

Exploration of the conformational space of SERF1a

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VERSITÉ ORRAINE CNS

EXPLORATION OF THE CONFORMATIONAL SPACE OF SERF1A Shu-Yu Huang(1), Chi-Fon Chang(2), Jung-Hsin Lin(1)and Thérèse E Malliavin(3)

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Experimental measurements

NMR spectra were recorded at 298K on Bruker Avance 800MHz equipped with cryoprobe, using samples of 0.5mM ¹³C- ¹⁵N- labeled SERF1a in 20mM NaPi, and 20mM NaCl buffers. Spectra were processed with TopSpin 3.6.5 (Bruker) and peak picked with SPARKY. SAXS data were measured at NSRRC by Dr Orion Shih and Yi-Qi Yeh.

Function of SERF1a

TAiBP approach

General scheme for generation of IDP Input : regions of ϕ, ψ angles **iBP step** : iBP algorithm with varying systematically the values of angles VanHam et al. Identification of MOAG-4/SERF as conformations ϕ,ψ within their regions to obtain conformations of protein fragments a regulator of age-related proteotoxicity. Cell 2010. **Assembly step** : Build the protein chain by assembling the fragments a positive regulator of aggregate formation TALOS-N. Shen, Bax. J Biomol NMR 56:227 δ2D-v 2.1.0 Camilloni, De Simone, Vranken MOAG-4/SE (2013) Vendruscolo. Biochemistry 51:2224 (2012) \rightarrow for polyglutamine diseases DATA SEQUENCE MARGNORELA ROKNMKKTOE ISKGKRKEDS LTASORKORD SEIMOEKO DATA PREDICTED SS LLLLLLHHH HLLLLLLLL LLLLLLLLL LL NATA CONFIDENCE 0789820133 1478778754 5689878888 8578888788 999985878 \rightarrow for amyloid-beta 50 10 20 30 40 pH = 6.8 pH = 6.8 \rightarrow for alpha-synuclein P5 P2 P3 P4 moac VSe pH = 6LYS/ARG ASP/GLU pH = 6 *i* BP⊥ i BP_ *i* BP Rescue from proteotoxic SEQUENCE ANEKKSMOTR FK 5 LLLLLLLLL L 3537778877 4 C. elegans H. sapiens (SERF) fragment4 fragment5 fragment1 fragment2 fragment3 H. sapiens (SER TALOS threshold=0.01 Fitting of M. mulatta M. musculus SAXS data TAiBP Sets of protein B. taurus D. rerio KGDSKAK-Q SOM TALOS threshold=0.02 Malliavin, Mucherino, Lavor, Liberti, Systemati conformations Fragments assembly Pooling of C. intestinalis Exploration of Protein Conformational Space Clustering D. melanogaster GKR-TD-NLTVEORKARI --- AAAGTSK--- EEA (MDAnalysis) Using a Distance Geometry Approach. With NOE conformation C. briggsae EKAAA---KKA-EEAAAA--SANAKKVAKVDPLKM (Bouvier et al, J Chem Inf Model. 2019 δ2D threshold=0.1 AAAA---KKA-AEEAAA-RAEKNKKLQVFDPL-K B. malayi No NOE sets 2014) 5. purpuratus KAAAAAAKKT-EG----AAGSSKK-Worley, Delhommel, Cordier, Malliavin, Bardiaux, N. vectensis -SEHDANKGONLTDR Wolff, Nilges, Lavor, Liberti. Tuning interval S. cerevisiae -NOK-KSG--DPKKRMESDAEILROKOAA---ADARRE-AEKLEKLKAEKTRR-Branch-and-Prune for protein structure Protein Determination. J Glob Optim 2018 $\diamond \diamond \diamond \diamond$ conformation Collab. JH Lin, S Huang and C-F Chang Van Ham et al, Cell 2010 Academia Sinica, Taiwan **Calculation examples Pocket detection** Fitting SAXS data TAiBP run: examples of iBP steps Pooling of conformations selected by Local maxima of Ten BioEn runs on BioEn with 40 % of conformations Fitting of SAXS curves CRYSOL FOR SAXS CURVES SIMULATED the set of TAIBP conformations δ2D 0.1 obtained with applying NOE restraints pocketness observed





Examples of possible binding pockets sampled in conformations of SERF1a



around basic residues

Merle et al. J Mol Biol 2019.

Experimental effects of mutations

on charges residues of SERF1a

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(c) mutation K₀-values [µM] wt 2.56±0.32 R11A 2.52±0.54 R11E 6.54±0.74 Q12A 3.61±0.39 K13A 33.89±8.56 K13E no saturable binding N14A 37.76±18.41 K16A 124.91±8A.49 K16F no saturable

no saturable binding

I7A 83.71±33.88 I7E no saturable binding 8A 2.04±0.44 aSynC-pSer129

K17A

Secondary chem aSyn binding

Human (075920-2) Drosophila (Q9VEW2) S. cerevisiae(Q3E7B7 C. elegans (Q9BKU8)



Procedure of calculation

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