

The Role of NAD and Non-Canonical Caps in RNA-RNA interaction

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Background*: Nicotinamide adenine dinucleotide (NAD), a key metabolic cofactor, plays also crucial roles in immunity and RNA regulation. Its depletion, particularly during viral infections, can disrupt essential cellular processes, underscoring its broader significance beyond classical metabolism. Recently, NAD has been identified as a non-canonical RNA cap in human cells, expanding our understanding of RNA regulation. Other metabolites, such as diadenosine tetraphosphate (Ap_4A), diadenosine diphosphate (Ap_2A), and flavin adenine dinucleotide (FAD), have similarly been discovered to function as RNA caps across various organisms.

Methods*: In this project, we aim to investigate how alternative RNA caps affect RNA-RNA interactions, focusing on the binding of U1 snRNA to HIV-1 splice sites. To achieve this, we will analyze the structural and functional consequences of cap variation using a combination of biophysical and structural techniques, including thermal melting analysis, molecular dynamics simulations, and nuclear magnetic resonance (NMR) spectroscopy.

Results*: Our recent findings reveal that specific isoforms of U1 small nuclear RNA (snRNA) carry NAD caps at their 5' ends, which participate in exon-intron recognition during splicing. Importantly, we found this non-canonical capping of U1 snRNA influences HIV-1 infectivity by modulating its binding to HIV-1 pre-mRNA.

Conclusion*: This work aims to deepen our understanding of RNA-mediated regulation during viral infection and may uncover novel targets for therapeutic intervention.