

**Stony Brook University
The Graduate School**

Doctoral Defense Announcement

Abstract

Structure-Function Studies of Mitochondrial DNA Polymerase

By

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Mitochondrial DNA polymerase γ (pol γ) is the only DNA polymerase within mitochondria, and is responsible for both mtDNA replication and repair. Mutations of pol γ have been implicated in several human diseases and cause accelerated aging in mice. Contrast to yeast, which only contains the catalytic subunit, an accessory subunit (pol γ B) has been observed in higher eukaryotes like *Drosophila* and mammals and shown to enhance processivity and substrate binding of the catalytic subunit (pol γ A). *Drosophila* pol γ has been reported to be a heterodimer containing one pol γ A and one pol γ B polypeptide. However, mouse pol γ B, when crystallized, forms a homodimer. In this study, using various biophysical approaches, human pol γ has been determined to be a heterotrimer formed by one catalytic subunit and two accessory subunits. Furthermore, the integrity of the stoichiometric composition of pol γ A and pol γ B within the human pol γ holoenzyme is shown to be important for maintaining pol γ processivity. A deletion derivative of pol γ B which is unable to dimerize consequently is impaired in its ability to stimulate processive DNA replication. For a better understanding of the subunit interaction, regions within pol γ B and pol γ A were identified that are required for complex formation. A pol γ B interacting domain was mapped to the spacer region of pol γ A which is located between the catalytic domain and the exonuclease domain of pol γ A. In addition, the structure of human pol γ B was determined at 3.2 Å by molecular replacement.

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