J Mol Model (2013) 19:1507–1514
DOI 10.1007/s00894-012-1705-8

ORIGINAL PAPER

# Rational design of the survivin/CDK4 complex by combining protein–protein docking and molecular dynamics simulations

**Jana Selent · Agnieszka A. Kaczor · Ramon Guixà-González · Pau Carrió · Manuel Pastor · Cristian Obiol-Pardo**

Received: 2 May 2012 / Accepted: 19 November 2012 / Published online: 21 December 2012


**Abstract** Survivin, the smallest inhibitor of apoptosis protein (IAP), is a valid target for cancer research. It mediates both the apoptosis pathway and the cell cycle and has been proposed to form a complex with the cyclin-dependent kinase protein CDK4. The resulting complex transports CDK4 from the cytosol to the nucleus, where CDK4 participates in cell division. Survivin has been recognized as a node protein that interacts with several partners; disruption of the formed complexes can lead to new anticancer compounds. We propose a rational model of the survivin/CDK4 complex that fulfills the experimental evidence and that can be used for structure-based design of inhibitors modifying its interface recognition. In particular, the suggested complex involves the alpha helical domain of survivin and resembles the mode of binding of survivin in the survivin/borealin X-ray structure. The proposed model has been obtained by combining protein–protein docking, fractal-based shape complementarity, electrostatics studies and extensive molecular dynamics simulations.

**Keywords** Molecular modeling · Survivin · CDK4 · Protein–protein interactions · Molecular dynamics · Protein-protein docking · Apoptosis · Cell cycle · Cancer

## Introduction

Survivin, the smallest inhibitor of apoptosis protein (IAP) is one of the most tumor-specific proteins [1]. As a member of the IAP family, it participates in modulating the apoptosis pathway by inhibiting caspases, but its unique structure, containing only a single baculovirus IAP repeat (BIR), lacking the RING finger (a characteristic IAP domain) and its uncommonly long alpha helix domain, unveils survivin as a protein that plays several roles apart from its IAP function. Notably, among other processes, survivin plays an essential role in mitosis, chromosomal attachment and in the regulation of TRAIL-mediated apoptosis [2].

From a medical point of view, survivin is a molecular signature for an unfavorable cancer outcome [3] and a valid target for cancer drug discovery [4].

Over the years, several complexes of survivin and other proteins have been identified, revealing an unexpectedly flexible function that goes far beyond its initial IAP role. As representative examples, survivin associates to the proteins Smac [5], XIAP [6], HSP90 [7], aurora kinase B [8] and borealin [9]. Moreover, several works have [10–13] demonstrated that survivin forms a complex with the cyclin-dependent kinase 4 (CDK4), providing a link to cell cycle progression. These studies have demonstrated that survivin interacts competitively with the complex formed by CDK4 and its suppressor $p16^{INK4a}$ [10, 11]. Survivin

**Electronic supplementary material** The online version of this article (doi:10.1007/s00894-012-1705-8) contains supplementary material, which is available to authorized users.

Jana Selent and Agnieszka A. Kaczor contributed equally to this work.

J. Selent · A. A. Kaczor · R. Guixà-González · P. Carrió · M. Pastor · C. Obiol-Pardo (✉)
Research Programme on Biomedical Informatics (GRIB), IMIM/Universitat Pompeu Fabra, Dr. Aiguader 88, 08003 Barcelona, Spain
e-mail: cobiol@intelligentpharma.com

A. A. Kaczor
Department of Synthesis and Chemical Technology of Pharmaceutical Substances, Faculty of Pharmacy, Medical University of Lublin, 4A Chodźki, 20093 Lublin, Poland

*Present Address:*
C. Obiol-Pardo
Intelligent Pharma, Barcelona Science Park C/ Baldiri Reixac, 4, 08028 Barcelona, Spain

forms a transient complex with CDK4, releasing $p16^{INK4a}$, and could then act as a transporter of CDK4 from the cytosol to the nucleus. There, CDK4 can participate in the G1 and S phases of the cell cycle.

However, the binding mode of both proteins in the survivin/CDK4 complex remains unsolved, although the availability of their crystal structures [14, 15] opens the door for its prediction by means of molecular modeling methods. Understanding the association of survivin and CDK4 at the molecular level is important for designing new anticancer agents that could disrupt the protein–protein interactions in this complex. Here, we propose a model for the survivin/CDK4 complex that has been obtained by combining several molecular modeling methods in order to reinforce our hypothesis. Specifically, we used protein–protein docking guided by the experimental evidence of $p16^{INK4a}$ competition, followed by shape and electrostatics complementarity studies and molecular dynamics simulations.

We suggest that survivin binds to CDK4 mainly using its alpha helix domain, similarly to the observed binding mode of survivin in the survivin/borealin crystallized complex [9].

The extensive interface area of the survivin/CDK4 complex is analyzed and several mutations that potentially disrupt its formation are highlighted. We also address how a small compound could disrupt the formation of this complex. The obtained model has been made public and can be used for further drug design purposes.

