Protein-Protein Docking Analysis and Refinement of the Ubiquitin- and Tetraubiquitin-associated IκBα / NF-κB Complex

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The discovery about 40 years ago that certain proteins are ubiquitinated before degradation was awarded the Nobel Prize in Chemistry in 2004. Ubiquitin-mediated destruction and signaling play essential roles in DNA repair, cell-cycle regulation, cell growth, and immune response function. [1]

Nuclear Factor- κB (NF-κB) is a dimeric transcription factor that contains p50 and p65 subunits and is involved in the control of a large number of physiological cellular and organismal processes (i.e., cell growth, apoptosis, immune and inflammatory responses). The inhibitor proteins (i.e., IκBα) bind directly to the NF-κB and inhibit its transcriptional activity. In resting cells, the half-life of NF-κB dimers bound to IκBα is on the order of days, thus virtually no dissociation of the complex is seen in the cell in the absence of stimulation. However, when IκBα is phosphorylated at Serine amino acids at positions 32 and 36 and then ubiquinated at positions Lys21 and/or Lys22 and degraded by the proteasome, it frees NF-κB. Thus, ubiquitin signaling in the NF-κB pathway is so crucial that misregulation may lead to serious diseases such as cancer, neurodegenerative and immunological diseases. [2, 3]

We investigated the ubiquitination of IκBα / NF-κB at positions Lys21 and Lys22 in the phosphorylated and unphosphorylated IκBα forms. ROSETTA Molecular Modeling Suite is used for rigid-body protein/protein docking and for each complex 10000 docking poses is generated. *Clustering* module is then used for filtering out the similar conformations using a certain threshold value of RMSD. Final models are then energy minimized using MM/OPLS force field and structures that have the lowest energy is selected for further analyses (MD simulations). In this talk, protein-protein interaction analysis and refinement of the ubiquitin and tetraubiquitin-associated IκBα / NF-κB complex will be detailed.

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