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Analysis of HIV-1 *nef* from patients presenting with rapid progression and delayed progression to AIDS

Poonam Gupta[1,2], Arvind Rai[1], Charoo Hans[3], Supriya Singh[1], Megha Singhal[1], Uma Sharma[1], L. S. Chauhan[1] and Mohammad Husain[2]

[1]Division of Biochemistry & Biotechnology, National Centre for Disease Control (NCDC), Dr. Ram Manohar Lohia Hospital, India
[2]Department of Biotechnology, Jamia Millia Islamia, Dr. Ram Manohar Lohia Hospital, India
[3]Department of Microbiology, Dr. Ram Manohar Lohia Hospital, India

Introduction: HIV-1 *nef* is reported to perform multiple functions including CD4 and MHC-I down regulation, infectivity, actin remodeling, and viral spread leading to clinical progression to AIDS. These functions are accomplished through amino-acid motifs present at specific sites. Interactions between these motifs and associated host molecules have been suggested to be responsible for difference in disease progression resulting in rapid progression or delayed progresssion. In the present study, we wanted to elucidate differential genomic changes in the *nef* obtained from patients showing rapid progression or delayed progression to disease.

Methods: Seventeen rapid progressors (RPs) and three delayed progressors (DPs) attending AIDS clinic at RML Hospital, New Delhi were included in this study. PBMCs were isolated from whole blood and genomic DNA was extracted. Nested PCR was done with primers specific for amplification of ~ 620 bp *nef* gene. The amplified product was sequenced and data was analyzed using BioEdit, MEGA and Clustal W softwares.

Result: Majority of the patients were found to be infected with HIV-1 subtype C. We found various motifs of *nef* such as N-Myristoylation, $PxxP_{3,}$ PKC, PPT, dileucine and PxxP near C-terminus highly conserved in most subjects. However, a comparison between the deduced amino-acid sequences of RPs and DPs revealed presence of certain amino-acids more frequently in any one of both the groups. Strikingly, RPs exhibited altogether different amino-acid variations (Y40, T51, F121) than DPs, who revealed amino-acid changes at A15, H40, N51, H103 and Y121.

Conclusion: High degree of conservation of functionally known motifs suggests that the Nef protein in both the groups is intact. The substitution of tyrosine (Y) at 103 in RPs to histidine (H) in DPs may have biological implications as it is in the vicinity of basic residue (position 105-107) that plays important role in viral replication. Similarly, preference for phenylalanine (F) at position 121 in RPs over tyrosine (Y) in DPs may have positive impact on *nef*-mediated endocytosis and down-modulation of CD4 and MHC-I. On the other hand, variation at amino-acid position 15, 40 and 51 remains functionally to be explored. Additionally, more data from DPs will provide clearer and better analytical advantage.