## Methods

### Modeling of the survivin/CDK6 complex

The crystal structure of the complex between human CDK6 and $p16^{INK4a}$ (pdb code 1BI7) [16] was used to build a rough model of the survivin/CDK6 complex. Protein sequence alignment between human survivin (complete, BIR domain and alpha helix domain) and $p16^{INK4a}$ was performed with the ALIGN server [17]. The results of this alignment were used to build the complex by simple backbone superposition of the conserved parts of both sequences using VMD [18]. The crystal structure of human survivin (pdb code 1E31) [14] was used in this step. After removing $p16^{INK4a}$, the resulting survivin/CDK6 was used as an initial guide for filtering the most reliable survivin/CDK4 complexes.

### Survivin and CDK4 refinement

The structure of human CDK4 was retrieved from the crystallized complex with Cyclin D1 (pdb code 2W96) [15]. Mutations D172T, G43E and G44E were changed backwards and the missing residue fragment G43–G47 was built with Modeller [19]. The missing fragment in residues P239–V260 was built with the loop refinement module of Modeller, taken the best scored solution. After this process, a minimization step was carried out with MOE [20] employing the AMBER ff99 [21] forcefield and implicit Born solvation. Similarly, the structure of human survivin was retrieved from the crystallized dimer (pdb code 1E31) [14] and minimized with MOE employing the same protocol. The structures of CDK4 and survivin so obtained were submitted to the protein–protein docking protocol.

### Modeling of the survivin/CDK4 complex

The minimized structures of survivin and CDK4 were submitted to the web server PatchDock [22] to perform protein–protein docking, with default parameters. No binding site was indicated (blind docking). After that, the PatchDock best ten solutions of the complex were used as input for the Rosetta program [23] to perform a fine rotational and translational refinement. Fifty solutions of Rosetta were inspected visually and superposed with VMD [18] to the ones obtained in PatchDock. The five most similar complexes compared to the PatchDock best model were considered to be reliable candidates for the survivin/CDK4 complex and were submitted to molecular dynamics simulations. Neglected solutions showed less contact area between the two proteins or were in contradiction with the constructed rough model of the survivin/CDK6 complex and the p16 hypothesis.

#### *Electrostatic potential and shape complementarity study*

Charge complementarity of survivin and CDK4 proteins was explored by calculating the electrostatic potential by means of the APBS software [24] and by mapping this potential to the 3D structure of the protein using Pymol software [25].

Shape complementarity was assessed by calculating the surface fractal dimension using the Renthal methodology [26]. The main assumption is that surface roughness (and conversely, surface softness), defined by the surface fractal dimension, should fit in the proposed protein–protein interface. Fractal dimension, *df*, can be calculated according to Eq. 1:

$$df = 2 - \frac{d \log SES}{d \log r} \quad (1)$$

where *SES* corresponds to the solvent excluded surface area calculated with the MSMS software [27] and *r* is the probe size used to calculate the SES that has been varied from 1.2 Å to 2.8 Å in increments of 0.2 Å [26]. The differential term in Eq. 1 is obtained by plotting *SES* over the probe size,

and calculating the slope of the graph after linear regression. Thus, fractal dimension denotes the rate of change in the protein surface area with respect to the probe size used to measure it; the higher the fractal dimension, the rougher the protein surface. For visual simplicity, the calculated fractal dimension per residue was mapped to the 3D structure of the protein using VMD software [18].

*Molecular dynamics simulation of the survivin/CDK4 complexes*

The structural zinc atom of survivin was parameterized with the early described dummy approach of Pang [28] that was also used in other studies with IAP proteins with remarkably good results [29, 30]. The Leap program of the AMBER-10 suite with ff03 force field [31] was used for implementing such parameters and for solvating the system with a cubic box of water molecules (TIP3P model) adding a physiological NaCl concentration of 150 mM. After that, molecular dynamics was performed with the GPU-driven software ACEMD [32] employing the AMBER forcefield using the following protocol: (1) minimization step, (2) NPT equilibration step, (3) NVT production run of 20 ns. The stability of each molecular dynamics was monitored by calculating the root mean square deviation (RMSD) of the system throughout the simulation. After convergence, several protein–protein features of the complexes were analyzed by means of the ProtorP server [33].

## Results

The aim of this study was to model a plausible molecular structure of the complex between the IAP protein survivin and CDK4. A graphical outline of this study is shown in Fig. 1. As a first hypothesis, we modeled the survivin/CDK6 complex based on a structurally close analogue complex CDK6/p16$^{INK4a}$ (pdb code 1BI7) (rough model, Fig. 1). Later, following a different strategy, we used protein–protein docking techniques that allow an improved sampling of the conformational space to build the survivin/CDK4 complex (Fig. 1). The results were validated by electrostatics and shape complementarity studies. The generated complexes were refined by means of molecular dynamics simulations leading to a promising stable candidate. The observed protein–protein interactions within the stable survivin/CDK4 complex were analyzed and used to suggest possible small molecule disruptors.

