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Technology Offer

Novel antiviral therapy against HIV-1 and alphaviruses: reducing frameshifting by increasing $tRNA^{Leu}$ concentrations

Antiviral therapy against retroviruses and alphaviruses using tRNALeu(UUA) overexpression

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Background

Many viruses use programmed ribosome frameshifting (FS) to increase genome-coding capacity and to regulate the stoichiometric ratio between viral proteins. Among them are human-pathogenic viruses HIV-1 and alphaviruses such as Semliki Forest virus (SFV). Two major HIV-1 genes, *gag* and *pol*, overlap by 205 nucleotides. Synthesis of the Gag-Pol polyprotein requires –1FS. The ratio between Gag and Gag-Pol is crucial for virus propagation and its dysregulation is detrimental for replication, particle formation and infectivity of HIV-1. In SFV –1FS defines the ratio between the two structural proteins, 6K and TransFrame, which contribute to virus infectivity.
FS takes place when the ribosome translates a so-called “slippery site” (SS). In HIV-1, SS1 of the gag-pol mRNA is the heptamer sequence U UUU UUA (Fig. 1), encoding Phe (UUU) and Leu (UUA) in the 0-frame. Upon –1FS, SS1 can give rise to two FS products: one containing the 0-frame peptide Phe-Leu followed by the –1FS sequence (the FLR product) and another with a second Phe incorporated instead of Leu (the FFR product). –1FS in HIV-1 occurs at a rate of roughly 10% of all translation events and leads to 7% FLR and 3% FFR products. SFV contains an SS identical to that of HIV-1. Similarly to HIV-1, –1FS in SFV gives rise to two different FS products originating from alternative kinetic routes.
Because constant FS efficiency is crucial for virus survival, interference with the FS activity may constitute a promising approach to effectively inhibit HIV-1 and SFV propagation.

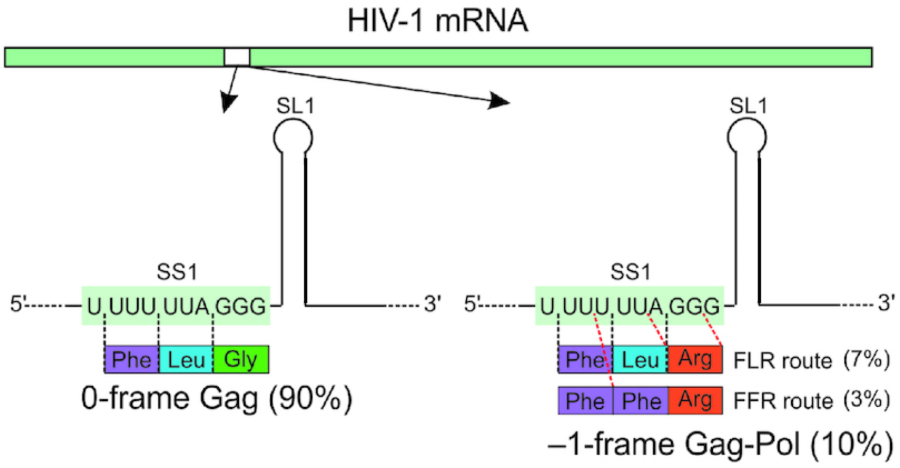

Figure 1: The slippery site SS1 of the HIV-1 gag-pol mRNA. Frameshifting occurs with a frequency of 10% at the SS1 that usually encodes a Phe-Leu-Gly peptide. –1FS can occur via one of the alternative routes: the FLR route (giving rise to a Phe-Leu-Arg peptide) occurs at a frequency of 7% while the FFR route (giving rise to a Phe-Phe-Arg peptide) occurs at a frequency of 3%. Figure modified from (1).

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Scientists from the Max Planck Institute (MPI) for Biophysical Chemistry in Göttingen found that in both HIV-1 and SFV the pathway and efficiency of –1FS is determined by the availability of Leu-tRNA$^{Leu(UUA)}$ (1). This tRNA isoacceptor is reading the UUA codon, which is rare in human cells, especially in CD4+ T-lymphocytes, the primary target cells for HIV-1 infection in humans. However, 45% of all Leu in late expressing HIV-1 genes (including *gag* and *pol*) is encoded by this rare codon. Thus, the HIV-1 open reading frame seems to act like a sponge for tRNA$^{Leu(UUA)}$ and additionally reduces its availability for the SS1 translation in infected cells.
The –1FS product of the preferred FLR route requires tRNA$^{Leu(UAA)}$ and its low availability could impair virus propagation. However, the results of the MPI scientists showed that upon decreasing concentrations of tRNA$^{Leu(UUA)}$ the ribosome switches to the FFR route, leading to robust –1FS independently of tRNA$^{Leu(UUA)}$ fluctuations. The same scenario applies to SFV. Therefore, further artificial shortage of the rare tRNA$^{Leu(UUA)}$ is unlikely to constitute a successful approach for either HIV-1 or SFV treatment.
Surprisingly however, the MPI scientists revealed that increasing tRNA$^{Leu(UUA)}$ concentration leads to a significant reduction in overall –1FS efficiency suggesting that tRNA$^{Leu(UUA)}$ overexpression in virus-infected human cells could become a new approach in antiviral therapy against retroviruses and alphaviruses.

We are currently looking for cooperation partners for the further development and exploitation of this technology.

Patent Information

A European priority application was filed in July 2018.

Literature

(1) Korniy N. et al., Nucleic Acids Res. 2019, doi: 10.1093/nar/gkz202.