Supporting Information

for

Recognizing the binding pattern and dissociation pathways of p300 Taz2 - p53 TAD2 complex

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Classic molecular dynamics (MD) and steered molecular dynamics (SMD) simulations

Classic all-atom molecular dynamics (MD) was used to investigate the changes in structure and dynamics of p53 TAD2 in the isolated and bound states. Steered molecular dynamics (SMD) simulations were used to investigate the unbinding processes of the p300 Taz2-p53 TAD2 complex.

The CHARMM36m force field\textsuperscript{1} with explicit solvents and the Groningen Machine for Chemical Simulations (GROMACS) package\textsuperscript{2-4}, version 2020.4, were used to investigate the structural and dynamic changes in p53 TAD2 in isolation and in complex with p300 Taz2. Classic all-atom simulations have been carried out for two systems with experimentally determined structures: 1) the p53 TAD2 monomer (extracted from PDB ID: 2MZD\textsuperscript{5}), and 2) the p300 Taz2-p53 TAD2 complex (PDB ID: 2MZD\textsuperscript{6}). These all-atom simulations can be used to compare the changes in structure and dynamics of p53 TAD2 in isolation and the bound state. A cubic TIP3P water box with a side of 110Å containing neutralized systems was used for all MD simulations. For the p300 Taz2-p53 TAD2 complex, three 6 µs independent simulations were carried out, for a total of 18 µs. For the isolated p53 TAD2, three 12 µs independent simulations were carried out, for a total of 36 µs. Each system was prepared using CHARMM-GUI.\textsuperscript{6,7} Short-range nonbonded interactions were cut off at 1.4 nm. Long-range electrostatics were calculated using the particle-mesh Ewald (PME) algorithm.\textsuperscript{8,9} Periodic boundary conditions were applied in all directions.

For the steered molecular dynamics (SMD) simulations, the experimentally determined structure of the p300 Taz2-p53 TAD2 complex (PDB ID: 2MZD\textsuperscript{6}) was used as the starting structure. The CHARMM36m force field\textsuperscript{1} was used to conduct SMD simulations. The complex was placed in a rectangle box (80 Å × 80 Å × 160 Å) of TIP3P water at 300 K, with 100 mM NaCl concentration. Steepest-descent minimization was carried out, followed by constant-pressure (NPT) equilibration. The p300 Taz2-p53 TAD2 complex was dissociated by applying a harmonic force on p300 Taz2 and p53 TAD2 and maintaining positional restraints on Taz2. Taz2 was used as a fixed reference and the center of the mass distance between Taz2 and TAD2 was considered as the reaction coordinate of dissociation. In the pulling simulation, p53 TAD2 was pulled away from p300 Taz2 along the z-axis for 3.7 nm, with a spring constant of 1000 KJ mol\textsuperscript{-1} nm\textsuperscript{-2} and a pulling rate of 0.1 nm ns\textsuperscript{-1}. Fifty replicas of 37 ns SMD simulations were carried out, for a total simulation time of 1.85 µs.

Self-organizing maps (SOMs)

SOMs are considered a type of unsupervised artificial neural network with an explicit visual representation of data on a two-dimensional map. They have been widely used for the analysis of different types of data\textsuperscript{10-12}, including protein conformations extracted from MD simulations.\textsuperscript{13-15}

Single conformations from the SMD trajectories were represented by the set of intermolecular distances between the C\textbeta{} atoms of TAD2 and Taz2. Distances were computed for each of the n\textsuperscript{th} frames of the simulation (preprocessed with a stride of 10 ps). This yielded a set of 2250 input features that were used to train the SOM. Training is performed over 5000 cycles. In each cycle, the input vectors representing the single conformations are presented in random order to the map and assigned to the neuron with closer weights, also called the best matching unit (BMU). The weights of the BMU and its neighbors are modified to be closer to the values of the input vector. The magnitude of the modification decreases with the distance from the BMU and along with the training. This process is iterated, and the resulting SOM preserves the topological relationship between neurons, keeping similar original input data close on the map. In a second step, the neurons are further grouped in a small, but representative, number of clusters by agglomerative hierarchical clustering using Euclidean distance and complete linkage. The optimal number of clusters, (10 in this case), was selected based on the Silhouette profiles. In this work, we used an 8x8 sheet-shaped SOM (without periodicity across the boundaries) with a hexagonal lattice shape. We set a capping value of 1.2 nm for the distance values, to remove uninformative differences between frames in unbound conformations.