Modeling of the survivin/CDK6 complex: first hypothesis

It has been demonstrated that survivin interacts competitively with CDK4 in complex with the cell cycle suppressor p16$^{INK4a}$ (CDK4/p16$^{INK4a}$ complex) [10, 11] and therefore the structures of survivin and the suppressor must share the same binding site. The complex CDK4/p16$^{INK4a}$ has not yet been crystallized, but the close analogue complex CDK6/p16$^{INK4a}$ is available (pdb code 1BI7) [16]. We used the

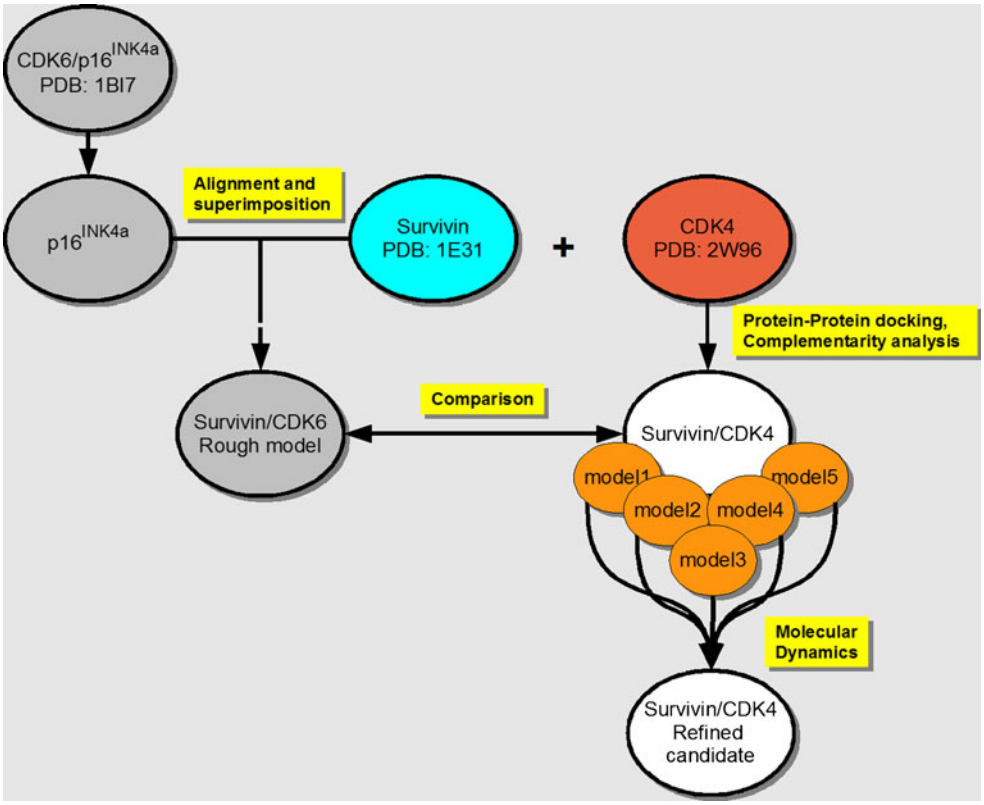


**Fig. 1** Graphical outline of the methods used in the modeling of the survivin/CDK4 complex

latter to elaborate a first hypothesis about the binding mode of survivin to CDK6. First, a protein sequence alignment between survivin and $p16^{INK4a}$ was performed (see Methods). No common alignment was found when using the complete sequences of both proteins. The same was found for the residues of survivin belonging only to the globular BIR domain. Notably, the N119–A134 residues of the alpha helical domain of survivin can be aligned with a fragment of $p16^{INK4a}$ in residues D84–A100 (Fig. 2a) showing a rather high similarity of 59 % (64 % after the gap). Interestingly, this fragment of $p16^{INK4a}$ also maintains an alpha helical structure in the crystallized complex with CDK6. The structure of the F124–A134 fragment of human survivin (pdb code 1E31) [14] was superimposed to the aligned fragment F90–A100 of $p16^{INK4a}$ (see Methods) yielding a backbone RMSd of 0.5 Å (Fig. 2b). This result suggests that survivin could bind to CDK6 (and CDK4) by using some of the residues within N119–A134 which is part of the alpha helix domain. Bearing this in mind, we next built a rough model of the survivin/CDK6 complex by superimposing the structure of this helical fragment of survivin to $p16^{INK4a}$ in the $p16^{INK4a}$/CDK6 complex. The structure of the resulting complex is shown in Fig. 2c after removing $p16^{INK4a}$. In this rough model, survivin interacts with CDK6 through the hydrophobic residues of its alpha helix, and highly resembles the binding mode of survivin in the crystallized complex with borealin [9]. Remarkably, the hydrophobic residues of the alpha helix of survivin interact both in the proposed rough CDK6 complex and in the borealin complex (pdb code 2RAW) [9].

