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Structure and function of the human telomeric POT1-TPP1 complex and its role in cancer

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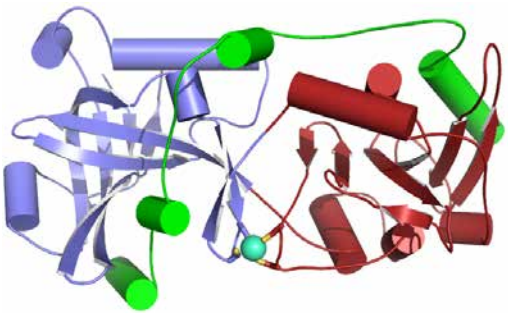
The telomeric shelterin, POT1-TPP1 sub-complex is involved in telomere length regulation and maintenance. POT1 binds the telomeric overhang with high affinity and specificity and represses ATR-dependent DNA damage response (DDR). TPP1 is involved in telomerase recruitment to telomeres. Several naturally occurring POT1 mutations are implicated in chronic lymphoid leukemia and familial glioma and melanoma. However, the mechanism of POT1-TPP1 binding and how naturally occurring POT1 mutations contribute to cancer remains unknown. Here, we report the crystal structure of the interacting portions of POT1-TPP1 which includes the POT1 C-terminus (POT1C) and the POT1 binding domain of TPP1 (TPP1 (PBD)). POT1C consisting of an OB-fold and a holiday junction resolvase domain. TPP1 (PBD) consists of several loops and helices involved in extensive interactions with POT1C. The structure reveals that several of the POT1C cancer associated mutations partially disrupt the POT1-TPP1 complex. Biochemical and cell-based assays show that disruption of POT1-TPP1 leads to decreased POT1 telomere binding efficiency resulting in persistent telomerase activity at telomeres. This leads to longer and fragile telomeres resulting in undesired DDR, genomic instability and cancer.



Biography

Prashanth Shastrula has his expertise in protein nucleic acid assemblies that maintain the integrity of the ends of our chromosomes referred to as telomeres. His long-term goal is to understand how naturally occurring mutations on the human telomeric shelterin complex contribute to cancer and identify methods to treat this disease.

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