HIV-1 Rev/RRE Functional Activity Variation Between Subtypes is Largely Due to Changes in Rev

Patrick E. H. Jackson1, Denis M. Tebit1, David Rekosh1, Marie-Louise Hammerskjold2*

1Division of Infectious Diseases and International Health, Department of Medicine and 2Department of Microbiology, Immunology, and Cancer Biology, University of Virginia, Charlottesville, VA

BACKGROUND

HIV replication is a highly regulated process. The binding of the viral Rev protein to the Rev Response Element (RRE) is essential for the nucleocytoplasmic export of mRNAs that retain introns and thus for packaging of genomic RNA.1,2,3 Previous studies have shown that there is variation in both Rev and RRE sequence between patients and between viral quasispecies isolated from a single patient.4 We previously assessed the functional activity of the Rev-RRE regulatory system in viruses isolated from five patients at two different time points in the course of infection. Variation of Rev/RRE function was observed between patients and within a patient as HIV disease progressed.4 The global HIV epidemic exhibits considerable genetic diversity and naturally occurring isolates can be categorized into groups and subtypes. Occasionally, viruses from different subgroups can recombine to create a fit hybrid which circulates in the population.5 One such circulating recombinant form (CRF), known as CRF02_AG, has an RRE region contributed by parental subtype A and both exons of rev contributed by parental subtype G (Figure 1). In the present study, we investigate variations in Rev-RRE functional activity between HIV genotypes and the contributions of the Rev and the RRE to that variation.

RESULTS

There was a 24-fold difference in functional activity between the most and least active naturally occurring Rev-RRE cognate pairs (Figure 2). There was no clustering between subtypes. When selected Rev and RRE sequences were tested with NL-4.3 RRE and Rev, the relative activity could not be predicted from the activity of the cognate pair (Figure 3). A similar result was found using the virus 6 (Uzbek AG) as a reference. In a linear regression, there was low correlation of RRE activity but high correlation of Rev activity with the functional activity of the original cognate pair (Figure 4). For the subtype G viruses, the cognate pair functional activity appears to track most closely with the Rev rather than the RRE component in the artificial pairs. However, the less active B-G Rev appears to have about twice the steady-state expression as the more active 9-G Rev (Figure 5). There was low correlation of steady-state Rev expression with functional activity for all tested viruses (Figure 6).

DISCUSSION

Rev-RRE functional activity varies dramatically between naturally occurring cognate pairs. This functional variation is primarily driven by variation in Rev activity. Our results indicate that Rev activity variation does not track with steady-state expression as measured by Western blot, though it is unclear whether this result reflects total Rev expression or differences in stability. The clinical significance of this finding is unclear, but variation in Rev-RRE activity may play a role in viral fitness and replication dynamics and may be reflective of host immune pressure. Identification of the most efficient Rev-RRE combination would likely be of use in optimizing lentiviral vector systems for gene therapy.

REFERENCES