MedicalXpress

Big picture of how interferon-induced genes launch antiviral defenses revealed

April 10 2011

When viruses attack, one molecule more than any other fights back. Interferon triggers the activation of more than 350 genes, and despite the obvious connection, the vast majority have never been tested for antiviral properties. A team of researchers, led by scientists from Rockefeller University, for the first time has carried out a comprehensive, systematic evaluation of the antiviral activity of interferon-induced factors. The findings, published online today in the journal *Nature*, are a first step toward unraveling how these naturally occurring molecules work to inhibit viruses.

"We hope this study will open the door to future work on the mechanisms of antiviral molecules," says first author John Schoggins, a postdoctoral associate in Charles M. Rice's Laboratory of Virology and Infectious Disease at Rockefeller. "Such mechanistic studies may set the stage for the development of new and much needed drugs to combat a diverse array of viruses that pose significant health threats to people worldwide."

The researchers were interested in type I interferon, a cellular molecule that is made when a person becomes infected with certain viruses. Type I Interferon is used clinically in the treatment of some viral diseases, such as hepatitis C, and its presence has been shown to significantly limit the severity of certain viral infections.

Schoggins and his colleagues, including researchers from the Aaron Diamond AIDS Research Center and the Howard Hughes Medical

Institute, systematically evaluated the majority of common interferon-induced genes, one by one, to determine which of them had antiviral activity against a panel of disease-causing viruses, including the hepatitis C virus, HIV, West Nile virus, the yellow fever virus and chikungunya virus.

The scientists used a cell-based "screen" to measure the ability of each gene to halt the growth of the viruses: One by one, genes were delivered into the cells that were then infected with virus. In cells that had no interferon-induced genes delivered, Schoggins and his team observed normal levels of virus replication. In cells that had interferon-induced genes delivered, they occasionally found "hits" that could significantly impair virus replication.

Overall, Schoggins and his colleagues found that each virus tested was susceptible to inhibition by a unique subset of these interferon-induced genes, with some genes having specific effects on only one virus, and other genes having more broad effects on multiple viruses.

The researchers also showed that two genes in combination were more potent than either gene alone, supporting the long-standing hypothesis that many interferon-induced factors work in a combinatorial fashion. A number of the factors, the researchers found, work by interfering with the process by which viral RNA is translated in protein.

"It's fascinating that evolution has provided us with an array of hundreds of molecules that can be summoned by the host upon viral infection," says Schoggins. "Even more interesting is that none of these factors on their own are 'magic bullets' that can eradicate the virus. Instead, the cell relies on the cooperative action of numerous factors to effectively shut down the virus."

Schoggins and his colleagues hope their work will ultimately help inform

the design of new antiviral drugs.

"This study is a first step toward unraveling how these previously uncharacterized, naturally occurring interferon-induced factors inhibit viruses," says Rice, who is the Maurice R. and Corinne P. Greenberg Professor at Rockefeller and scientific director of the Center for the Study of Hepatitis C. "In future studies, we hope to reveal the exact mechanisms by which these molecules suppress viral replication. If this can be done, then we will have a platform for the development of novel drugs that may be beneficial for combating viral infections."

Provided by Rockefeller University