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DNA mismatch repair complex of malaria parasite *Plasmodium falciparum* to fight drug resistance

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Abstract

Malaria is a global disease and a major health problem. The control of malaria is a daunting task due to the increasing drug resistance. Therefore there is an urgent need to identify and characterize novel parasite specific drug targets. This drug resistance might be due to defective mismatch repair (MMR) in the parasite. Here we report the detailed biochemical characterization of the main components of MMR complex, MLH and the parasite specific UvrD helicase, from *P. falciparum*. MLH is an ATPase and it can incise covalently closed circular DNA in the presence of Mn^{2+} or Mg^{2+} ions. Using IFA we report that peak expression of MLH in both 3D7 and Dd2 strains of *P. falciparum* is mainly in the schizont stages of the intraerythrocytic development, where DNA replication is active. The N-terminal fragment (PfUDN) containing UvrD helicase domain, which consists of helicase motifs Q, Ia-Id, II, III and most of motif IV and the C-terminal fragment (PfUDC1) containing UvrD helicase C terminal domain, consisting of remaining part of motif IV and motifs IVa-IVc and 161 amino acids of intervening sequence between motif IV and V possess ssDNA-dependent ATPase and DNA helicase activities *in vitro*. Using immunodepletion assays we show that the ATPase and helicase activities are attributable to PfUDN and PfUDC1 proteins. The helicase activity can utilize the hydrolysis of all the NTPs and dNTPs and the direction of unwinding is 3' to 5'. The endogenous *P. falciparum* UvrD contains the characteristic DNA helicase activity. PfUDN interacts with PfMLH and modulates the endonuclease activity of PfMLH and PfMLH positively regulates the unwinding activity of PfUDN. We show that PfUvrD is expressed in the nucleus distinctly in the schizont stages of the intraerythrocytic development of the parasite and it colocalizes with PfMLH. These studies will make an important contribution in understanding nucleic acid transaction in the malaria parasite.

Biography

Currently Renu Tuteja is a Staff Research Scientist at International Centre for Genetic Engineering & Biotechnology (ICGEB), New Delhi, India. She has done her education (M.Sc., and Ph.D.) in Biochemistry and Chemistry from University of Lucknow and Kanpur and postdoc at NIH, Bethesda & UCLA, Los Angeles. She is elected fellow of the environmental science academy (FNESA). Only in helicase field she has published more than 55 papers in high impact journals. Dr. Tuteja's overall work in parasite biology has led to annotation of a number of novel genes in PlasmoDB. She received Top Cited Paper Award from FEBS J. Publications: ~100; Book Edited: 4.