Identification of Novel Host Factors for HIV Transcription

Koh Fujinaga
University of California, San Francisco
Basic Biomedical Sciences
2014

From entry to egress, HIV utilizes host cellular machineries at almost every step of the viral replicative cycle. Also, HIV has evolved to counteract host cell's anti-viral defense mechanisms. Thus, identifying cellular factors involved in these processes is also necessary for developing new anti-viral therapies. To this end, removing single genes from host cells is the most straightforward approach. Currently, genetically removing cellular genes from adult human cells is a very time and labor-intensive procedure. Instead, more common approaches to study the role of host genes are to "knock down" the gene products (proteins) by using small RNA molecules (such as small interfering RNA and small hairpin RNA). While these small RNA-based approaches have provided important information regarding the roles of cellular genes in HIV replication, they have several shortcomings such as incomplete knock down of the target gene and non-specific off-target effect on other genes. To circumvent these problems, the proposed study will utilize a unique experimental system using haploid cells to remove cellular genes encoding HIV co-factors very efficiently. These cells have already been used to identify several important host factors for other human diseases, and this proposed study is the first to use the haploid cells for HIV/AIDS research. In particular, I will identify the host factors involved in regulation of HIV transcription. HIV establishes proviral latency early in infection, where only short transcripts from viral long terminal repeat (LTR) are expressed. The highly active antiretroviral therapy (HAART) can only eliminate replicating HIV while a small population of HIV latently infected cells harboring fully replication competent proviruses remains in the host. To eradicate these latently infected cells, it is critical to develop effective methods to reactivate viral transcription, which is regulated by cellular and viral factors. There are several host cellular genes involved in HIV transcription, and my preliminary results indicate several previously uncharacterized genes are involved in this process. These cellular gene products form a complicate network to regulate HIV transcription, and it is crucial to identify the precise mechanism of such regulation. Using haploid genetic mutation will help to determine the roles of these proteins unambiguously. After identifying and characterizing the role of cellular factors required for HIV transcription from latency, these proteins will be targeted to obtain optimal HIV reactivation from latently infected cells, which is a mandatory step for eradication of these cells from patients.