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Mechanism underlying the coordination of high fidelity replication with mutagenesis translesion synthesis

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Statement of the Problem: Replicative polymerases (Pols), such as *E. coli* Pol III, cannot replicate past most DNA lesions, leading to stalled replication forks. Organisms have therefore evolved specialized Pols that function in translesion DNA synthesis (TLS), a mechanism that bypasses DNA lesions and permits continued replication. Recent evidence supports the view that TLS Pol IV switches with the replicative *E. coli* Pol III to coordinate replication with lesion bypass. As part of this mechanism, genetic evidence and in silico modeling suggests that direct interactions of both Pols with β clamp and each other are required for switching. In previous work, a Pol IV mutant bearing a T120P substitution (Pol IV-T120P) was impaired for the Pol III-Pol IV switch. Here we show Pol IV is capable of directly interacting with Pol III core ($\alpha\epsilon\theta$), including the Pol III α catalytic and the Pol III $\epsilon\theta$ proofreading subassemblies. Biochemical evidence suggests Pol IV binds two distinct sites on both Pol III α and the Pol III $\epsilon\theta$. Further, Pol IV-T120P is impaired for these interactions as only a single binding site between Pol IV-T120P-Pol III α and Pol IV-Pol III $\epsilon\theta$ was identified. Mutagenesis of the region surrounding T120 and subsequent analysis in a genetic assay suggests a distinct surface on Pol IV is required to displace Pol III during the Pol III-Pol IV switch. Additionally, we have identified a novel interaction between the β clamp and Pol IV. Taken together, these results support a new model for the Pol III-Pol IV switching mechanism. Interestingly, Pol-Pol interactions are not unique to Pol III-Pol IV, as Pol-Pol interactions were also identified among other *E. coli* Pols, suggesting a fundamental role for these interactions in Pol switching.

Biography

Mark Sutton has expertise in DNA replication, DNA repair, and DNA damage tolerance. He uses a combination of genetic and biochemical approaches to understand the coordination of these functions with a focus on defining the mechanisms underlying the coordination of the actions of replicative, repair and translesion synthesis DNA polymerases.

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