Although a steric clash was observed in the globular BIR domain of survivin (Fig. 2c), the generated complex seemed adequate as a first hypothesis to guide the fine modeling of the survivin/CDK4 complex

## Modeling of the survivin/CDK4 complex: protein–protein docking

The structures of survivin (pdb code 1E31) [14] and CDK4 (pdb code 2W96) [15] were minimized (see Methods) and

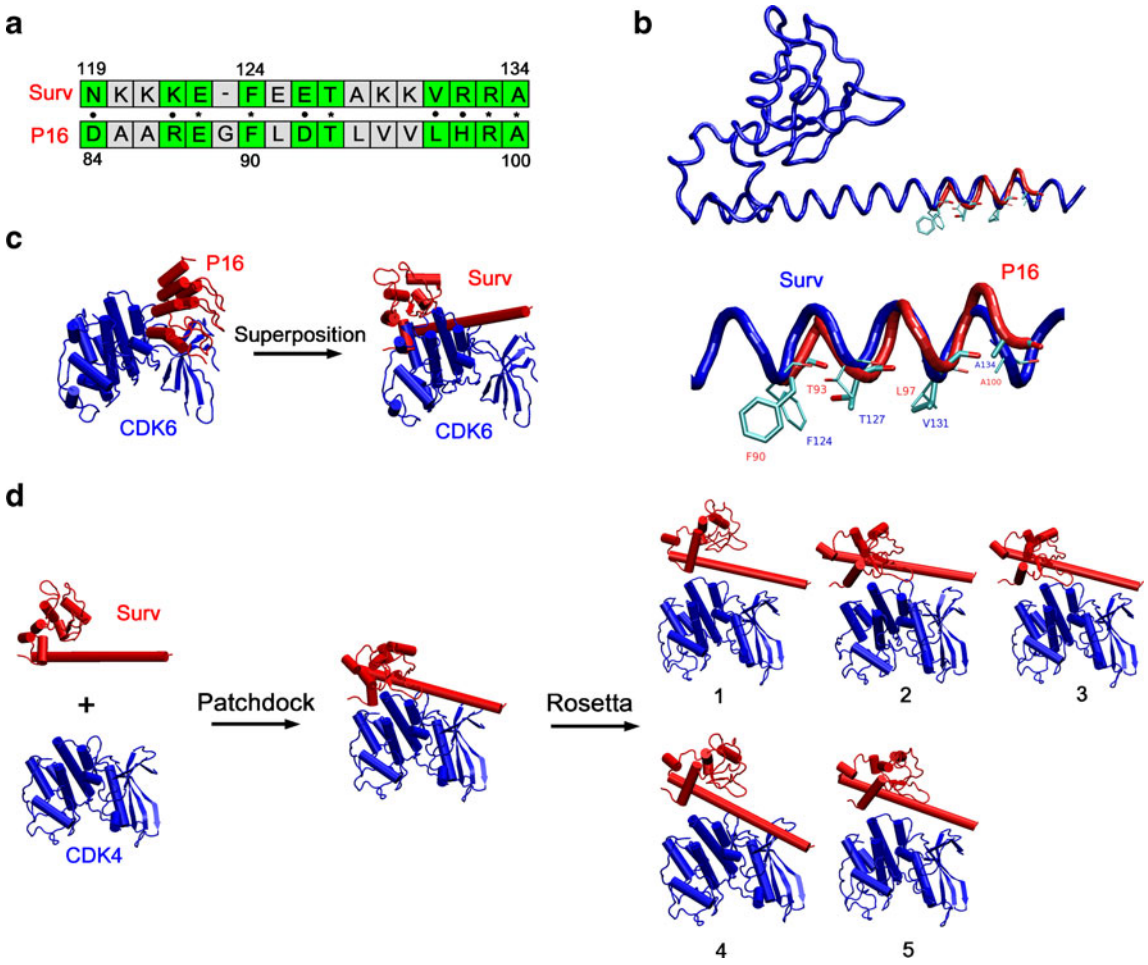


**Fig. 2** **a** Sequence alignment between survivin (alpha helix fragment) and $p16^{INK4a}$ (alpha helix fragment). **b** Superimposition of the alpha helix fragment of survivin and the fragment of $p16^{INK4a}$. **c** Obtained rough model of the survivin/CDK6 complex. **d** Protein-protein docking procedure employed to model the survivin/CDK4 complex

protein–protein docking was performed. For this task, we used the automatic server PatchDock (see Methods) without any a priori orientation of both proteins. Remarkably, the first scored solution of PatchDock, shown in Fig. 2d, highly resembled our first hypothesis in the survivin/CDK6 rough model. Indeed, in this solution, survivin interacts with CDK4 through the alpha helical domain and there is also an interaction in its N-terminal residues. In this case, no steric clash was detected and the contact surface between survivin and CDK4 in the model involved an area of 1,532 $Å^2$. Next, we performed a refinement of the complex obtained in PathDock using the Rosetta program. The initial complex was refined through fine rotations and translations, obtaining 50 new models. These complexes were inspected visually and superposed to the first proposed complex of PatchDock (see Methods) and the five candidates with the lowest RMSD were selected (Fig. 2d). Although they show a very similar overall structure, survivin binds to CDK4 with slightly rotated positions.

