Postdoctoral Position in Molecular Modeling of Intrinsically Disordered Protein Complexes

Project Title : Prediction of the three-dimensional structure of the AIF/CHCHD4 complex

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Duration : 18 months, starting October 2022.

Project Description : The protein-protein complex composed of the mitochondrial proteins AIF (Apoptosis Inducing Factor) and CHCHD4 (Coiled-coil-Helix-Coiled-coil-Helix Domain containing 4) controls the mitochondrial import and the proper folding of defined cysteine containing proteins in the mitochondrial intermembrane space in human cells [1, 2]. Thus, AIF/CHCHD4 complex shapes the mitochondrial proteome and confers to mitochondria the flexibility to adapt their functions and metabolism to maintain cell homeostasis. Recently, it has been demonstrated that AIF/CHCHD4 complex plays a key role in tumorigenesis in lung cancer [3], linking metabolism to cancer. It is consequently hypothesized that modulating the AIF/CHCHD4 association with protein-protein interaction (PPI) inhibitors might reduce the metabolic flexibility of cancer cells and kill them by apoptosis.

Unfortunately, the three-dimensional structure of the AIF/CHCHD4 complex is still unknown, impeding the rational design of inhibiting ligands. In this context, the proposed research project aims at characterizing the 3D structure of the AIF/CHCHD4 complex by *in silico* approaches, to identify the protein-protein interface and allow structure-based inhibitor design of this PPI. The tertiary structure of the full-length human AIF protein was resolved by X-ray crystallography (PDB ID : 1M6I) [4] and will serve as a basis for the modeling the AIF/CHCHD4 complex structure. An experimental 3D structure of human CHCHD4 is also available in the Protein Data Bank, but only its folded CX9C-CX9C domain (residues 45-109) could be resolved (PDB ID : 2K3J) [5]. However, Hangen *et al.* excluded the participation of this CHCHD4 domain in the interaction with AIF and rather demonstrated that its intrinsically disordered 27-residues N-terminal segment is necessary and sufficient for binding AIF [1].

To predict the structure of protein-IDP complex, we have developed an efficient protocol in three steps [6, 7] : (i) Enhanced molecular dynamics (MD) simulations of the disordered region to sample its conformational ensemble. (ii) Identification of the transient conformations with secondary structures and docking of these conformations into the IDP partner. (iii) MD simulations of the most promising complexes to refine their structures and quantify their binding free energies. We propose here to apply this approach to the case of AIF/CHCHD4 complex.

Profile : Candidates must have a PhD in computational biophysics or biochemistry with a strong background in molecular dynamics (MD) simulations. They should also have knowledge and practice of Linux shell scripting and scientific programming.

Application : tap.ha-duong@universite-paris-saclay.fr (attach a single PDF file including cover letter, curriculum vitae, list of publications, and two recommendation letters).

Références

[1] Hangen, E. *et al*. Interaction between AIF and CHCHD4 Regulates Respiratory Chain Biogenesis. *Mol. Cell* **2015**, *58*, 1001–1014.

[2] Reinhardt, C. *et al*. AIF meets the CHCHD4/Mia40-dependent mitochondrial import pathway. *Biochim. Biophys. Acta - Molecular Basis of Disease* **2020**, *1866*, 165746.

[3] Rao, S. *et al*. AIF-regulated oxidative phosphorylation supports lung cancer development. *Cell Res.* **2019**, *29*, 579–591.

[4] Ye, H. *et al*. DNA binding is required for the apoptogenic action of apoptosis inducing factor. *Nat. Struct. Mol. Biol.* **2002**, *9*, 680–684.

[5] Banci, L. *et al*. MIA40 is an oxidoreductase that catalyzes oxidative protein folding in mitochondria. *Nat. Struct. Mol. Biol.* **2009**, *16*, 198–206.

[6] Chan-Yao-Chong, M. *et al*. Investigation into Early Steps of Actin Recognition by the Intrinsically Disordered N-WASP Domain V. *Int. J. Mol. Sci.* **2019**, *20*, 4493.

[7] Chan-Yao-Chong, M. *et al*. Structural ensemble and biological activity of DciA intrinsically disordered region. *J. Struct. Biol.* **2020**, *212*, 107573.