Cooperation among viral variants helps hepatitis C survive immune system attacks

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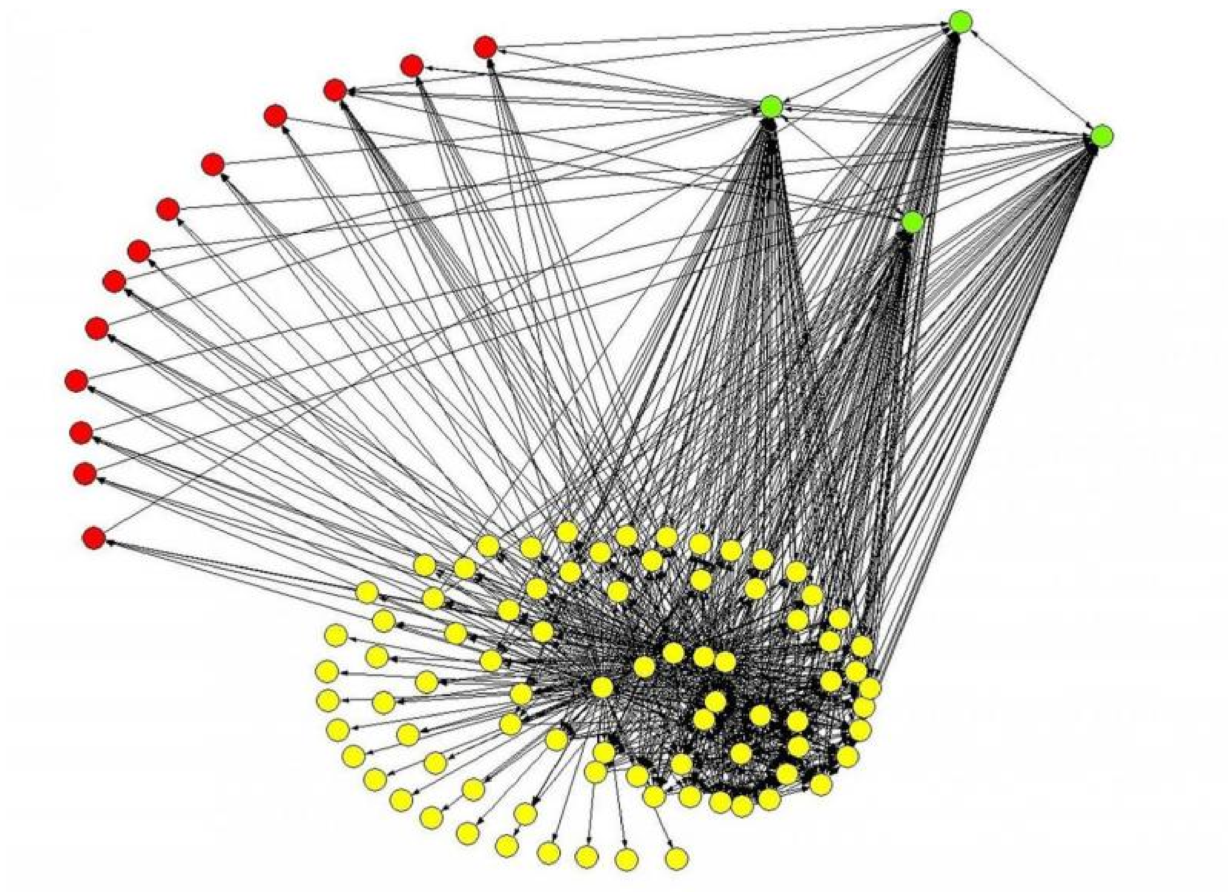

Graph shows a cross-immunoreactivity network (CRN) composed of 100 viral variants. Altruistic variants are shown in green, persistent variants in red, and others in yellow. Credit: Georgia Tech/CDC

Warring armies use a variety of tactics as they struggle to gain the upper hand. Among their tricks is to attack with a decoy force that occupies the defenders while an unseen force launches a separate attack that the defenders fail to notice.

