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# Targeting APP IRE mRNA to Combat Amyloid -β Protein Expression in Alzheimer's Disease

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**Abstract :** Alzheimer's disease is characterized by the accumulation of the processing products of the amyloid beta peptide cleaved by amyloid precursor protein (APP). Iron increases the synthesis of amyloid beta peptides, which is why iron is present in Alzheimer's disease patients' amyloid plaques. Iron misregulation in the brain is linked to the overexpression of APP protein, which is directly related to amyloid-β aggregation in Alzheimer's disease. The APP 5'-UTR region encodes a functional iron-responsive element (IRE) stem-loop that represents a potential target for modulating amyloid production. Targeted regulation of APP gene expression through the modulation of 5'-UTR sequence function represents a novel approach for the potential treatment of AD because altering APP translation can be used to improve both the protective brain iron balance and provide anti-amyloid efficacy. The molecular docking analysis of APP IRE RNA with eukaryotic translation initiation factors yields several models exhibiting substantial binding affinity. The finding revealed that the interaction involved a set of functionally active residues within the binding sites of eIF4F. Notably, APP IRE RNA and eIF4F interaction were stabilized by multiple hydrogen bonds with residues of APP IRE RNA and eIF4F. It was evident that APP IRE RNA exhibited a structural complementarity that tightly fit within binding pockets of eIF4F. The simulation studies further revealed the stability of the complexes formed between RNA and eIF4F, which is crucial for assessing the strength of these interactions and subsequent roles in the pathophysiology of Alzheimer's disease. In addition, MD simulations would capture conformational changes in the IRE RNA and protein molecules during their interactions, illustrating the mechanism of interaction, conformational change, and unbinding events and how it may affect aggregation propensity and subsequent therapeutic implications. Our binding studies correlated well with the translation efficiency of APP mRNA. Overall, the outcome of this study suggests that the genomic modification and/or inhibiting the expression of amyloid protein by targeting APP IRE RNA can be a viable strategy to identify potential therapeutic targets for AD and subsequently be exploited for developing novel therapeutic approaches.

**Keywords :** Alzheimer's disease, Protein-RNA interaction analysis, molecular docking simulations, conformational dynamics, binding stability, binding kinetics, protein synthesis.
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