# Coordinated activity of the human mitochondrial DNA polymerase and SSB proteins at the replication fork

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Mitochondrial DNA polymerase gamma (Polγ) is the sole polymerase responsible for replication of the mitochondrial genome. It is well established that defect in mtDNA replication lead to mitochondrial dysfunction and disease. To date, approximately 150 disease mutations in Pol γ have been identified, which places Pol γ as a major locus for mitochondrial disease. To understand the molecular basis of these diseases, it is important to define the molecular mechanisms that govern the enzymatic activity of Polγ. To this end, we are using optical tweezers to: 1) study the real-time kinetics of individual Pol γ molecules during primer extension and strand displacement DNA synthesis and, 2) to determine the effect of human mitochondrial single stranded binding proteins (HmtSSB) on these reactions. Our results show that HmtSSB strongly modulates the real time kinetics of Pol γ. During primer extension HmtSSB plays a crucial role establishing the template-primer structure at the polymerase active site, increasing in this way the polymerase processivity and nucleotide incorporation rate. During strand displacement, DNA binding of HmtSSB to the displaced strand destabilizes the replication fork, favoring the polymerase advance. We will discuss the implication of these findings on the mtDNA replication context.