Friedreich Ataxia: A Computational Dynamic Model of the Key Proteins Involved in the Yeast Fe-S Cluster Biogenesis

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INTRODUCTION:

Friedreich ataxia (FRDA) is a neuro-degenerative and hereditary disease which affects the equilibrium, movements coordination, muscles and heart. It is the most common autosomal recessive ataxia and it is associated with a pronounced lack of a protein named Frataxin. This protein has been associated with iron inside the mitochondria and seems to play an important role in the mitochondrial Fe-S clusters (ISCs) assembly/maturatation. There are supposed high similarities between the human and yeast molecular mechanism that involve Frataxin. Moreover, in yeast it has been experimentally demonstrated that the yeast Frataxin (Yfh1, PDB code: 2GA5) interacts with the protein Isu1, while Isu1 interacts both with the proteins Isu2 and Nfs1. These four proteins together generate the central platform for the ISC biogenesis, where Isu1/Isu2 are the scaffold proteins and Yfh1 and Nfs1 are the iron and sulfur donors respectively (see Figure 1).

METHODS:

The sequence, structure and function of the proteins Yfh1, Isu1, Isu2 and Nfs1 were studied in detail applying different bioinformatics tools. These information was compared with the current literature as well as several interactomics databases. Dockings were made for the couples of proteins Yfh1/Isu1, Isu1/Isu2 and Isu1/Nfs1. The Escher NG protein-protein automatic docking system of the Vega ZZ project was used as the basic method for the docking experiments. BIGGER-Chemera 3.0 and Hex 5.1 were employed to validate the docking results. To extract the significant solutions from the docking output-datafile, an unsupervised and automatic clustering program, which is now under submission and is called DockAnalyse, was developed with the R software environment. DockAnalyse was applied to choose the best docking solutions and, therefore, to model the dynamic protein-protein interaction mechanism among these four proteins. Tertiarydimensional structure studies and representations were made using UCSF Chimera, PyMOL and RasMol.

RESULTS:

A detailed bioinformatics study of the key proteins involved in the yeast ISC biogenesis process has been carried out. These proteins are: the yeast frataxin Yfh1 (PDB code: 2GA5), the scaffolding proteins Isu1/Isu2 and the cysteine desulfurase Nfs1. The 3D structures of the proteins Isu1, Isu2 and Nfs1 have been theoretically modeled because its real three-dimensional structures have not been solved yet. Iron and sulfur atoms were added to Yfh1 and Nfs1 respectively. The Autodock force field and the Gasteiger method was used to compute the molecule charge in VEGA ZZ. To eliminate the wrong added ions, the molecular modeling program ArgusLab was employed. Docking experiments, together with an exhaustive analysis of the docking output-datafile, were made for the protein pairs which have been shown to physically and functionally interact. These protein pairs are: Isu1/Yfh1, Isu1/Isu2 and Isu1/Nfs1. The developed program DockAnalyse was applied to each of the docking output-databyes and the obtained representative solutions are shown in Figure 2. Owing to all the studies mentioned above, a dynamic interaction mechanism with which the four analysed proteins generate the ISCs inside the yeast mitochondria has been postulated. For the scaffolding proteins Isu1/Isu2, iron binding pockets, which presumably are the ISC links, were identified in a suitable position and interaction sites were also localized. Isu1 and Isu2 tails seem to enable the ISC scaffolding function as they have been predicted as interaction regions. In the case of Yfh1, negatively charged residues implicated in the iron handling, which are high evolutionary conserved, were analysed and seem to be very close to the Isu1/Isu2 iron binding pockets after the docking experiment. This suggests that Yhf1 can act as the iron donor for the ISC biogenesis process. The function of this group of electro-negative residues, together with the identified interaction region that is also high evolutionary conserved, fit properly with the current literature and the proposed model. Regarding Nfs1, it is the protein that seems to act as the Sulfur donor. These iron and sulfur atoms are very close to the Isu1 iron binding pocket. The Isu2 iron binding pocket might help that of Isu1 to form the entire ISC (see Figures 2 and 3).

CONCLUSION:

- The sequence, structure and function of the proteins Yfh1, Isu1, Isu2 and Nfs1 have been bioinformatically studied.
- Protein-protein docking experiments have been applied to these proteins and a new clustering method has been developed to analyse the docking results.
- A model by which these proteins dynamically interact together to generate the ISC inside the yeast mitochondria has been suggested.
- This hypothesis would be helpful to better understand the function and molecular properties of Frataxin and be useful for a future treatment of FRDA.

WORK IN PROGRESS

References:

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