**The association between the lncRNA Cytor and HIV latency**

The advent of antiretroviral therapy (ART) has limited the spread of the Human Immunodeficiency Virus (HIV) and improved clinical outcomes that are associated with viral infection. However, fully curative treatment options remain out of reach for infected patients, as HIV persists in a latent state within a long-lived cellular reservoir that is refractory to both therapy and the immune response. To design effective therapeutic options that will eradicate these infected reservoir cells, there is a need for a detailed understanding of how HIV gene expression and latency are regulated. ***However, while the mechanisms by which host proteins govern HIV gene expression and viral latency are relatively well-understood, the emerging role of non-coding RNAs as regulators of cellular gene expression has not yet been carefully studied in the context of T cell activation, HIV gene expression, and viral latency***. In preparing this proposal, we monitored changes in the transcriptome of HIV-infected T cells derived from the Jurkat cell line in response to T cell simulation. As expected, a marked change in cellular gene expression, including the expression of long non-coding RNAs (lncRNAs) was documented and was further validated in primary CD4+ T cells. Among the lncRNAs that were most strongly differentially expressed relative to unstimulated cells, we identified **Cytoskeleton Regulator RNA (Cytor).** Preliminary gain and loss-of-function studies revealed that Cytor activates HIV gene expression and suppresses latency establishment. Furthermore, Cytor is recruited to the viral promoter and associates with the cellular Positive Transcription Elongation Factor (P-TEFb), which is known to promote transcriptional elongation. Cytor knockdown decreases the levels of RNA Polymerase II and histone activation markers on the HIV promoter and inhibits HIV infection in stimulated primary CD4+ T cells. Along with these direct effects, Cytor indirectly affects HIV gene transcription, as its depletion results in a broad change in the expression of cellular genes. Interestingly, Cytor depletion reduces the number of cells that respond to T cell activation with proper spreading and actin polymerization. In light of these findings, ***we hypothesize that in primary CD4+ T cells, Cytor activates HIV gene expression by directly recruiting P-TEFb and the host transcriptional elongation machinery to the HIV promoter while simultaneously affecting T cell activation and actin remodeling through target gene regulation, thereby indirectly enhancing HIV transcription and suppressing viral latency.*** To test this hypothesis, **Aim 1** will place our study in a clinically relevant context, assessing the physiological relevance of Cytor in the control of HIV gene expression and latency in resting CD4 primary T cells, which constitute the HIV latent reservoir. We expect these studies to clarify the role of Cytor in resting primary CD4+ T cells and its function in the establishment and reversal of HIV latency. **Aim 2**will then study the direct mechanisms by which Cytor activates HIV gene expression. We will confirm interactions between P-TEFb and Cytor in primary CD4+ T cells and *in vitro*, verifying that Cytor is recruited to the HIV promoter and activates HIV gene expression. Finally, **Aim 3** willexplore whether Cytor exerts its effects indirectly through linking T cell activation and actin remodeling to HIV gene expression in primary CD4+ T cells. New target genes of Cytor will be identified, and their roles in regulating these processes will be investigated. Overall, we expect that our study will provide important insights into the functions of lncRNAs in fine-tuning the processes of T cell activation, actin remodeling, and subsequent HIV transcription and latency. The successful completion of this work will open paths to the design of novel RNA-based therapies that will support current clinical protocols for latent HIV reservoir elimination.