As explained in Motta et al\textsuperscript{16}, we traced the SMD pathways on the SOM from the annotation of the BMU associated with each frame of the simulation. This made it possible to construct the path covered by each simulation on the map. Using this time-dependent annotation, we estimated an approximate transition matrix between each pair of neurons. The matrix was then transformed into a row stochastic matrix, and a graph was then built with nodes represented by neurons and edges set to the negative logarithm of the transition probability between the corresponding neurons. Properties such as the forces applied during SMD simulations and the helical content of TAD2 were displayed assigning to the neuron a color code proportional to the average value of the property for the frames belonging to that neuron. All the analyses were performed in the R statistical environment\textsuperscript{17} using the Kohonen package\textsuperscript{18} for the SOM training and igraph package\textsuperscript{19} for graph construction.

Time-resolved force distribution analysis (TRFDA)
Time-resolved force distribution analysis (TRFDA)\(^{20}\) was developed to trace the interaction force changes at atomic resolution for the atoms/residues of interest resulting from a perturbation, such as binding/unbinding simulations of ligands. The forces acting on atoms can be transformed into punctual stresses, which can be applied to analyze the evolution of punctual stresses on each residue in the SMD simulations. TRFDA was carried out to obtain the punctual stresses between residues of Taz2 and TAD2 and was averaged every 40 frames for the 50 replicas of SMD trajectories. According to the results of dissociation pathways determined by SOMs, punctual stresses were averaged over the SMD trajectories grouped into the same pathway. In other words, the punctual stresses of pathway 1 were averaged over 14 replicas of SMD trajectories, and those of pathway 2 were averaged over 36 trajectories. In addition to the stress analysis performed over the entire system, per residue TRFDA was performed on some critical Taz2 residues to observe their evolution of interactions with the entire TAD2. In this way, we could identify which residues in TAD2 interacted with the selected residue of Taz2 and how the interactions varied during simulations. Similar analyses were performed on TAD2 residues to check the interactions between one TAD2 residue and the entire Taz2. The cartoon structures were generated using PyMOL.\(^{21}\) Some figures were prepared using the MDTraj\(^{22}\) or Bio3D packages\(^{23-26}\).

**Contact maps of other complexes involving Taz2 and TAD**

The formation of the Taz2-TAD2 complex involves not only the binding between Taz2 and TAD2 but also the folding of the intrinsically disordered TAD2. Therefore, further analysis is required to study the factors influencing the folding status of TAD2 in the complex and the binding mode of Taz2-TAD2 in-depth. In this work, we considered 1) two complexes involving TAD2 and 2) eight complexes involving Taz2 with unique TADs to reveal consistent factors within each complex that may play a pivotal role in determining the binding mode of the Taz2-TAD2 complex. To compare the folding status of TAD2 in different complexes, TAD2 in complex with the Taz2 domain of p300 or the PH domain of TFIH p62 were used to compare the residue composition of the binding pocket and the structure of TAD2 in the complexes. In order to analyze the binding mode of the complexes involving Taz2, we built the contact map of the p300 Taz2-p53 TAD2 complex using the 15 NMR-determined models (PDB ID: p53 TAD2 - 2MZD\(^3\)). Similarly, the contact maps of other seven complexes of p300 Taz2 (1726-1812) or its paralog CBP Taz2 (1764-1850) with transactivation domains (TADs) derived from different transcriptional factors (p53 TAD1 - 2K8F\(^7\), STAT1 TAD - 2KA6\(^{28}\), E1A - 2KJE\(^{29}\), p53 TAD2 - 5HP0\(^{30}\), p53 TAD - 5HPD\(^{30}\), p63 TAD - 6FGN\(^{31}\), and p73 TAD1 - 6FGS\(^{31}\)) were built using the experimentally determined structures deposited in the protein data bank. To identify the common binding region in the Taz2 complexes, the probability for each Taz2 residue in forming contacts with TAD was calculated by summing up all contacts formed between the residue in Taz2 with all TAD residues in one single complex and then rescaled in the range of 0-1. Next, the probability for each residue in the eight complexes was calculated by averaging the probabilities for each residue and then rescaled in the range of 0-1.

