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Analysis of mutations in the helicase domain of hepatitis E virus derived from patients with fulminant hepatic failure

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Fulminant hepatic failure (FHF) is the severe form of hepatitis E virus infection. Virus sequence analyses from severe cases have shown presence of unique and highly conserved mutations in the helicase domain of genotype 1, 3 and 4 viruses. We evaluated role of two amino acid replacements (L1110F) and (V1120I); found to be frequent in genotype 1 FHF-E viruses from India. Three mutant helicase proteins (two with single point mutations and one with dual mutations) were expressed in E.coli and evaluated for their ATPase and RNA unwinding activities. Both L1110F and V1120I helicase mutants showed marginal decrease in ATPase activity, while L1110F/V1120I dual mutant showed normal ATPase activity. All three mutants proteins showed RNA unwinding activities comparable to wild type protein. Corresponding mutations were made in the helicase domain of HEV RLuc replicon and replication efficiencies were tested in the S10-3 (Huh 7) cells. The mutant replicon V1120I showed lower replication as compared to L1110F and L1110F/ V1120I mutants. However, all three replicon mutants showed lower replication efficiencies as compared to the wild type replicon. Walker A and Walker B motif mutant HEV replicons were unable to replicate indicating essential role of the virus encoded helicase domain during HEV replication. FHF-E associated helicase mutations resulted in only marginal decrease in the virus replication suggesting alternate function/s of the helicase protein. Mutations in the helicase domain of FHF-E viruses may be responsible for changing virus or host-virus protein-protein interactions, causing alterations in the host responses, causing severe disease.

Biography

Kavita Lole completed Ph.D. at the University of Pune, India and analyzed stress response of the mosquito Anopheles stephensi'. After three years postdoctoral research at the Pune and Johns Hopkins University, USA joined the National Institute of Virology, Pune, India in 1998. Major research interests being molecular epidemiology of hepatitis viruses, development of vaccines against hepatitis viruses and emerging viruses, development of diagnostic tests for viruses. She is currently heading the Hepatitis group, studying molecular mechanisms of hepatitis E virus replication and pathogenesis. Hepatitis E virus is a major public health concern in India and also in several developing countries.

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