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Inhibiting HIV-1 reverse transcription by targeting the reverse transcription complex

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Reverse transcription, the process which converts viral genomic RNA into a double strand DNA, is the central defining feature of HIV-1 replication and a major target for anti-retroviral therapy. Along with reverse transcriptase (RT), viral protein including IN, CA, and Vpr and cellular proteins including eukaryotic translation elongation factor 1A (eEF1A) are important for the process. We previously showed that eEF1A stabilized the RTC in cells and was important for late steps of reverse transcription. Our recent experiments show a direct interaction between RT and eEF1A that can be down regulated by amino acid substitutions in the RT thumb domain, and which lead to downregulated late reverse transcription. Moreover we show that drugs which bind to eEF1A are potent inhibitors of reverse transcription. Experiments to determine if eEF1A binding drugs negatively affect the RTC in cells will be presented. Recently we also showed that a Tat mutant called Nullbasic inhibits reverse transcription. Our recent data shows that Nullbasic is an RT binding protein that is found in viral particles. *In vitro* uncoating assays show that virions containing Nullbasic undergo accelerated uncoating kinetics, and analysis of cells infected with HIV-1 containing Nullbasic indicates that the levels of RTCs are reduced, consistent with the uncoating defect. We have recently made Jurkat cell line expressing Nullbasic which appear to be highly resistant to HIV-1 infection. In chronically infected Jurkat cells, introduction of Nullbasic can decrease HIV-1 mRNA levels from 150-to 800 fold. The mechanisms responsible for strong inhibition of HIV-1 will be presented. The combined evidence indicates investigations of interaction between RT and viral and cellular proteins could enable new antiviral strategies.

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