**Changes in structures and dynamics of p53 TAD2 in isolation and in complex**

The transient helix in TAD2 (residues 47-55) is primarily intrinsically disordered in isolation. The low propensity of the transient helix in isolated TAD2 is the result of the balance of the preference between the helical structure and entropic contributions. The dynamics of TAD2 in the complex, especially the fuzzy N-terminus, is a way to reduce the influence of unfavorable entropy decrease in the process of association.

Principle component-based hierarchical cluster analysis with Ward's minimum variance method was used to cluster the simulations of the p53 TAD2 in isolation and in the complex into eight clusters. Before the hierarchical cluster analysis, principal component analysis was carried out to obtain the first two principal components which were used as the coordinates feeding into the hierarchical cluster analysis as inputs. The cluster results show that the helix can be stabilized dramatically in the Taz2-TAD2 complex. Among the eight clusters generated for each system, the top five clusters accounting for 76% and 80% of snapshots are the representative structures of isolated TAD2 and the Taz2-TAD2 complex, respectively (Figures S1A and S1B). While the isolated TAD2 (Figure S1A) was relatively flexible, the Taz2-TAD2 complex (Figure S1B) was more stable. Specifically, the TAD2 \(\alpha\)-helix (residues 47-55) was much longer and more stable, but the terminal regions, especially the TAD2 N-terminus (Figure S1B), remained dynamic even in the Taz2-TAD2 complex. These results are consistent with the finding of the fuzzy p53 NTD in complex with EGCG.\(^{32}\) The correlation map (Figures S1C and S1D) shows that the degree of motion between the p53 N-terminus and the C-terminus decreases (the motion is displayed in Figure S1A), and the correlation pattern in the helical region of TAD2 changed in the bound state in comparison to that in the isolated state. For example, in the Taz2-TAD2 complex, the negative correlation between the N-terminus (residues 35-39) and C-terminus (residues 53-58) of TAD2 decreased, and the negative correlation between residues 39-42 (colored in red in Figure S1B) and residues 46-48 (colored in blue in Figure S1B) increased. The more negative correlation between residues 39-42 and residues 46-48 was related to the dynamic helical structure of TAD2 residues 39-42. The correlation pattern of TAD2 at residues 47-55 changed in the bound state where this region can fold into a stable helical structure. More dynamic properties of TAD2 in isolation and in the Taz2-TAD2 complex were investigated in the previous work.\(^{33}\)
Figure S1. Representative structures of the top five clusters of p53 TAD2 in the isolated state (A) and in the complex (B). p53 TAD2 is colored in cyan and Taz2 in grey. The arrows in panel A indicate the motions between the p53 TAD2 N- and C-terminus. In panel B, the residues 39-42 are colored in red, and the residues 46-48 are colored blue. Cross-correlation maps of isolated p53 TAD2 (C) and p53 TAD2 in the complex (D). The scale bar on the right of panels C and D represent the correlation between motions of two residues, with 1 denoting their motions are correlated, -1 denoting their motions are anti-correlated, and 0 denoting their motions are not correlated.

