Retrovirology

Poster presentation

New actors in regulation of HIV-1 *tat* mRNA production

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Regulation of the retroviral protein production largely depends upon regulation of the alternative splicing of the viral transcript. The Tat protein is required for transcription of full-length HIV-1 RNA and therefore is essential for virus multiplication. However, as the Tat protein has apoptotic properties, virus HIV-1 limits *tat* mRNA production through a strong down regulation of splicing at site A3, an HIV-1 splicing site specifically dedicated to *tat* mRNA production. Splicing at this site is modulated by a complex array of silencer and enhancer elements contained in a long stem-loop structure SLS3, which is located downstream from site A3. Earlier studies have shown that the main inhibitory element ESS2 is a strong hnRNP A1 entry site, allowing further hnRNP A1 binding on the SLS3 region and leading to limitation of the U2AF splicing factor association. The SR proteins SC35 and SRp40 binding sites overlap ESS2, and their association strongly activates splicing at site A3. We found that two other SR proteins, ASF/SF2 and 9G8 also activate site A3 utilization. However, our experimental study revealed different pattern of interaction of these proteins with SLS3, as compared to SC35 and SRp40. They have short juxtaposed binding sites that overlap a C-to-U mutation position 5396 which was shown to induce a strong decrease of *tat*1 mRNA production *in cellulo*. The analysis by mass spectrometry of the proteins bound on SLS3 with a C or a U residue at position 5396 revealed the presence of the inhibitory splicing protein DAZAP1. Its binding is strongly reinforced by the C to U substitution. Based on our present data, the activation properties of ASF/SF2 and 9G8 proteins on site A3 are based on their capability to block DAZAP1 binding to SLS3. Taken together, the data reveal that numerous nuclear factors of the infected cells are involved in the complex regulation of HIV-1 RNA splicing.