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Role of CCR5 levels in HIV-1 evolution and pathogenesis

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CCR5 co-receptor expression levels in the host play an important role in HIV pathogenesis not only by regulating viral entry but also disease progression. Several genome wide association studies have recently linked the CCR5 genotype to HIV pathogenesis. Interestingly, the best evidence for the role of CCR5 levels in HIV pathogenesis comes from HIV+ individuals heterozygous for the CCR5delta32 gene that show a marked delay in progression to AIDS. CCR5 levels are also regulated by promoter polymorphisms in humans resulting in a complex role in HIV infection and disease progression. However, it remains unknown how varying CCR5 levels affect HIV evolution and disease progression. We recently showed using T cell lines expressing low levels of CCR5 that co-receptor expression on cell surface affects HIV Envelope mediated bystander apoptosis while supporting virus replication. In these cells expressing low levels of CCR5, HIV replication studies resulted in the emergence of an adapted virus harboring the mutations E170K in V2 loop and N298Y in the V3 loop. The adapted virus maintained CCR5 tropism although the mutations arising in this study have been associated with CXCR4 tropism in patients. Interestingly, the adapted viruses exhibited an increase in Maraviroc IC50 presumably by evolving higher affinity for CD4 and or CCR5. *In vivo*, in HIV infected patients, the CCR5 promoter polymorphisms 59353C, 58934G, 59029A and 59402A were associated with lower CD4 counts as well as prevalence of AIDS. Haplotype determination showed that the above polymorphisms were found in the non-HHC haplotype. Thus, CCR5 co-receptor levels may alter diseases progression rate as well as virus evolution in HIV infected individuals. Hence, caution needs to be implemented with recent gene therapy approaches as well as drugs targeting the CCR5 receptor for HIV treatment.

Biography

Anjali Joshi is an Assistant Professor in the Department of Biomedical Science at Texas Tech University Health Sciences Center. She has completed her PhD in Feline Immunodeficiency Virus from North Carolina State University, USA. She has received four years of Post-doctoral training at the National Cancer Institute, Frederick on retrovirus assembly and release. Her research interests include the role of cellular factors and viral domains in determining the site and process of retrovirus assembly, HIV pathogenesis and anti-HIV gene therapy.

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