CALIFORNIA HIV/AIDS RESEARCH PROGRAM

Reactivation of Latent HIV: Role of Integration Sites

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Existing treatments for HIV infection are capable of controlling the virus, but are unable to completely eradicate it from the body. This is because HIV incorporates its genetic DNA material into the host, where it is maintained in a state of very low to absent activity (latency). In this state, the virus is invisible to the immune system and therapeutic agents. Current dogma suggests that HIV can be therapeutically activated from its latent state, thus making infected cells visible to the immune system, while spread of the virus to uninfected cells is inhibited by the presence of anti-retroviral treatments. Clinical trials have demonstrated that some small-molecule compounds are effective in reactivating HIV; however, these treatments have not resulted in the reduction of the number of cells containing latent virus. Maintenance of HIV in a latent state may depend on the location of viral DNA within host DNA. For example, it may depend on the activity of surrounding host genes, and the presence or absence of regulatory factors that control activity of the host genes. It is unclear how the ability of small molecule compounds to reactivate latent HIV relates to the location of its viral DNA within host DNA. Will a potent compound reactivate more HIV from DNA locations with similar characteristics, or will it reactivate HIV from a broader range of many different locations? Compounds that are capable of reactivating HIV from a broad spectrum of locations in host DNA are likely to be more successful at reducing the number of latently infected cells. The proposed research will begin to address this question by identifying and characterizing the HIV DNA locations within host DNA, from which the virus can be reactivated with selected treatments. We will use an experimental model of HIV latency, where the cells will be subjected to HIV-reactivating stimuli. Cells responsive to treatment (i.e. in which the virus is reactivated) and non-responsive cells (where virus remains latent) will be experimentally separated and recovered. They will then be compared across different treatment regimens. To test whether the activity of HIV-reactivating stimuli are similar in cells across different stages of development, we will perform a similar experiment using cells that have been separated into different developmental subsets. This research will be significant for demonstrating the features of HIV DNA location within host DNA that contribute to the potency of HIV-activating treatments, and for its high potential to identify treatments that are able to activate HIV from a broad spectrum of DNA locations. The knowledge gained will impact the process for selecting candidate drug compounds, and could be used in clinical trials to reduce the number of latently infected cells in vivo.

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