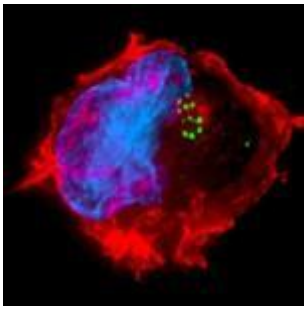
What causes the high mutation rates of HIV-1 in the human body?



It has been known for a long time that HIV-1 mutates rapidly, and does so to escape the pressure from either host immunity (both cellular and humoral) and/or antiretroviral drug treatment. The mechanism behind such mutations is thought to be due to the inability of the viral reverse transcriptase to accurately transcribe RNA to DNA. Indeed, the rates of these spontaneous mutations determine the genetic diversity and evolution of RNA viruses. Up until now, much of this information has been gleaned from in vitro and from cell culture models and very little information is known from in vivo.

In the most recent PloS Biology, Cuevas and colleagues quantify the HIV-1 genome-wide rate of spontaneous mutation in DNA sequences from peripheral blood mononuclear cells. They reveal a mutation rate 4×10^{-3} per base per cell, which is the highest reported mutation rate for any biological entity. When they sequenced plasma-derived HIV-1, they found the mutation rate was 44 times lower: “indicating that a large fraction of viral genomes are lethally mutated and fail to reach plasma.” Most interestingly, the authors showed that the viral reverse transcriptase accounts for only 2% of mutations, with the remaining 98% of viral genetic variation a result from editing by host cytidine deaminases.

What is the clinical significance of this? The authors went on to show that hypermutated virus is less abundant in patients with rapid disease progression compared to typical progressors. The authors found that low-level cytidine deaminase editing is “more abundant in rapid progressors than in normal progressors, suggesting that failure of cytidine deaminase to inactivate the virus by hypermutation may promote HIV-1 intrapatient diversity and pathogenesis.” The study also reveals that viral sequences from plasma grossly underestimates the HIV-1 mutation rate.

Cuevas, J. et al, 2015. Extremely High Mutation Rate of HIV-1 In Vivo. *PLOS*.