Before introducing further refinement on the complexes and in order to validate the models, a complementarity study was performed involving both electrostatics potential maps and shape complementarity. Firstly, Fig. 3a shows the electrostatic potential surface of survivin calculated with the APBS server (see Methods) on the Rosetta output number 2, considered as a representative example. The helix of survivin has a very marked amphiphilic nature; the negatively charged part (in red) is solvent exposed in the model, whereas the more hydrophobic part (in white) is in direct contact with CDK4, whose electrostatic potential is shown in Fig. 3b. This is the expected behavior of protein–protein association in aqueous solution by making use of the hydrophobic effect that buries the most hydrophobic patches upon binding. Additionally, a positively charged small patch of survivin (Fig. 3a, left) corresponds with a negatively charged patch of CDK4 (Fig. 3b, left). Moreover, the C-terminus residues of survivin, at the end of the helix and with negative charge (Fig. 3a, right) correspond with a positively charged patch of CDK4 (Fig. 3b, right). The non-polar residues F124, V131, I135 and A139 of survivin are in the hydrophobic face of the helix, while polar residues E126, K129, R132 and E136 are pointing to the solvent in the negatively charged face of the helix.

The shape complementarity was assessed by calculating the surface fractal dimension per residue (see Methods). Protein roughness is characterized by high fractal dimension, whereas a soft and planar protein patch is characterized by a lower fractal dimension. In a protein–protein complex, these features should correspond in the two partners and could guide the filtering of unrealistic complexes [26]. The mapped surface fractal dimension is depicted on survivin (Fig. 3c) and CDK4 (Fig. 3d). The major part of both proteins is reddish (Fig. 3c,d) denoting a low fractal dimension (that is, protein softness). On the contrary, a small patch of high fractal dimension (that is, protein roughness) is found in the BIR domain of survivin (blue in Fig. 3c).

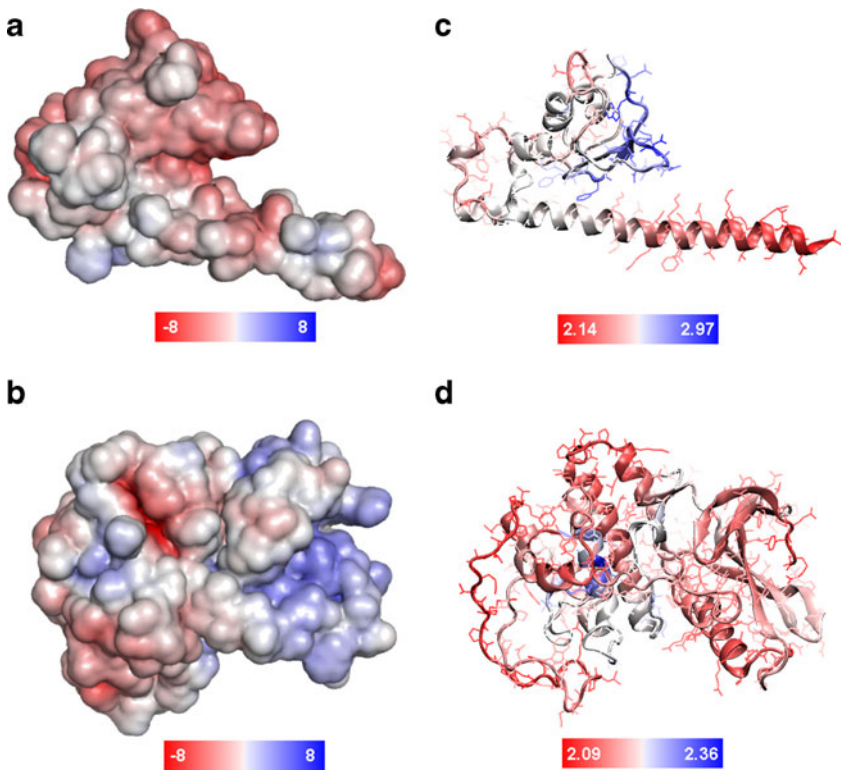


**Fig. 3** **a**, **b** Colored electrostatic potential of survivin (**a**) and CDK4 (**b**), ranging from positive potential, 8 $k_BT/e$ ($T$=300 K) in *blue*, to negative potential, −8 $k_BT/e$ ($T$=300 K) in *red*. **c**, **d** Colored surface fractal dimension of survivin ranging from 2.14, in red to 2.97, in blue (**c**) and CDK4 ranging from 2.09, in *red* to 2.36, in *blue* (**d**)

Generally, the observed fractal dimension fits well in the protein–protein interface, which is characterized by moderate (red) to low (white) roughness (Fig. 3c, d). Interestingly, the rough part in the BIR domain of survivin (blue in Fig. 3c) is not in contact with CDK4 in the proposed complex.

Moreover, the results of a more planar surface (that is, low fractal dimension) in the proposed protein–protein interface are in agreement with the findings of Nooren and Thornton [34], who found this feature for transient complexes, as in the case of survivin interacting with CDK4. We also applied the same methodology recently to study several GPCR proteins, finding interesting trends for drug binding site identification [35].

