

Mutant host cell protein sequesters critical HIV-1 element

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Scientists have identified a new way to inhibit a molecule that is critical for HIV pathogenesis. The research, published by Cell Press in the January 16th issue of the journal *Molecular Cell*, presents a target for development of antiretroviral therapeutics that are likely to complement existing therapies and provide additional protection from HIV and AIDS.

Infection of human cells with HIV-1 requires multiple events that involve complex interactions between viral elements and cellular proteins. The virus must copy key parts of its DNA as mRNA molecules through a process called transcription. The mRNA molecules must be properly "spliced", or rearranged, and then transported out of the cell nucleus and into the cytoplasm where the mRNAs can be "translated" into viral proteins.

"Although there has been a great deal of effort directed at understanding HIV-1 transcription, mRNA splicing and nuclear export, little is known about the translational control of HIV-1 RNA in the cytoplasm," says senior study author, Dr. Johnny J. He from the Center for AIDS Research at Indiana University School of Medicine.

Dr. He and colleagues examined a protein called HIV-1 Nef that is translated from completely spliced HIV-1 RNA. Nef is very important for HIV pathogenesis and AIDS disease. "It is highly conceivable that intervention with Nef expression may complement the current anti-HIV therapies that are mainly targeted at HIV-1 protease and reverse

transcriptase, providing a better treatment outcome," explains Dr. He.

The researchers found that a mutant form of Src-associated protein in mitosis of 68kDa (Sam68), a host cellular protein involved in HIV-1 pathogenesis, specifically interacts with nef mRNA and directly suppresses Nef expression. This particular Sam68 mutant was previously shown to inhibit HIV-1 replication by overriding its wild-type counterpart's function in nuclear export of unspliced and incompletely spliced HIV RNA. However, the mutant Sam68 was present in the cytoplasm, suggesting that it may serve some function in the cytoplasmic stage of the HIV-1 life cycle.

The ability of the Sam68 cytoplasmic mutant to interfere with Nef correlated with its ability to induce stress granules in the cytoplasm. Stress granules regulate gene expression at the translational level in response to a variety of external stimuli. Importantly, nef mRNA was targeted to and enriched in the stress granules.

"Taken together, these results demonstrate that stress granule induction and nef mRNA sequestration account for this translational suppression of Nef expression and offers a new strategy for development of anti-HIV therapeutics to buttress our fight against HIV/AIDS," concludes Dr. He.

Source: Cell Press

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