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G-quadruplexes are associated with mitochondrial genetic variants and stall the mitochondrial replisome

Jun Ding
National Institute on Aging, NIH, USA

Mutations in the mitochondrial (mt) genome have been correlated with cancer and aging. G-quadruplexes (G4), secondary DNA structures that arise in guanine (G)-rich templates, potentially stall the mt replisome and thereby promote mutagenesis. We used computational analyses of genome sequence data from two Italian cohorts to demonstrate an association between G4s and mt variation. We used the software G4Hunter to predict G4-forming regions in the mtDNA and found statistically significant enrichment of mutations in stable G4 regions, with preferential enrichment of variants in G4 loops. *In vitro* biochemical data demonstrate that G4s potently block the mt replicative polymerase gamma (Pol γ). Addition of mt replisome-associated factors, including TWINKLE helicase, mt single-strand binding protein, and mt transcription factor A were each unable to stimulate Pol γ synthesis through the G4 block; however, the G4-resolving helicase Pif1, known to partly reside in mt, allowed Pol to make fully extended product using the G4 template. We show that mt primase-polymerase PrimPol further catalyzes error-prone nucleotide incorporation into G4 structures, suggesting that it might be involved in G4 bypass with accompanying increased risk of mutation. Altogether, the computational and biochemical approaches indicate that mt point mutations are enriched at stable G4 structures, consistent with replisome stalling at G-quadruplexes and reliance on error-prone DNA synthesis.

Biography

Dr Jun Ding is currently a staff scientist in the Laboratory of Genetics at National Institute on Aging, NIH. His primary research interest is in the development of statistical methods for analysing human genetic data. Specifically, his methodology work focuses on developing new statistical methods for genome-wide association studies of gene expression and my applied research projects focus on the genetic studies of psoriasis.

jun.ding@nih.gov

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