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Exploring the Direct Interaction of Epitalon with Human Telomerase Reverse Transcriptase via Molecular Modeling

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Human telomerase reverse transcriptase (hTERT) is the catalytic subunit essential for telomere elongation and is closely linked to cellular aging and tumorigenesis. The synthetic tetrapeptide Epitalon (Ala-Glu-Asp-Gly) has been reported to increase telomerase activity in cellular assays, but the mechanism of action remains unclear. Several cryo-EM structures of human telomerase are available at near-atomic resolution. However, variability in side-chain conformations is observed across models, particularly in flexible domains such as TEN and IFD. These structural variations complicate the identification of consistent peptide-binding sites and provide a rationale for computational modeling approaches. In this study, we collected and refined structural data of hTERT and defined candidate surfaces for peptide docking. Molecular docking of Epitalon was performed, and the resulting poses were analyzed by RMSD-based clustering and interaction profiling. The docking results showed heterogeneous binding modes across structures, with clusters recurring near flexible domains but without a single dominant binding site. These findings indicate that molecular dynamics simulation is required to identify stable binding interactions of Epitalon with hTERT, as docking results are heterogeneous and side-chain conformations differ across available structures. This study provides structural insight for the direct-binding hypothesis of Epitalon and suggests a basis for further computational and experimental validation.