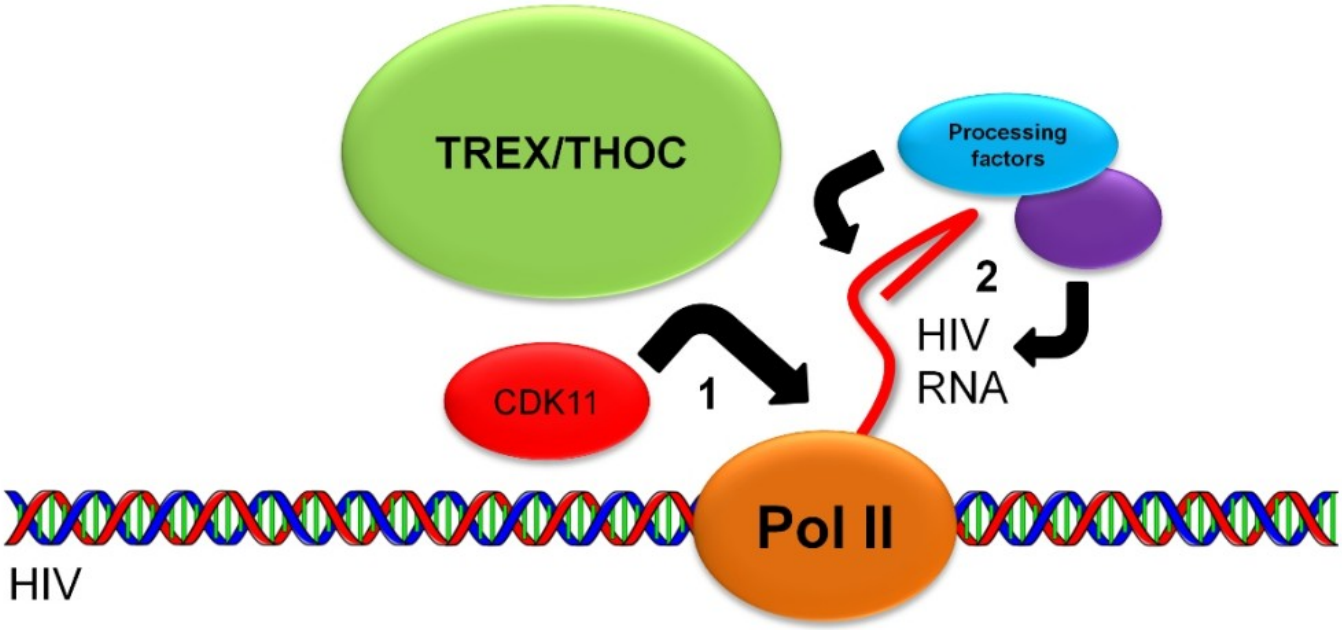
A factor that regulates the expression of HIV genes

Proteins are the machinery of life. Nearly everything in a cell is manufactured by, regulated by or composed of proteins, which are encoded in genes. When a cell needs a particular protein, the DNA encoding the protein in question is first copied into RNA. RNA is structurally similar to DNA but far less stable. The RNA is read by complexes called ribosomes, which synthesize the protein. The RNA eventually degrades.



Graphical summary of CDK11's role in HIV RNA processing. CDK11 is recruited to RNA Pol II by TREX/THOC, where RNA is copied from the viral DNA (1). CDK11 subsequently recruits various factors (2), which help stabilize the HIV RNA.

This sounds simple enough, but the process is highly regulated at every step. Like a complicated bureaucracy demanding all paperwork be properly dated and signed before filing it, cells extensively process, edit, and tag RNA before finally sending it to a ribosome. Failure to, say, add an end cap and tail may destabilize the RNA before it can be read. This applies not only to native genes but genes that have been inserted into a genome by a virus, such as HIV - the virus responsible for Acquired Immune Deficiency Syndrome (AIDS) in humans. Exactly how viral genes interact with their host's RNA regulatory machinery is of great interest to researchers. If HIV RNA could be prevented from being processed, i.e., unable to exploit host factors, no viral proteins would be manufactured and the virus would fail to replicate. Alternatively, a better understanding of these interactions could be useful in activating latently infected cells as part of a 'shock and kill'

strategy - flushing HIV infected cells out of hiding and eliminating them. This would represent a functional cure for HIV as opposed to simply suppressing the virus with antiretroviral drug therapy.

Cyclin-dependent kinase 11 (CDK11) is a member of a large and diverse family of proteins that regulate cell growth and RNA processing. Its role until recently was not understood. Our research suggests that CDK11 stabilizes RNA as it is being copied. Specifically, CDK11 recruits processing factors that cut nascent RNA and add a tail that protect it from being broken down before it has a chance to be read by a ribosome. Absence of CDK11in an infected cell results in depletion of the processing factors and reduction of HIV RNA. Conversely, when there is a lot of CDK11, levels of viral RNA and protein rise and HIV grows faster. Close examination of HIV RNA revealed that reduction of CDK11 resulted in excessively long, unstable RNA consistent with compromised RNA processing. When cells were saturated with CDK11, HIV RNA was stabilized.

CDK11 associated not only with RNA processing factors but also components of TREX/THOC - a complex of proteins - which, among other things, is responsible for transporting RNA around the cell. We determined that TREX/THOC recruits CDK11 to newly synthesized RNA. Inhibition of TREX/THOC reduced CDK11 levels, which in turn destabilized HIV RNA similarly to inhibition of CDK11 itself. Thus we elucidated a mechanism where TREX/THOC brings CDK11 to HIV RNA, where it recruits processing factors that promote RNA stability, enhancing production of viral proteins. It’s worth noting that CDK11 also plays a role in several forms of cancer, including osterosarcoma, liposarcoma and breast cancer. Thus CDK11 represents a promising new target for both anti-HIV and anti-cancer drugs.

Publication

CDK11 in TREX/THOC Regulates HIV mRNA 3' End Processing.
Pak V, Eifler TT, Jäger S, Krogan NJ, Fujinaga K, Peterlin BM.
Cell Host Microbe. 2015 Nov 11