Structural and Functional Study of the Bloom Syndrome Protein

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Bloom Syndrome (BS) is an autosomal recessive human disorder characterized by genomic instability and a predisposition to a wide variety of cancers. The gene mutated in BS encodes a three domains enzyme, the Bloom Syndrome Protein (BLM), which C-terminal extension can be divided in two subdomains: RecQ-Ct and HRDC.

We report herein that the RecQ-Ct domain, responsible for DNA unwinding, contains a zinc finger motif. In order to understand the role of this motif in BLM, we constructed a series of mutations altering its highly conserved residues. Experiments done with these mutants showed that they were severely impaired in DNA binding and for the subsequent ATPase and helicase activities, revealing the importance of the zinc finger motif for all the functions of the enzyme. We computed the three dimensional structure of the RecQ-Ct domain by homology modeling using the template structure of the RecQ helicase from *E. coli*. This model allowed us to study the consequences of mutations observed in the Bloom Syndrome Protein when associated to a cancer. The mutant enzymes have been expressed in *E. coli* and their activities have been compared to the wild type enzyme. In order to get new insight in the molecular basis of Bloom Syndrome disease, we underwent the crystallization of the RecQ-Ct and HRDC domains in presence of various DNA substrates.

Keywords: cancer, DNA-protein interactions, structure-function