## Molecular dynamics simulation of the survivin/CDK4 complex

The five most similar Rosetta solutions of the survivin/CDK4 complex (Fig. 2d) (see Methods) were submitted to a molecular dynamics protocol by means of ACEMD software [32] (see Methods). After 20 ns of production runs for each one, the best candidate of the survivin/CDK4 complex was selected following the results of the ProtorP server [33] as well as molecular dynamics stability and visual inspection. Out of the five complexes, we obtained one complex that satisfied the following criteria: (1) stable RMSd of the survivin/CDK4 complex calculated over heavy atoms throughout the simulation (see Supplementary Material), (2) stable helical structure of survivin throughout the simulation, and (3) orientation of the survivin's residue F124 towards the protein–protein interface enabling CDK4 binding. F124 is one of the conserved residues when aligning survivin to $p16^{INK4a}$ (Fig. 2a).

The obtained stable complex exhibits the following protein interface features: (1) polar residues in interface: 17 %, (2) non-polar residues in interface: 33 %, (3) charged residues in interface: 50 %, (4) alpha character in interface: 92 %, (5) hydrogen bonds: 3 and (6) salt bridges: 10. This complex is provided in pdb format as Supplementary Material. Table 1 describes its protein–protein interactions and Fig. 4 shows a close view of the complex. The complex establishes several hydrogen bonds (also salt bridge interactions) and van der Waals contacts including a π-stacking interaction between F124 of survivin and F31 of CDK4. This analysis led us to propose that either point mutations on the residues L102, I113, F124, K112, E116, K120 and E123 of survivin or mutations on the residues P110, L112, Y103, F31, K106, D97 and K22 of CDK4 could disrupt the regular complex formation. Moreover, the survivin/CDK4 complex could be disrupted by small drug-like compounds with potential anticancer activity. According to our results, an alpha helix small molecule mimetic of the short fragments K112–E116 or K120–F124 of survivin could be used as a promising candidate. In this sense, several chemical families such as peptoids, β-peptides, stapled peptides and pyridazine-based scaffolds [36] have been proposed to

**Table 1** Protein–protein interactions in the proposed survivin/CDK4 complex refined through molecular dynamics (final 20 ns structure)

| Survivin residue | CDK4 residue | Interaction type[a] |
|---|---|---|
| L102 | P110 | VDW |
| L102 | L112 | VDW |
| K112 | K106 | HB |
| I113 | Y103 | VDW |
| E116 | K106 | SB |
| K120 | D97 | SB |
| E123 | K22 | SB |
| F124 | F31 | VDW |

[a] *VDW* van der Waals; *HB* hydrogen bond; *SB* salt bridge

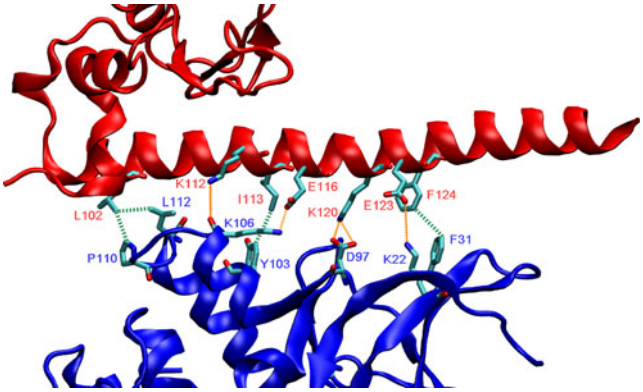


**Fig. 4** Close view of the interactions between survivin and CDK4 in the best model refined throughout molecular dynamics. *Orange dots* Polar contacts, *green dots* hydrophobic contacts

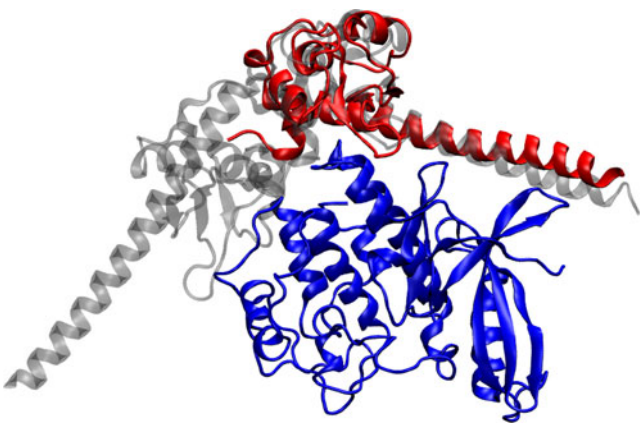

**Fig. 5** Proposed complex of the dimeric survivin and CDK4. The complex of survivin and CDK4 from molecular dynamics is depicted in *red* and *blue*, respectively. The crystallized dimer of survivin is depicted in *transparent grey*

mimic alpha helical domains, and could be used here for a rational disruption of the survivin/CDK4 complex.

Dimeric survivin and CDK4

There is still controversy about the in vivo stoichiometry of survivin. Although the dimeric form seems preferential [14], there is also evidence for the existence of a monomeric form [9]. Very recently the monomer was suggested to play an essential role in apoptosis, suggesting that survivin performs its functions partly as a monomer and partly as a dimer [37]. In this section we show that our proposed survivin/CDK4 complex is also consistent with a survivin dimeric form as the survivin dimerization site is not in contact with CDK4. The dimeric structure of survivin (pdb code 1E31) [14] was superposed to the refined survivin/CDK4 complex yielding the model in Fig. 5. Remarkably, our proposed model can accept a second unit of survivin with no important steric clashes, showing no contradiction with the proposed complex structure. Moreover, the structure of survivin in our complex remains stable after molecular dynamics refinement , showing a high similarity to the monomers of the crystallized dimer (backbone RMSd of 3.1 Å). However, further experimental evidence is needed to confirm the real stoichiometry of the survivin/CDK4 complex [10, 11].

