**Title of the Thesis: Investigating the molecular mechanism of DNA strand annealing by human RECQ1 helicase**


## Abstract

RECQ1 is the smallest and most abundant among the five human RecQ helicases and can unwind complex DNA substrates like replication and recombination intermediates with a 3′ to 5′ polarity in presence of ATP. RECQ1 is also capable of annealing complementary strands in absence of ATP. This strand annealing activity is thought to be important during branch migration and Holliday junction dissolution. RECQ1 comprises two RecA like domains and a RecQ C-terminal domain containing the zinc-binding (ZnD) and winged-helix (WH) domain. Mutations or deletions on the tip of a β-hairpin located in the WH domain are known to abolish the unwinding activity. Interestingly, the same mutations on the β-hairpin of annealing incompetent RECQ1 mutant (RECQ1$^{T1}$) have been reported to restore its strand annealing activity. In an attempt to unravel the strand annealing mechanism, the role of the β-hairpin and contribution of the WH domain in modulating the strand annealing activity was investigated. Analysis of the interface between ZnD and WH domain identified an α-helix located in ZnD that potentially interacts with the residues of the WH domain. These interactions play a significant role in strand annealing activity. The present study shows that deletion of the α-helix or mutation of specific residues on it restores strand annealing activity of annealing deficient constructs of RECQ1. The results obtained also demonstrate that mutations on the α-helix induce conformational changes and affects DNA stimulated ATP hydrolysis and unwinding activity of RECQ1. This study, for the first time, provides insight into the conformational requirements of the WH domain for efficient strand annealing by human RECQ1.



Keywords: RECQ1, strand annealing, winged-helix, conformational change, DNA binding