**Dissociation pathways for each SMD trajectory**

The structural transition pattern for each steered molecular dynamics (SMD) trajectory can be traced when all frames extracted from one SMD trajectory were projected on the map. Neurons with similar weights were grouped into the same cluster (Figures S2 and S3). Considering the transition pattern at the cluster level, dissociation pathways 1 and 2 visited quite different clusters (Figures S4 and S5). Similar to Figure 2, the pulling force and the helical fraction are projected to the SOM in Figure S6. To trace the structural transition for each cluster, the difference in contacts between the two clusters is carried out (Figure S7). The top panels (Figure S7) reveal the lost interactions between Taz2 and TAD2 and are used to illustrate the unbinding degree in these clusters. The bottom panels (Figure S7) reveal the lost interactions within TAD2 and are used to illustrate the folded status of TAD2 in these clusters. TAD2 Helical fraction and number of contacts between TAD2 and Taz2 are mapped on SOM (Figure S8). Additionally, we explored the variation of TAD2 helical SASA and TAD2 helical fraction (Figure S9).
Figure S2. Self-organizing Map with neuron numberings.
Figure S3. In the diagram of trained SOM, each hexagon stands for one neuron and neurons with similar weights are grouped into the same cluster. Neurons in one cluster are shown with the same color. The representative structure of each neuron was mapped on SOM. Taz2 is colored in white and TAD2 is colored in rainbow from the N-terminus (blue) to the C-terminus (red).
Figure S4. 14 SMD replicas of SMD simulations followed pathway 1.
Figure S5. 36 SMD replicas of SMD simulations followed pathway 2.
Figure S6. The average pulling forces (A) and the helical fractions of TAD2 (B) were mapped on SOM. They were labeled with neuron indexes. In panel B, the helical fraction is in the range of 0-1, with 0 denoting there is no helical structure and 1 denoting all residues forming helical structure.

Figure S7. The differences in contacts in the Taz2-TAD2 complex (panels A-E) and in TAD2 (panels F-J) between two clusters. The first three columns, involving clusters I, F, J, and H, are related to pathway 1. And the last two columns, involving clusters I, C, and A, are related to pathway 2. For example, in panel A, the contacts between Taz2 and TAD2 in cluster I and cluster F were analyzed, with black marks representing the common contacts in both clusters, green marks representing disappeared contacts in cluster F, and red marks representing the new contacts in cluster F. In panel F, it is the same case as panel A, but the contacts are those in TAD2 instead.
Figure S8. TAD2 Helical fraction and number of contacts between TAD2 and Taz2 mapped on SOM. Neurons exclusive for simulations following pathway 1 or pathway 2 were grouped with green and purple line respectively. Comparison of the two images shows that following pathway 1, folding of TAD2 is preserved in later stages of the simulations.

Figure S9. The overlap between the secondary structure distribution and helical SASA of TAD2 of pathway 1 (A, replica 48) and pathway 2 (B, replica 27). The legend for the color of secondary structure elements is displayed on the right of the residue index bar. The helical SASA is the curved orange line at the back of the secondary structure distribution diagram and increases from about 12 nm$^2$ to 15 nm$^2$.
Figure S10. For replicas in pathway 1, the distance of Taz2 K1760-TAD2 D57, the number of hydrogen bonds, SASA of the TAD2 α-helix, RMSD of TAD2 with TAD2 in the experiment determined complex as the reference, and the helical fraction of TAD2 was conducted to evaluate the unfolding status of TAD2 and the unbinding status of Taz2-TAD2 complex.
Figure S11. For replicas in pathway 2, the distance of Taz2 H1795-TAD2 Q38, the number of hydrogen bonds, SASA of the TAD2 α-helix, RMSD of TAD2 with TAD2 in the experiment determined complex as the reference, and the helical fraction of TAD2 was conducted to evaluate the unfolding status of TAD2 and the unbinding status of Taz2-TAD2 complex.

