Role of Rothmund-Thomson Syndrome Helicase in DNA Replication Initiation

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DNA replication is essential for the accurate transmission of genetic information during cell division. The Rothmund-Thomson syndrome helicase (RECQ4) plays a crucial role in replication initiation, yet its precise function and regulation remain poorly understood. Mutations in RECQ4 are linked to Rothmund-Thomson, RAPADILINO, and Baller-Gerold syndromes, while its overexpression has been associated with cancer, highlighting the need for a better understanding of its role. This study investigates RECQ4's interactions with the key replication proteins MCM10 and CDC45, focusing on their effect on RECQ4's DNA binding and phase separation properties. I found that MCM10 enhances both functions, whereas CDC45 inhibits them. Interestingly, despite these opposing effects, all three proteins form a complex, suggesting a regulatory model in which CDC45 maintains RECQ4 in an inactive state until MCM10 promotes its activity to initiate replication. Furthermore, these results indicate a possible important role of phase separation in regulating replication initiation by concentrating replication factors at the origin, ensuring precise and efficient activation. These findings offer new insights into the spatial and temporal regulation of DNA replication and enhance our understanding of RECQ4's role, which may contribute to uncovering the molecular basis of RECQ4-associated diseases and pave the way for potential therapeutic advancements.

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