Unconventional Interrogation Yields HIV’s Escape Plan

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http://dx.doi.org/10.1016/j.chom.2017.06.003

Chasing HIV-1 across the genotype landscape, unequipped to anticipate its maneuvers, the antibody variable-region genes pursue the virus in futility. In this issue of Cell Host & Microbe, Dingens et al. (2017) exhibit a powerful technology that reveals the escape pathways of HIV-1 and may enable its capture.

The sustained interaction between human immunodeficiency virus (HIV) and the immune system of an infected person is often likened to an arms race. The term hearkens back to the Cold War, when any increase in weaponry on one side was matched and raised by the other. A more appropriate metaphor, however, is that of the police chase. Such a chase is asymmetric—the good guys constantly running toward the bad guys, and the bad guys simply running away. The pursuit of HIV by the adaptive immune system takes place on the more rarefied landscape of dual-genotype spaces: one for the virus and one for the antibody. Both viruses and antibodies move through their respective genotype spaces by mutating their nucleotide sequences (and thereby their amino acid sequences). The advantage in this chase is clearly held by HIV. It’s easier to run away than to run toward in such a high-dimensional space. More concretely, we know that serum from an infected subject typically neutralizes viruses predating the serum by months, but not contemporary viruses (Wei et al., 2003).

In some individuals, after several years of HIV infection, a B cell clone may evolve to the point where its antibody is capable of neutralizing a large number of distinct viral genotypes. Such antibodies are called broadly neutralizing antibodies, or BNAbs. It is fair to say that a great deal of effort in HIV vaccine research over the last few years has been directed toward the elicitation of BNAbs by immunization. But most of the patients who make BNAbs are not themselves protected by them. BNAbs have proven effective in animal models of passive immunization, but even there, escape mutants arise.

In HIV infection, the chase does not end with the simple apprehension of the perpetrator, but only when most or all of the escape pathways are blocked. This achievement is particularly elusive when using a Darwinian mutation and selection strategy, which can only react to present conditions—future conditions cannot be anticipated. For the chaser, this strategy entails a significant disadvantage; for the chasee, it represents a great opportunity. The B cell system does not “know” what all the escape pathways are for HIV. It is, after all, an enormously difficult problem, given the vast size and number of directions there are in the amino-acid sequence space of any given viral gene. But now, due to extraordinary high-throughput technology and thoughtful experimental design taking full and careful advantage of the voluminous data generated, we are closer to knowing these crucial escape pathways ourselves.

Dingens et al. (2017) have applied a technique developed in the Bloom lab called “mutational antigenic profiling” (Doud et al., 2017) to produce all of the single amino-acid mutations in the HIV Envelope gene and determine which of them confer resistance to neutralization by the broadly neutralizing antibody PGT151 (Falkowska et al., 2014). The investigators started with a single proviral sequence and created mutant libraries through a PCR-based technique developed previously in the lab. These products were passaged through T cells to eliminate mutations abating viral replication competence and passaged a second time either with our without PGT151 present. Mutation frequencies following the second passage were obtained through deep sequencing with unique molecular
identifiers, which provides more precise estimates of read abundance in a population. The impact of PGT151 on the survival of each mutation is evident in the frequency ratios. Their results show not only which sites are important for binding, but which mutations specifically abrogate binding. The collection of such results is capable of generating biochemical insights into the binding and escape processes, as shown by Dingens et al. (2017). These results are made possible through massively parallel assays and made reliable through biological triplication and consistent error-checking throughout.

Let’s pause here to appreciate the advance in experimental power ushered in with this method. The investigators measured the effects of 12,559 distinct mutations—all of the potential escape routes for the Env gene—on survivability in the presence of a potent BNAAb. Many others have performed analyses of the influence of mutations on HIV-host dynamics, with most looking at viral variants that arise naturally in the course of infection. None come close to the sheer number of mutants examined here. The raw increase in numbers is crucial because it matches the extraordinary connectivity of the genotype space. The naturally occurring escape variants that have been the subject of many previous mutation studies are very likely just the lucky ones that happened to arise first. The researchers who invested such considerable time and effort in these earlier important studies may well be the most grateful for the availability of these novel tools. Indeed, Dingens et al. (2017) rediscovered escape mutants identified in these earlier, laborious studies, but they also discovered new and unanticipated escape paths. It is a certainty that the virus eventually discovers them, too.

It will be valuable to see how far the application of these techniques can be pushed. It is not hard to imagine designing antibody cocktails collectively blocking viral escape routes as well as broad neutralization. The Bloom lab has shown that equally impressive insights can be gained by applying similar methods to influenza-host interactions (Doud et al., 2017). There are many other pathogenic viruses and microorganisms that could yield up their secrets to such an onslaught of inquiry.

REFERENCES


