Retrovirology

Poster presentation

Fourth NF-κB site in HIV-1 subtype-C LTR confers functional advantage to viral gene expression

Mahesh Bachu*[1], Rajesh V Murali[1], Anil MHKH Babu[1], Venkat SRK Yedavalli[2], Kuan-Teh Jeang[2] and Udaykumar Ranga[1]

Address: [1]Molecular Virology Laboratory, Molecular Biology and Genetics Unit, Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore, India and [2]Molecular Virology Section, Laboratory of Molecular Microbiology, National Institute of Allergy and Infectious Diseases, the National Institutes of Health, Bethesda, Maryland 20892-0460, USA

* Corresponding author

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Subtype-C strains of HIV-1, among the various viral subtypes, are responsible for ~50% of the global and 85-99% of Indian infections. Among others, the most significant molecular feature differentially conserved in the subtype-C promoter is the polymorphism within the enhancer region constituted by NF-κB sites. While the viral promoter of majority of the subtypes contains two NF-κB sites, subtype-C promoter consists of three canonical motifs. Notably, a minority of clade-C primary isolates contain κB or κB-like sites, in addition to the canonical κB sites. Previous studies from our laboratory identified nearly 6% (34/609) of the primary isolates from India to demonstrate κB-site polymorphism in C-LTR. The functional importance of additional κB or κB-like sites in C-LTR has not been evaluated. We confirmed the subtype nature of the viral isolates by sequencing and phylogenetic analysis of LTR, Tat and Env in 20 of 34 samples demonstrating κB-site polymorphism. Sequence analysis of the additional κB- or κB-like sites identified extensive variation among the viral isolates. Among them, a particular sequence variation, constituting the κB-like site GGGACTTTCT, with a C-T variation at position 10, was found to be the most common. The functional importance of the κB-like site in C-LTR has been evaluated by reporter gene expression from isogenic LTR promoters and EMSA. We compared gene expression pattern of LTR constructs in Jurkat cells under different conditions of cell activation including TNF-α, PMA, PHA and combinations that activate NF-κB pathway. The data demonstrate the strongest reporter gene expression from the LTRs containing the additional κB-like sites especially under synergistic activation conditions. Gel shift experiments with TNF-α activated Jurkat cell nuclear extracts showed the recruitment of p50/p65 heterodimer to the variant κB-like site. Our data for the first time provide experimental evidence that the κB-like site in C-LTR is an authentic κB-site and this site confers quantitative and qualitative gain of function. Furthermore, we hypothesize that this gain of function may augment viral fitness and hence contribute to global predominance of subtype-C infections.