Researchers Trace HIV Mutations that Lead to Drug Resistance

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Susan Brown

Chemists at UC San Diego and statisticians at Harvard University have developed a novel way to trace mutations in HIV that lead to drug resistance. Their findings, once expanded to the full range of drugs available to treat the infection, would allow doctors to tailor drug cocktails to the particular strains of the virus found in individual patients.

"We want to crack the code of resistance," said Wei Wang, associate professor chemistry and biochemistry at UC San Diego who led the collaboration along with Jun Liu of Harvard. The team reports their work in this week's early online edition of the *Proceedings of the National Academy of Sciences*.

HIV replicates quickly, but the copies are imprecise. The constant mutation has made HIV infection difficult to treat, much less cure, because drugs designed to interrupt the cycle of infection fail when their targets change.

To better understand which mutations matter for drug resistance, the researchers compared sequences of HIV taken from patients treated with specific drugs to those from untreated patients. Using a novel statistical method, they identified clusters of mutations that seemed to be working together to help the virus escape treatment.

One drug, indinavir, targets a protein called protease, which the virus needs to assemble the capsule it uses to invade new cells. Substitutions in ten different places on protease occurred in patients who were taking the drug, but what combination of mutations would hinder the action of the drug wasn't clear before this analysis.

Chemists can determine how a drug fits to a particular protein using computer modeling, but those computations take considerable time. Evaluating all possible combinations of those 10 substitutions is impractical. The statistical screen narrowed down the possibilities.

"People never looked at this, because they didn't know which mutation or which combination of mutations to study," Wang said. "That's the advantage of using the statistical method first to find the patterns. After the statisticians discovered the connections between mutations, then we focused on those combinations. We built structural models to understand the molecular basis of drug resistance."

Using the computing resources of the Center for Theoretical Biological Physics at UC San Diego where Wang is a senior scientist, they worked out how the substitutions would change the shape of protease and its affinity for the drug. One set of changes, for example, would tend to dislodge the drug from the pocket where it normally fits.

The researchers also determined that the mutations must happen in a particular order for replicants to survive treatment with indinavir, a window into how drug resistance develops.

Looking back into the database at samples taken from individual patients at several different times during the course of their treatment, the team found that mutations accumulated in the orders that they predicted would be possible during drug treatment. Sequential mutations that their models predicted would leave the virus vulnerable to drug treatment were not observed.

The team reports its results for two additional drugs, zidovudine and nevirapine, which target a different viral enzyme, in this paper and is extending its work to all nine drugs currently approved by the FDA to treat HIV.

Additional authors include Jing Zhang at Harvard University and Tingjun Hou, a former postdoctoral fellow at UC San Diego now at Soochow University in Suzhou, China. Grants from the National Science Foundation and the National Institutes of Health supported this work.

Media Contact: Kim McDonald, 858-534-7572 or scinews@ucsd.edu

Comment: Wei Wang, 858-822-4240 or wei-wang@ucsd.edu

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