Using math to understand hep. C: Patterns paint picture of who will respond to treatment

December 22 2008

Genetic patterns are like the tea leaves in the bottom of a cup for predicting which patients are likely to respond to medical therapy for life-threatening viruses such as hepatitis C, Saint Louis University researchers have discovered. Their findings are published in the Dec. 22 early online issue of the *Journal of Clinical Investigation*.

"We identified mathematical patterns, which are called 'covariance networks,' to analyze the sequence of proteins in the genes or 'genetic patterns' of hepatitis C virus in two groups of patients – those who responded to and those who resisted traditional therapy," said John Tavis, Ph.D., professor of molecular and microbiology at Saint Louis University and a lead author of the paper.

"What we found will allow a doctor to predict whether or not a medication will work in a patient."

Similar covariance network analysis could tell us more about other RNA viruses, such as HIV or influenza virus, Tavis said.

About 3.8 million Americans are infected with hepatitis C, which is spread by blood-to-blood contact and can cause advanced scarring – or cirrhosis – of the liver, and induce liver cancer or liver failure. Hepatitis C causes the deaths of between 10,000 and 12,000 Americans each year.

Patients with hepatitis C typically are treated with a 24- to 48-week course of two powerful drugs – pegylated interferon and ribavirin, Tavis said. The therapy, which can cause patients to "feel like they have a very bad case of the flu for a year," clears the virus from about half of the patients but fails in the others. Scientists are baffled as to why it works in some patients, but not others.

Interferon is part of the body's natural defenses against viruses, and it triggers multiple protective mechanisms. But the hepatitis C virus actively fights back against the effects triggered by interferon.

"The body's interferon responses and the virus' counter-responses are like evenly-matched boxers -- about half of the time during therapy the virus wins, and in about half of the time the body wins," Tavis said.

Tavis and his collaborators, Rajeev Aurora, Ph.D., and Maureen Donlin, Ph.D., used a mathematical model to draw a map of the viral genome of 94 hepatitis C patients who responded and did not respond to standard therapy.

They found a complex web of amino acid interactions in the viral proteins that resembled an airline map, with amino acid hubs that linked to many other amino acids in much the way that certain cities are centers of activity for incoming and outgoing flights.

"The hubs may be valuable targets for new antiviral drugs," Tavis said.

The team also identified "subnetworks" that are always associated with the failure of therapy, which they believe are "biomarkers" that can help predict whether standard hepatitis C therapy will be effective.

He suggests scientists could design a test to see if the viruses infecting these patients have these genetic characteristics to determine whether or

not standard hepatitis C therapy is likely to work.

"The side effects of the medicines to treat hepatitis C are terrible," Tavis saids. "Why beat on a patient for a year if the treatment isn't going to work anyway?

"On the other hand, if we know the medicine is likely to work, we can coax patients to stick with the therapy. It would help doctors to positively support their patients through trying times."

In addition, hepatitis C therapy is very expensive, with a course of treatment costing up to $30,000. A custom test that determines whether a patient would benefit from the treatment could be developed for about $100 per sample and given to patients before the standard treatment is prescribed, Tavis said.

"If the test shows the treatment won't work, physicians could counsel against interferon-based therapy, avoiding tens of thousands of dollars in expenses and painful side effects for the patient," Tavis said. "It's wasteful to spend millions of dollars on medicine that won't work."

Source: Saint Louis University