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What is this all about?

Major reason that a cure for HIV continues to elude us is that the virus hides away in cells, forming a persistent reservoir in which the virus is dormant (i.e. latent), and in such cells the virus is not visible to the immune system and to antiretroviral therapy. Consequently, latency persists, cannot be eliminated and represent a major hurdle to finding a cure. **Latency** is a very complex phenomenon and results from multiple molecular mechanisms that block HIV expression (i.e. the process in which HIV genetic information is transcribed into viral RNA and then translated into viral proteins). Most of the characterized molecular mechanisms of HIV latency suppress the HIV transcription (**transcriptional latency**), however virus can also be inhibited at the steps following HIV transcription (**posttranscriptional latency**). We will study novel posttranscriptional block that lead to the inhibition of HIV expression and the involvement in this process of two cellular proteins called **MATR3 and PSF**. These two proteins are known to play important roles in cellular gene expression and apparently, also HIV uses these factors for expression of its own genes.

Why should the public care?

There are almost 40 million people throughout the world living with HIV/AIDS. Since its discovery almost 35 years ago- there is still no cure. That's because, even when the antiretroviral therapy reduces HIV in the bloodstream to the undetectable levels using standard detection methods, it is not able to touch the hidden/dormant virus that escapes from therapy. Whenever a patient stops the antiretroviral regimen, the **latent virus rebounds quickly**. Therefore, HIV-infected patient has to take the antiviral medications their whole life. That's way new strategies aiming at eliminating the latent reservoirs are absolutely necessary in order to reach a cure. By unlocking the secrets of latency it may become possible to cure – not just control – HIV

What is happening now?

With no vaccine on horizon, several strategies are currently proposed in order to fight latent HIV. One of them is **"shock-and-kill"** that involved induction of hidden/latent viruses (HIV reactivation, "shock") while maintaining antiretroviral therapy ("kill") in order to prevent new spreading infection. This kind of strategy would allow latently infected cells to die from viral cytopathic effect or host immune response. However, scientists are aware now, that this strategy is not efficient enough to kill the reactivated cells and to eliminate the latent reservoir. Therefore, development of additional tactics is necessary.

Where is it going? What is the goal of the research?

Mechanisms that contribute to HIV latency are very complex and poorly understood. The goal of this research is to find out if MATR3 and PSF protein matters for HIV latency. Previously, we have demonstrated that MATR3 and PSF helps the virus during the HIV-1 replication cycles; more specifically at step following HIV transcription. In this research grant, we propose to test a hypothesis that absence of HIV helpers (i.e. MATR3 and PSF) could perturb the HIV expression and lead to latency. Results obtained from this project have **implications for therapy** and will serve as a base for **development of new drugs** against posttranscriptional latency. Consequently, targeting both transcriptional and posttranscriptional blocks may positively impact the development of more efficient "shock-and-kill" strategy.