Poster Presentation

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Molecular basis of TRF proteins and their interactions with peptides

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Telomeres are nucleoprotein complexes and specialized heterochromatic structures present at the ends of eukaryotic chromosomes which ensure their proper function. A group of proteins interacting with telomeric DNA is named shelterin complex and it includes TRF1 and TRF2 which in turn recruit RAP1, TIN2, TPP1 and POT1.[1] They are found abundant at chromosome ends and are present at telomere throughout the cell cycle, and their known functions are limited to telomeres. All these six proteins form a DNA protecting complex which allows cells to differentiate end of telomeric DNA from sites of DNA damage. In particular, TRF1 (Telomere Repeat Binding Factor 1) interacts specifically with the duplex DNA and is implicated in telomere replication, telomere protection, and telomere length maintenance. Whereas, TRF2 (Telomere Repeat Binding Factor 2) was identified as a TRF1 paralog.[1] TIN2 binds TRF1 and TRF2 simultaneously, and this link contributes to the stabilization of TRF2 on telomeres. TIN2 mediated co-operative binding of TRF1 and TRF2 to telomeres has an important role for the mechanism of telomere length regulation and protection.[1,2]
Shelterin complex functions not only to protect telomeres from being recognized as double strand breaks but also to maintain telomere length homeostasis, that is associated with tumorigenesis and aging.[1] Telomere dysfunction is believed to be significant factor in carcinogenesis. Reduced expression of TRF1 is associated with tumor progression and poor prognosis in cell carcinoma. The dynamic details of protein-peptide interactions at molecular level of such functionally important (shelterin) proteins were lacking. To elucidate the molecular basis of these proteins interactions at molecular level, we have carried out molecular dynamics simulations for 1000 ns on TRF1TRFH (TRFH=TRF homology domain) protein in complex with TIN2TBM (TBM = TRF-binding motif) and TRF2TRFH protein in complex with TIN2TBM/ApolloTBM.[3] Proteins crystal structures for TRFH domains of TRF1TRFH and TRF2TRFH proteins were retrieved from the protein data bank (PDB). Our study addressed structural and dynamic comparison of protein-peptide complexes including H-bond interactions and covered residues which may regulate binding of TRF proteins with peptides, especially focusing on interactions described in crystallographic data. This study revealed that TIN2TBM forms a well-defined binding mode with TRF1TRFH as compared to TRF2TRFH, and that the binding pocket of TIN2TBM is deeper for TRF2TRFH protein than ApolloTBM. Efforts were made to explain mutation done in crystallographic work for TRF proteins using data from MD. Our MD data together with previous X-ray structure bring a detailed view of the TRF-peptide binding mode and the structure of TRF1/2 binding pockets.[3] Particular TRF-peptide interactions were very specific for protein-peptide complex formation, TRF proteins could be used as a potential target for design of inhibitors/drugs modulating telomere machinery and for anticancer therapy.
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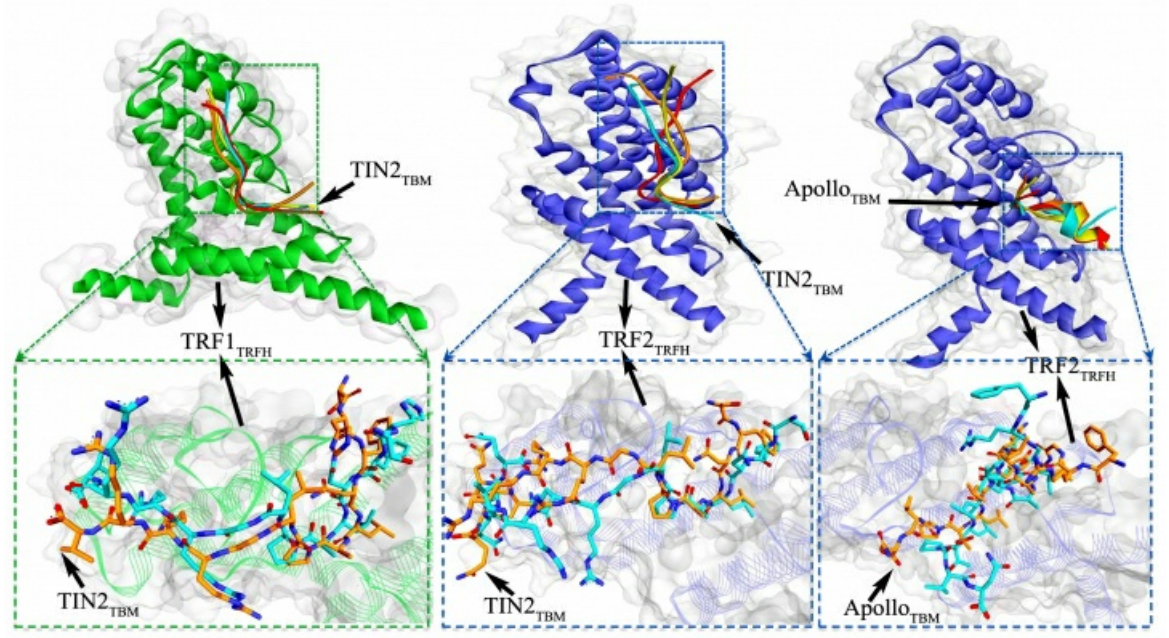

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