Computer Modeling of Protein-Protein Interactions with Hsp70 to Understand the SOD2 Import to Mitochondria for Regulation of Oxidative Stress

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Mitochondrial respiration produces an influx of reactive oxygen species (ROS), which are highly reactive molecules that attack other cell components. An excess of ROS leads to oxidative stress, which causes major diseases such as cancer, Asperger syndrome, ADHD, Parkinson's disease. Cells produce an enzyme called SOD2 to clear ROS. SOD2 is transported to the mitochondria by chaperone protein Hsp70. The detailed step-by-step mechanics of this process is unknown, and my goal is to understand this for potential drug design. I used molecular modeling to study the transport process, as it is much cheaper and time effective than a lab study. The published model of HSP70 is partially unsolved and not accurate to the body, therefore Homology Modeling and Molecular Dynamics simulations were used. I used a modified local perturbation protocol of RossettaCommons to model the protein binding. I had to use The cluster at PSC(Bridges) for the calculations. To visualize the proteins, I used the PyMOL visualization software. I generated the most likely dockings using a Monte Carlo simulation algorithm. The different dockings were ranked based on an energy scoring function. I found that the SOD2 transport is regulated by Hsp70 interactions with CHIP (which inhibits SOD2 binding) and OLA1 (which favors SOD2 binding) with both sharing the same binding sites of Hsp70. When a cell wishes to have more SOD2, it sends the AKT protein to phosphorylate Hsp70. The negatively charged phosphate repels the negatively charged residues of CHIP and attracts positively charged residues of Hsp70. This allows OLA1 to bind to the Hsp70, which facilitates the binding of SOD2 to Hsp70/OLA1 complex. Once the complex of three proteins is formed, Hsp70 can transport SOD2 to the mitochondria.