**Key residues determined from time-resolved force distribution analysis (TRFDA)**

While Figure 5 is used to display the averaged punctual stresses over trajectories of pathways 1 and 2, Figure S12 takes clusters 48 and 27 as an example (representing pathways 1 and 2, respectively). We analyzed the punctual stresses on some key residues and distances of some key residue pairs. In this work, per residue TRFDA was carried out to monitor the contributions of some key residues in the dissociation process. Here, we displayed the TRFDA results for more residues, including the remaining residues listed in Table S1. Therefore, the contribution of each critical residue (Figures S13 and S14) at different stages of the dissociation process is clear. Furthermore, for all SMD trajectories, we traced the structural transition in the dissociation process in terms of one pairwise distance between residues of Taz2 and TAD2, the number of H-bond, RMSD of the TAD2 α-helix with the TAD2 in the complex as the reference, SASA of the TAD2 α-helix, and the helical fraction of TAD2 (Figures S10 and S11).

**Table S1. Critical residue pairs determined from the punctual stress on Taz2 (Figures 4C and 4D)**

| Pathway 1                        | Pathway 2                        |
|----------------------------------|----------------------------------|
| K1760-D57 (positive-negative)    | H1795-Q38 (positive-negative)    |
| R1731-D48 (positive-negative)    | R1732-Q38 (positive-negative)    |
| R1731-E51 (positive-negative)    | R1732-D41 (positive-negative)    |
| R1737-E51 (positive-negative)    | R1731-D41 (positive-negative)    |
| I1781-W53 (hydrophobic-hydrophobic) | I1735-M44 (hydrophobic-hydrophobic) |
| S1734-E51 (polar-negative)       | Q1736-A39 (polar-hydrophobic)    |
| S1734-F54 (polar-hydrophobic)    | Q1740-S37 (polar-polar)          |
Figure S12. Critical residues of Taz2 in the dissociation pathway (A-D) and the corresponding pairwise distance change along the dissociation process (E and F) of replicas 48 (panels A, B, and E) and 27 (panels C, D, and F). A-D stands for the interactions between the selected Taz2 residue with the entire TAD2 to identify the critical interactions between the selected Taz2 residue with TAD2 residues. A and B are the punctual stress between Taz2 K1760 and R1731 with TAD2, respectively. C and D are the punctual stress between Taz2 R1731 and R1732 with TAD2, respectively.

Figure S13. Per residue TRFDA of critical residues for pathway 1, including Taz2 Q1784 (A), R1737 (B), I1781 (C), S1734 (D), S1757 (E), P1780 (F), TAD2 D57 (G), and E51 (H). The scale bars are 0-110 and 0-450 for panels A-F and panels G-H, respectively.
Figure S14. Per residue TRFDA of critical residues for pathway 2, including Taz2 R1731 (A), K1760 (B), Y1791 (C), I1735 (D), Q1736 (E), Q1784 (F), Q1740 (G), TAD2 D57 (H), and E51 (I). The scale bars are 0-370 and 0-140 for panels A-B and panels C-I, respectively.

The complexes involving TAD2 or Taz2

The contact maps for the complexes involving Taz2 (Figure S15) are overlapped. The binding pockets share similar regions but are slightly different from each other. As for the complexes involving TAD2, the structures of TAD2 in complex with Taz2 or the PH domain are completely different (Figure S16). TAD2 can rearrange itself to adapt to the binding pockets.
Figure S15. In panel A, the sequence alignment of different TADs. In panel B, the probability of forming contacts of Taz2 complexes with TADs from different transcriptional factors (The residue number is labeled according to the p300 Taz2). The Taz2 complexes (Taz2-p53 TAD2 - 2MZD, Taz2-p53 TAD2 - 5HP0, Taz2-p53 TAD - 5HPD, Taz2-p53 TAD1 - 2K8F, Taz2-p63 TAD - 6FGN, Taz2-p73 TAD1 - 6FGS, Taz2-STAT1 TAD - 2KA6, and Taz2-E1A - 2KJE).

Figure S16. The surface electrostatic potential of the Taz2-TAD2 complex (A) and the PH-TAD2 complex (B). The residues are colored in grey (hydrophobic residues), yellow (polar residues), blue (positively charged residues), and red (negatively charged residues).

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