## Conclusions

In this work, we have proposed a structural molecular model of the survivin/CDK4 complex that can be used as a guide for designing new anticancer drugs. The model was obtained by combining knowledge about the binding mode of $p16^{INK4a}$ and by applying protein–protein docking, electrostatics and shape complementarity studies, and molecular dynamics simulations. In our model, survivin interacts mainly with CDK4 by making use of its helical domain, similarly to the binding mode of this protein in the survivin/borealin crystallized complex. Moreover our refined model is consistent with a dimeric form of survivin. Based on the predicted survivin/CDK4 complex, we also suggest that a small compound acting as an alpha helix mimetic could bind in the proposed protein interface in order to disrupt the complex, which could serve as a novel anticancer agent. We also have indicated certain mutations on either residues of survivin or CDK4 that could impact greatly on complex formation. All in all, our model can be used in virtual screening campaigns and can encourage further experimental studies on this direction.

**Acknowledgments** This paper was funded by Foundation for Polish Science (FNP, Outgoing Fellowship Kolumb for Agnieszka A. Kaczor).

## References

1. Velculescu VE, Madden SL, Zhang L, Lash AE, Yu J, Rago C, Lal A, Wang CJ, Beaudry GA, Ciriello KM, Cook BP, Dufault MR, Ferguson AT, Gao Y, He TC, Hermeking H, Hiraldo SK, Hwang PM, Lopez MA, Luderer HF, Mathews B, Petroziello JM, Polyak K, Zawel L, Zhang W, Zhang X, Zhou W, Haluska FG, Jen J, Sukumar S, Landes GM, Riggins GJ, Vogelstein B, Kinzler KW (1999) Analysis of human transcriptomes. Nat Genet 23:387–388
2. Altieri DC (2008) Survivin, cancer networks and pathway-directed drug discovery. Nat Rev Cancer 8:61–70
3. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, Baehner FL, Walker MG, Watson D, Park T, Hiller W, Fisher ER, Wickerham DL, Bryant J, Wolmark N (2004) A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. N Engl J Med 351:2817–2826
4. Fesik SW (2005) Promoting apoptosis as a strategy for cancer drug discovery. Nat Rev Cancer 5:876–885
5. Sun C, Nettesheim D, Liu Z, Olejniczak ET (2005) Solution structure of human Survivin and its binding interface with Smac/Diablo. Biochemistry 44:11–17
6. Dohi T, Okada K, Xia F, Wilford CE, Samuel T, Welsh K, Marusawa H, Zou H, Armstrong R, Matsuzawa S, Salvesen GS, Reed JC, Altieri DC (2004) An IAP–IAP complex inhibits apoptosis. J Biol Chem 279:34087–34090
7. Fortugno P, Beltrami E, Plescia J, Fontana J, Pradhan D, Marchisio PC, Sessa WC, Altieri DC (2003) Regulation of survivin function by Hsp90. Proc Natl Acad Sci USA 100:13791–13796
8. Wheatley SP, Henzing AJ, Dodson H, Khaled W, Earnshaw WC (2004) Aurora-B phosphorylation in vitro identifies a residue of survivin that is essential for its localization and binding to inner centromere protein (INCENP) in vivo. J Biol Chem 279:5655–5660
9. Bourhis E, Hymowitz SG, Cochran AG (2007) The mitotic regulator Survivin binds as a monomer to its functional interactor Borealin. J Biol Chem 282:35018–35023
10. Suzuki A, Hayashida M, Ito T, Kawano H, Nakano T, Miura M, Akahane K, Shiraki K (2000) Survivin initiates cell cycle entry by the competitive interaction with Cdk4/$p16^{INK4a}$ and Cdk2/Cyclin E complex activation. Oncogene 19:3225–3234
11. Suzuki A, Ito T, Kawano H, Hayashida M, Hayasaki Y, Tsutomi Y, Akahane K, Nakano T, Miura M, Shiraki K (2000) Survivin initiates procaspase 3/p21 complex formation as a result of interaction with Cdk4 to resist Fas-mediated cell death. Oncogene 19:1346–1353
12. Ai MD, Li LL, Zhao XR, Wu Y, Gong JP, Cao Y (2005) Regulation of Survivin and CDK4 by Epstein-Barr virus encoded latent membrane protein 1 in nasopharyngeal carcinoma cell lines. Cell Res 15:777–784
13. Zhang L, Liu J, Lin H, Hu Q, Liu A, Hu Y (2006) Expression of survivin, CDK4, Ki-67 and clinical significance in pediatric acute leukemia. J Huazhong Univ Sci Technol 26:552–554
14. Chantalat L, Skoufias DA, Kleman JP, Jung B, Dideberg O, Margolis RL (2000) Crystal structure of human survivin reveals a bow tie-shaped dimer with two unusual alpha-helical extensions. Mol Cell 6:183–189
15. Day PJ, Cleasby A, Tickle IJ, O'Reilly M, Coyle JE, Holding FP, McMenamin RL, Yon J, Chopra R, Lengauer C, Jhoti H (2009) Crystal structure of human CDK4 in complex with a D-type cyclin. Proc Natl Acad Sci USA 106:4166–4170
16. Russo AA, Tong L, Lee JO, Jeffrey PD, Pavletich NP (1998) Structural basis for inhibition of the cyclin-dependent kinase Cdk6 by the tumour suppressor p16INK4a. Nature 395:237–243
17. ALIGN, http://xylian.igh.cnrs.fr/bin/align-guess.cgi
18. Humphrey W, Dalke A, Schulten K (1996) VMD-visual molecular dynamics. J Mol Graph 14:33–38

