Predicting Nucleolin Interactions in DNA Repair: An in silico Approach

Shivji, Sukaina (School: Staten Island Technical High School)
Fan, Laura (School: Staten Island Technical High School)

Protein-protein interactions guide essential life processes, including DNA repair. Nucleolin has many roles, but few efforts have been made to fully characterize its role in DNA repair. In this study, we used protein structure prediction and docking to analyze the interactions between nucleolin and key DNA repair proteins. We constructed a protein interactome of nucleolin with 23 potential DNA-repair interacting proteins, then chose four of these proteins for further study: MGMT, APEX1, RAD54B, and TERT. With an ultimate goal of conducting docking simulations that model the physical interactions, each protein underwent a thorough preparation process: we compared the results of multiple comparative modeling servers to generate a protein model that passed multiple accuracy analysis tools. From there, we refined each model and again used the most accurate ones. We used two docking servers, inputting nucleolin and one of our four DNA repair proteins separately. After ordering the interactions from the top ten models for each nucleolin-protein input, we predicted the 5 residues most consistently predicted to be involved in each interaction. These motifs are thus predicted to be most essential for nucleolin's role in expediting DNA repair and are candidates for targeting in rationally designed mutagenesis experiments. The models with the greatest number of top residues represent the most probable docking conformation. Experimentally mutating these select residues may cause loss of function by inhibiting the protein-protein interaction, confirming our results. As a result, DNA repair will proceed at a slower rate, leaving cancer cells more susceptible to chemotherapy treatments.

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