An Optimized Molecular Docking Protocol Targeting Musashi RNA-Binding Proteins for Cancer Drug Design

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Acute Myeloid Leukemia (AML) is a deadly blood cancer in which abnormal blast cells crowd out healthy blood cells in bone marrow. Although AML is the most common adult leukemia, its survival rate remains just 27.4%. The Musashi 2 (MSI2) protein, which regulates stem cell division, is necessary for AML progression and a promising drug target for AML targeted therapy. But due to its high flexibility as an RNA-binding protein (RBP), this “undruggable” protein lacks well-defined binding pockets. This presents significant challenges to conventional virtual screening that uses rigid-body docking calculations to evaluate binding affinities of MSI2 inhibitors, rendering RBP inhibitor design incredibly difficult. Because RBPs undergo extensive conformational changes upon ligand binding, it was hypothesized that incorporating protein flexibility in docking calculations will improve accuracy. In this study, rigid-body and flexible docking protocols were evaluated with known MSI2 inhibitors using its NMR and X-Ray structures. Ten actives and 1453 decoys of MSI2 were collected for retrospective docking using AutoDock. Docking performance was assessed through binding geometry, Enrichment Factor, and area under Receiver Operating Characteristic curve (AUC) analysis. Enabling flexibility of target site residues, using optimized rigid-body docking parameters and the NMR structure, significantly improved binding site specificity but diminished the accuracy of the docking scoring function. These findings suggest reasonable incorporation of receptor flexibility is essential for accurate docking of RBPs, including MSI2. The optimized docking protocol for this challenging class of drug targets is expected to advance novel drug lead discovery for a broad spectrum of diseases.

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