E1A Linear Motifs play an adaptive role in Mastadenovirus evolution

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INTRODUCTION

Many protein-protein interactions are mediated by short sequence elements named linear motifs which appear and disappear with only a handful of point mutations. Viruses use linear motifs to hijack the host cell machinery inducing pathogenesis. Viruses are under constant selective pressure because of the changing environment and host immune response. Viral linear motifs have been proposed to play a role in adaptive evolution, a claim supported by scarce evidence to date. The adenovirus E1A oncoprotein, unique to the mastadenovirus genus, is densely packed with linear motifs. The wealth of clinical and sequence information for E1A, the wide host diversity and the variability of linear motifs across viral serotypes makes E1A an attractive model to study the role of linear motifs in viral adaptive evolution. We studied the evolutionary pathway of linear motifs in over 100 sequences of E1A proteins and we analyzed the host-parasite co-phylogeny.

LINEAR MOTIF EVOLUTION BY ANCESTRAL SEQUENCE RECONSTRUCTION

Figure 1. Linear Motifs within the E1A protein. Linear Motifs are often found within intrinsically disordered regions [1]. E1A hosts 11 motifs and E1A consists of 4 intrinsically disordered regions, designated N (purple), CR1 (blue), CR2 (green) and CR4 (pink), and one globular region designated CR3 (yellow) which has 4 cysteine residues coordinating a zinc atom [2].


Figure 2. Phylogenetic reconstruction of the evolution of linear motifs in E1A sequences. The evolutionary history of linear motifs was traced on the phylogenetic tree of Mastadenovirus using ancestral sequence reconstruction [3,4]. Multiple independent appearance/disappearance events in different branches of the tree indicate that some instances of the motif did not have a common ancestry and are prone to convergent evolution. Similar results were obtained using Maximum Parsimony (data not shown). Linear Motif Presence/Absence are indicated in green/gray branches. Appearance/Disappearance events are indicated with Green/Red circles. The color code for linear motifs indicates domain identity as in Figure 1.


Figure 3. Motif appearance/disappearance events are not independent. Hypoergometric tests were used to evaluate motifs motifs appearance/disappearance events associations across mastadenovirus phylogeny confirming co-occurrence for several appearance/disappearance events (green circles), disappearance/disappearance events (red circles) and appearance/disappearance events (black triangles). The positive associations (corrected p-value < 0.05 [5]) are shown. The color code is the same as in Figure 1.


HOST-PARASITE CO-EVOLUTION ANALYSIS

Figure 4. Host Diversiy is explained by Co-Evolution, Host-Switch and Duplication Events. A tree reconciliation was performed to map the parasite phylogeny (Blue lines and Black Names) to the host phylogeny (Black lines and Red Names) using Jare [6]. Incongruences in the mapping were then reconciled by four co-evolutionary events. The set of costs used were Co-Speciation: 0, Partial Switch: 2, Duplication: 1 and Sorting: 1 (Total Cost=48). Host diversity of mastadenovirus can be explained, at all levels, mainly by host switch, meaning that the virus infects an unrelated host speciating in the process, or co-speciation events, meaning a simultaneous divergence of host and virus.


CONCLUDING REMARKS

- Motif evolutionary pathways are not independent and they follow motif specific trends. Motif appearance and disappearance events across mastadenovirus phylogeny are not independent. All this evidence suggests the existence of functional coupling among motifs.
- Co-divergence plays an important evolutionary role in mastadenoviruses diversification, however it is not the only event.
- Evolutionary events and the appearance and disappearance of the motifs across mastadenovirus phylogeny are not independent suggesting a contribution of motifs to adaptive evolution.

Figure 5. Motif-Motif Appearance/Disappearance Events Association. Hypoergometric tests were used to evaluate motifs appearance/disappearance and evolutionary events associations across mastadenovirus phylogeny confirming co-occurrence for disappearance events and Host-Switch events suggesting that Linear Motifs may play a role in adaptive evolution. The positive associations (corrected p-value < 0.05 [5]) are shown. The color code is the same as in Figure 1.

Figure 6. Motif Motif Appearance/Disappearance and Evolutionary Events Association

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