Deeper view of HIV reveals impact of early mutations

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Mutations in HIV that develop during the first few weeks of infection may play a critical role in undermining a successful early immune response, a finding that reveals the importance of vaccines targeting regions of the virus that are less likely to mutate. A new study in the journal *PLoS Pathogens*, led by researchers at the Ragon Institute of Massachusetts General Hospital, MIT and Harvard and the Broad Institute of MIT and Harvard, applied the same next-generation technologies that have revolutionized sequencing of the human genome to study how HIV adapts within the first few weeks after infection.

Ragon and Broad investigators applied an approach called pyrosequencing that allows the simultaneous sequencing of hundreds of viral variants within an individual over the course of infection. These data provided a substantially deeper and more sensitive view of the complexity of mutant strains circulating in a patient following HIV infection and how each of those strains evolves over time. Combining these genetic data with detailed immunological analyses enabled a comprehensive evaluation of viral-host interactions during the critical acute phase of HIV infection.

The study revealed that the majority of early, low-frequency mutations developing during the first few weeks after infection represent rapid adaptations to avoid the response of CD8 'killer' T cells, which play a key role in recognizing and eliminating HIV-infected cells. "These data reveal the ability of HIV to rapidly avoid front-line immune responses attempting to contain the infection," says Todd Allen, PhD, senior author

of the study and a Ragon Institute faculty member.

More importantly, Allen notes, their study revealed that rapid viral escape from a few dominant immune responses coincided with the inability of individual patients to maintain early control of HIV. "The ability to sensitively assess early virus evolution across the entire HIV genome revealed that limiting the ability of HIV to become resistant to the earliest immune responses may be a critical component of a successful vaccine," he says. "Therefore, the key to controlling a highly variable pathogen such as HIV may lie in a vaccine's ability to redirect immune responses towards more critical, highly conserved regions of the virus that are unable to successfully mutate."

An important component of the study was development of novel bioinformatics tools to handle the enormous and highly diverse sequence dataset and to assemble the thousands of sequencing reads into complete HIV genomes for analysis and detection of genetic mutations. While next-generation sequencing approaches have helped transform the sequencing of mammalian genomes, the high degree of sequence diversity within and between HIV strains has hindered the routine application of those powerful sequencing approaches to highly variable pathogens such as HIV. In the current study the researchers were able to apply their approach to successfully sequence the entire HIV genome from dozens of infected individuals.

"The genomic and computational tools developed as part of this study allow researchers to interrogate the complete HIV genome and to identify genetic variants of the virus with unprecedented resolution, allowing us to obtain a novel map of how the virus is changing during the course of an infection." says Matthew Henn, PhD, the lead author of the study and director of Viral Genomics at the Broad Institute.

Efforts to develop an effective vaccine against HIV have been thwarted

in large part because of the virus's ability to rapidly mutate and avoid host immune responses. However, notes Allen – an associate professor of Medicine at Harvard Medical School – "HIV is not able to mutate at will. Some of these mutations substantially cripple the virus' ability to replicate, which appears to be critical to enabling a few individuals to uniquely control HIV without the need for therapy."

Understanding more precisely how HIV evolves in an individual and how mutations correlate with the ability to control HIV may provide critical insight into the design of more effective vaccines to contain and possibly prevent infection altogether. Efforts are underway at the Ragon Institute to harness these findings to develop and test novel vaccine approaches against HIV that limit its ability to mutate and escape immune control.

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