996) Metastasis of mammary carcinomas in GRS/A hybrid mice transgenic for the mts1 gene. Oncogene 13, 1621–1630.
[8] Fernandez-Fernandez, M.R., Rutherford, T.J. and Fersht, A.R. (2008) Members of the S100 family bind p53 in two distinct ways. Protein Sci. 17, 1663–1670.
[9] Fernandez-Fernandez, M.R., Veprintsev, D.B. and Fersht, A.R. (2005) Proteins of the S100 family regulate the oligomerization of p53 tumor suppressor. Proc. Natl. Acad. Sci. USA 102, 4735–4740.
[10] van Dieck, J., Fernandez-Fernandez, M.R., Veprintsev, D.B. and Fersht, A.R. (2009) Modulation of the oligomerization state of p53 by differential binding of proteins of the S100 family to p53 monomers and tetramers. J. Biol. Chem. 284, 13804–13811.
[11] van Dieck, J., Teufel, D.P., Jaulent, A.M., Fernandez-Fernandez, M.R., Rutherford, T.J., Wyslouch-Cieszynska, A. and Fersht, A.R. (2009) Posttranslational modifications affect the interaction of S100 proteins with tumor suppressor p53. J. Mol. Biol. 394, 922–930.
[12] Scotto, C., Deloulme, J.C., Rousseau, D., Chambaz, E. and Baudier, J. (1998) Calcium and S100B regulation of p53-dependent cell growth arrest and apoptosis. Mol. Cell. Biol. 18, 4272–4281.
[13] Scotto, C., Delphin, C., Deloulme, J.C. and Baudier, J. (1999) Concerted regulation of wild-type p53 nuclear accumulation and activation by S100B and calcium-dependent protein kinase C. Mol. Cell. Biol. 19, 7168–7180.
[14] Lin, J., Blake, M., Tang, C., Zimmer, D., Rustandi, R.R., Weber, D.J. and Carrier, F. (2001) Inhibition of p53 transcriptional activity by the S100B calcium-binding protein. J. Biol. Chem. 276, 35037–35041.
[15] Mueller, A., Schafer, B.W., Ferrari, S., Weibel, M., Makek, M., Hochli, M. and Heizmann, C.W. (2005) The calcium-binding protein S100A2 interacts with p53 and modulates its transcriptional activity. J. Biol. Chem. 280, 29186–29193.
[16] Slomnicki, L.P., Nawrot, B. and Lesniak, W. (2009) S100A6 binds p53 and affects its activity. Int. J. Biochem. Cell Biol. 41, 784–790.
[17] Momand, J., Wu, H.H. and Dasgupta, G. (2000) MDM2–master regulator of the p53 tumor suppressor protein. Gene 242, 15–29.
[18] Wilder, P.T. et al. (2006) Recognition of the tumor suppressor protein p53 and other protein targets by the calcium-binding protein S100B. Biochim. Biophys. Acta 1763, 1284–1297.
[19] Schon, O., Friedler, A., Bycroft, M., Freund, S.M. and Fersht, A.R. (2002) Molecular mechanism of the interaction between MDM2 and p53. J. Mol. Biol. 323, 491–501.
[20] Yu, G.W., Rudiger, S., Veprintsev, D., Freund, S., Fernandez-Fernandez, M.R. and Fersht, A.R. (2006) The central region of HDM2 provides a second binding site for p53. Proc. Natl. Acad. Sci. USA 103, 1227–1232.
[21] Ang, H.C., Joerger, A.C., Mayer, S. and Fersht, A.R. (2006) Effects of common cancer mutations on stability and DNA binding of full-length p53 compared with isolated core domains. J. Biol. Chem. 281, 21934–21941.
[22] Ferreon, J.C., Lee, C.W., Arai, M., Martinez-Yamout, M.A., Dyson, H.J. and Wright, P.E. (2009) Cooperative regulation of p53 by modulation of ternary complex formation with CBP/p300 and HDM2. Proc. Natl. Acad. Sci. USA 106, 6591–6596.
[23] Toledo, F. and Wahl, G.M. (2007) MDM2 and MDM4: p53 regulators as targets in anticancer therapy. Int. J. Biochem. Cell Biol. 39, 1476–1482.