19. Eswar N, Mari-Renom MA, Webb B, Madhusudhan MS, Eramian D, Shen M, Pieper U, Sali A (2006) Comparative protein structure modeling with MODELLER. Current protocols in Bioinformatics. Supplement 15, Wiley, New York, pp 5.6.1–5.6.30, 200
20. MOE: Molecular Operating Environment; Chemical Computing Group, Inc. http://www.chemcomp.com/
21. Wang J, Cieplak P, Kollman PA (2000) How well does a restrained electrostatic potential (RESP) model perform in calculating conformational energies of organic and biological molecules? J Comput Chem 21:1049–1074
22. Schneidman-Duhovny D, Inbar Y, Nussinov R, Wolfson HJ (2005) PatchDock and SymmDock: servers for rigid and symmetric docking. Nucleic Acids Res 33:W363–W367
23. Gray JJ, Moughan SE, Wang C, Schueler-Furman O, Kuhlman B, Rohl CA, Baker D (2003) Protein–protein docking with simultaneous optimization of rigid-body displacement and side-chain conformations. J Mol Biol 331:281–299
24. Baker NA, Sept D, Joseph S, Holst MJ, McCammon JA (2001) Electrostatics of nanosystems: application to microtubules and the ribosome. Proc Natl Acad Sci USA 98:10037–10041
25. PyMOL Molecular Graphics System, Version 1.3, Schrödinger, LLC. http://www.pymol.org
26. Renthal R (1999) Transmembrane and water-soluble helix bundles display reverse patterns of surface roughness. Biochem Biophys Res Commun 263:714–717
27. Sanner MF, Olson AJ, Spehner JC (1996) Reduced surface: an efficient way to compute molecular surfaces. Biopolymers 38:305–320
28. Pang YP, Xu K, El Yazla J, Prendergast F (2000) Successful molecular dynamics simulation of the zinc-bound farnesyltransferase using the cationic dummy atom approach. Protein Sci 9:1857–1865
29. Obiol-Pardo C, Rubio-Martínez J (2007) Comparative evaluation of MMPBSA and XSCORE to compute binding free energy in XIAP-peptide complexes. J Chem Inf Model 47:134–142
30. Obiol-Pardo C, Granadino-Roldán JM, Rubio-Martínez J (2008) Protein–protein recognition as a first step towards the inhibition of XIAP and Survivin anti-apoptotic proteins. J Mol Recognit 21:190–204
31. Case DA, Darden TA, Cheatham TE III, Simmerling CL, Wang J, Duke RE, Luo R, Crowley M, Walker RC, Zhang W, Merz KM, Wang B, Hayik S, Roitberg A, Seabra G, Kolossváry I, Wong KF, Paesani F, Vanicek J, Wu X, Brozell SR, Steinbrecher T, Gohlke H, Yang L, Tan C, Mongan J, Hornak V, Cui G, Mathews DH, Seetin MG, Sagui C, Babin V, Kollman PA (2008) AMBER 10. University of California, San Francisco
32. Harvey MJ, Giupponi G, de Fabritiis G (2009) ACEMD: accelerating biomolecular dynamics in the microsecond time scale. J Chem Theory Comput 5:1632–1639
33. Reynolds C, Damerell D, Jones S (2008) ProtorP: a protein—protein interaction analysis server. Bioinformatics 25:413–414
34. Nooren IM, Thornton JM (2003) Structural characterisation and functional significance of transient protein-protein interactions. J Mol Biol 325:991–1018
35. Kaczor AA, Guixà-González R, Carrió P, Obiol-Pardo C, Pastor M, Selent J (2012) Fractal dimension as a measure of surface roughness of G protein-coupled receptors: implications for structure and function. J Mol Model 18:4465–4467
36. Ross NT, Katt WP, Hamilton AD (2010) Synthetic mimetics of protein secondary structure domains. Phil Trans R Soc A 368:989–1008
37. Pavlyukov MS, Antipova NV, Balashova MV, Vinogradova TV, Kopantzev EP, Shakhparanov MI (2011) Survivin monomer plays an essential role in apoptosis regulation. J Biol Chem 286:23296–23307