A study published earlier this month in the journal *Proceedings of the National Academy of Sciences* suggests that the Hepatitis C virus (HCV) may employ similar tactics to distract the body's natural defenses. After infecting patients, Hepatitis C evolves many variants, among them an "altruistic" group of viral particles that appears to sacrifice itself to protect other mutants from the body's immune system.

The findings, reported by researchers from the Georgia Institute of Technology and the Centers for Disease Control and Prevention (CDC), could help guide development of future vaccines and treatments for the virus, which affects an estimated 170 million people in the world. Developing slowly over many years and often without symptoms, Hepatitis C can cause severe liver damage and cancer. There are currently no vaccines for the disease.

"The members of viral populations in Hepatitis C don't act like separate entities; the different variants work together almost like a team," said Leonid Bunimovich, a Regent's Professor in the Georgia Tech School of Mathematics. "There is a clear separation of responsibilities, including variants we call 'altruistic' because they sacrifice themselves for the good of the whole viral population. These variants seem to draw the immune system attack on themselves."

The findings resulted from mathematical modeling done by the scientists, who first developed a model for how the virus variants and immune system antibodies interact. They then used the model to analyze and explain data gathered from a group of patients infected with Hepatitis C, some of whom had been followed for as long as 20 years.

The virus evolves differently in each person, producing a mix of genetically-related variants over time, Bunimovich noted. Ultimately, the virus variants and the antibodies form a complex network in which an antibody to one variant can react to another variant - a phenomenon known as cross-immunoreactivity.

But how do viruses, which lack brains or even neural cells, produce a level of teamwork that's often difficult for humans to achieve?

"The virus variants do not communicate directly with one another, but in this system of viruses and antibodies, they interact through the antibodies," explained Bunimovich. "When one antibody-producing cell responds to one variant, and then to another, that is a form of interaction that affects both variants. An indirect interaction occurs when the virus variants interact with the same antibody in the network."

Unlike HIV - to which it is often compared - Hepatitis C virus doesn't suppress the body's immune system. Many scientists believe that the viral infection evolves like an "arms race," with the virus mutating to stay one step ahead of the body's immune system. Using next-generation gene sequencing data, the research team - which included regular fellow Pavel Skums and microbiologist Yury Khudyakov from the CDC's Division of Viral Hepatitis - analyzed viral populations in detail. The scientists studied the genetic compositions of the populations, and even saw evolution in blood samples taken from the same persons over time.

The populations of variants rose and fell, some remaining in small numbers and others reappearing after they had been seemingly wiped out by the immune system. At late stages of the persistent infection development, the evolution of new variations almost stopped, though the immune system remained strong. The "arms race" theory fails to explain these observations, Bunimovich said.

Using their model to track both variants and antibodies, the researchers found that certain variants were drawing the immune system response on themselves to protect others. They called this newly-observed phenomenon "antigenic cooperation." The antibodies suppressed only the altruistic variants, leaving other viral members of the network unharmed.

"The altruistic variants allow the antibodies to attack them, thereby sacrificing themselves, so other variants can survive," said Skums, the paper's first author. "The altruistic variants fool the immune system, rendering the immune system response to other variants ineffective. In essence, the surviving variants use the altruistic (sacrificing) variants as an umbrella to protect themselves."

The researchers were surprised by the sophisticated behavior, which occurs because the viral variants are part of the complex interconnected network - a social network not unlike the ones created in such environments as Facebook.

"Even such simple organisms as viruses can organize into a network," Skums explained. "Because they are part of a network, they can develop this kind of complex behavior, fighting the immune system through team efforts."

The findings, if supported by additional research, could alter the strategy for developing vaccines for Hepatitis C. Both vaccines and treatment would have to take into account how the virus evolves differently in individuals. The researchers also hope to examine the activity of other viruses to see if this complex interaction may also be found in other viral networks, Bunimovich said.

For the researchers, mathematics allowed them to see patterns that might otherwise have remained hidden in the complex patient data.

"Now that we see this from the mathematical model, everything makes sense," said Skums. "When you look at this mathematically, you can see the whole picture."

More information: "Antigenic cooperation among intrahost HCV variants organized into a complex network of cross-immunoreactivity," *Proceedings of the National Academy of Sciences*, published ahead of print May 4, 2015. www.dx.doi.org/10.1073/pnas.1422942112

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