Studying the Interactions between Small Molecule Ligands and Eukaryotic Translation Initiation Factors eIF5B and eIF4E

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Eukaryotic translation initiation is a highly regulated process that requires several initiation factors and their coordination for successful protein synthesis. Under stress conditions, when the α-subunit of eIF2 gets phosphorylated, global mRNA translation is attenuated. However, it has been suggested that eukaryotic translation initiation factor 5B (eIF5B) parallels the role of eIF2α after its phosphorylation. This provides a critical survival switch to the cell under stress conditions. Indeed, eIF5B has been shown to play an essential role in the survival of cells by facilitating the translation of anti-apoptotic proteins to preclude programmed cell death. Cancer cells take advantage of this function of eIF5B to bypass apoptosis. Many cancers including glioblastoma multiforme (GBM), hepatocellular carcinoma (HCC) and lung adenocarcinoma (LUAD) have shown high eIF5B protein levels. Recently, a small molecule compound called LWW31 was suggested to bind at the N-terminal region (248-351 aa) of eIF5B, while other experiments suggest that this region does not seem to have functional significance. As protein can have multiple binding sites for ligands, we used a computational approach to understand whether LWW31 can bind in the highly conserved functional C-terminal region of eIF5B (587-1220 aa). Additionally, we also studied the interaction of ribavirin (RBV) with eukaryotic translation initiation factor 4E (eIF4E), which plays a crucial role in oncogenesis just like eIF5B. Initially, comparative protein modelling and molecular dynamics (MD) simulations were performed for eIF5B as there is no reliable three-dimensional structure available, while MD simulations were performed based on accurate crystal structures for eIF4E to understand protein structural dynamics. Then, we performed docking calculations to determine the preferred LWW31 binding sites. Finally, MD simulations of the eIF5B-LWW31 and eIF4E-RBV complexes were performed to gain additional information about the stability of ligand binding. We also investigated the cell and molecular biology aspect to test the small molecule RBV and its potential to be used as a therapeutic. The computational and experimental data obtained will lay the groundwork for future biological testing of RBV and LWW31 for cancer treatment.