Study identifies human genes required for hepatitis C viral replication

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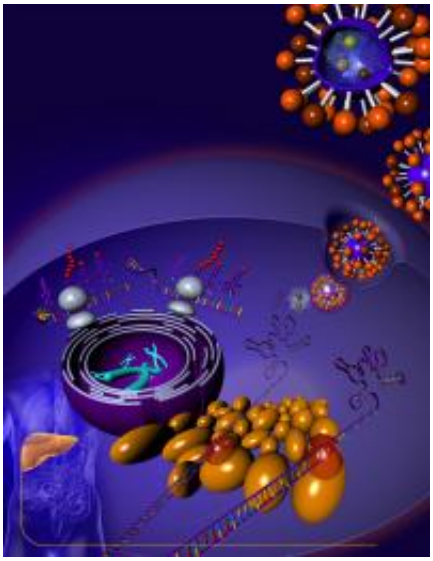

Upper right, virus particle enters cell followed by uncoating and release of positive-stranded HCV RNA genome. Viral genome is translated at the endoplasmic reticulum into the viral polypeptide (upper left). Viral replication complexes (red) are then assembled onto host-derived small membranous vesicles (yellow ovoids).

Massachusetts General Hospital (MGH) researchers are investigating a new way to block reproduction of the hepatitis C virus (HCV) - targeting not the virus itself but the human genes the virus exploits in its life cycle. In the March 19 *Cell Host & Microbe*, they report finding nearly 100 genes that support the replication of HCV and show that blocking several

of them can suppress viral replication in cultured cells.

"We identified a large number of genes that have not been previously known to be involved in hepatitis C replication," says Raymond Chung, MD, director of Hepatology in the MGH Gastrointestinal Unit, the study's senior author.

Lead author Andrew Tai, MD, PhD, also of the MGH Gastrointestinal Unit, adds, "We may be a few years away from developing therapies based on these findings, but this study is a proof of principle that targeting host factors is a viable therapeutic strategy."

Usually spread by blood-to-blood contact, HCV infection becomes chronic in 70 to 80 percent of patients, and long-term infection can lead to liver failure or liver cancer. Today HCV-related liver disease is the most common diagnosis underlying the need for liver transplantation. HCV infection is usually treated with a six- to eleven-month regimen combining peginterferon and the antiviral drug ribavirin, but treatment is not successful in many patients and has serious side effects some cannot tolerate. Other therapies targeting viral enzymes are being developed, but there is concern that HCV's ability to mutate rapidly would lead to the emergence of resistant strains, so strategies directed against factors in the infected host rather than the virus may offer a complementary approach.

These strategies are being explored in a number of diseases - including influenza, West Nile virus and HIV - and previous studies have scanned a limited number of human genes for host cofactors of HCV infection. For the current study the researchers examined whether blocking each of the approximately 21,000 predicted messenger RNA transcripts in the human genome with small interfering RNAs (siRNAs) had any effect on HCV replication. Chung notes that this approach does not rely on any prior assumptions about gene function and can thereby identify genes

not previously suspected of involvement.

The siRNA scan found 96 genes that appear to have a role in viral replication, and the research team studied several of them in greater detail. One gene codes for an enzyme called PI4KA, which is believed to be involved in the formation of membrane structures within the cell that may be the site of HCV replication. Another group of genes contribute to formation of the COPI coat that covers several types of cellular vesicles and is known to have a role in the replication of poliovirus. The researchers also focused on the gene for hepcidin, a liver protein that regulates iron absorption, since iron levels in the blood and liver rise in chronic HCV infection. They found that blocking each of these genes also blocked HCV replication, as did drugs that inhibit PI4KA and COPI, although the tested agents might not be suitable for therapeutic use.

Source: Massachusetts General Hospital (news : web)