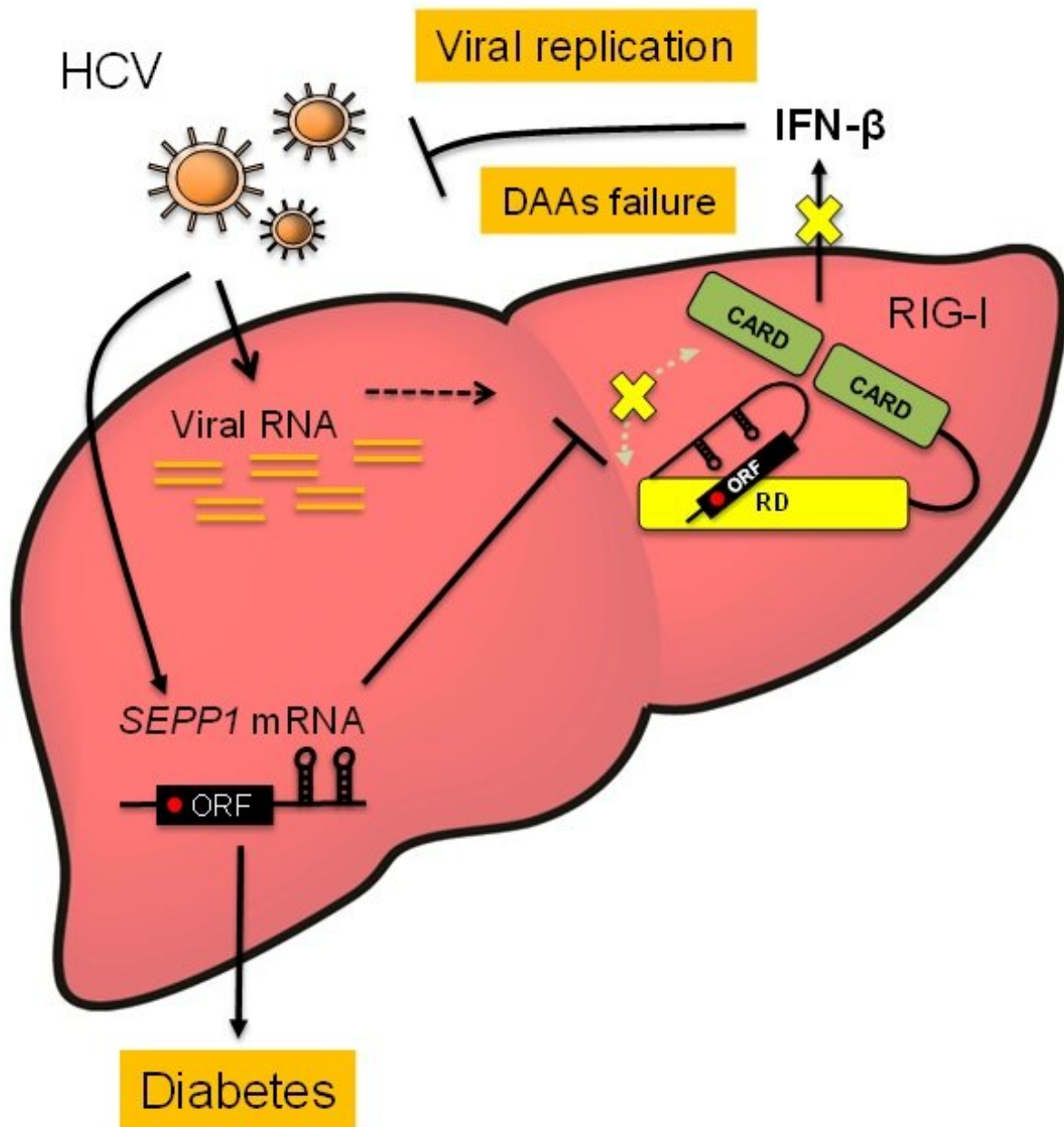


Discovery of a host mRNA that inhibits immune functions of antiviral protein RIG-I

April 10 2019



The liver infected by HCV augments selenoprotein P expression. Selenoprotein P gives rise to insulin resistance, accelerating pathogenesis of type-2 diabetes. On the other hand, mRNA of selenoprotein P binds to the regulatory domain (RD) of RIG-I, inhibiting production of type I interferon (IFN- β) that has antiviral activity. As a result, viral replication is augmented which causes resistance against antiviral treatments. Credit: Kanazawa University

Hepatitis C virus (HCV) is a hepatotropic virus, with about 80 million chronic infections confirmed worldwide. HCV infection leads to the development of chronic hepatitis, cirrhosis, and in some instances, hepatocellular carcinoma. The recent development of highly potent direct-acting antiviral drugs (DAAs), targeting viral proteins, facilitates virus elimination in >90 percent of treated individuals. However, the mechanism of DAA failure in the remaining 10 percent is not understood.

The liver is a vital organ with functions in the metabolism of carbohydrates, proteins and lipids, the clearance of toxins and pathogens, and the regulation of immune reactions. Previously, the present research group discovered selenoprotein P (SeP), a liver-derived secretory protein; they reported that SeP contributes to the induction of [insulin resistance](#) and is involved in the pathogenesis of type 2 diabetes. Interestingly, patients with both [chronic hepatitis C](#) (CHC) and type 2 diabetes show a tendency to be unresponsive to DAAs. In the present study, the group investigated the pathogenic and clinical relationship of HCV infection and type 2 diabetes, focusing on SeP.

The group at Kanazawa University investigated the effects of SeP on antiviral immune responses in the liver, using cultured [cells](#), mice and

clinical specimens. They found that HCV infection augmented SeP expression in cultured cells. By analyzing clinical specimens, they found that serum SeP levels were higher in HCV-infected patients than healthy controls, and that treatment with DAAs was less effective in patients with higher levels of SeP expression.

On the other hand, a remarkable repression of HCV replication was observed in the cultured cells with suppressed expression of SeP. These cells were also found to have an augmented production of interferon (IFN), which has antiviral activity. Humans are known to have a system to detect virus invasion into cells and to induce IFN production. RIG-I and MDA5 (melanoma differentiation-associated gene 5) recognize virus-derived RNA and induce IFN production. Although RIG-I and MDA5 have a highly homologous helicase domain, they recognize different RNAs depending upon RNA structure, as well as base alignment (PAMP: pathogen-associated molecular pattern). HCV is thought to be recognizable by both RIG-I and MDA5. By performing experiments using a RIG-I knockout cell line and a MDA5 knockout cell line, SeP was found to specifically regulate RIG-I pathway-dependent innate immune responses.

In more detailed experiments using purified SeP and synthetic RNA, repression of innate immunity by SeP was shown to be brought about not by the protein but by the SeP mRNA. Upon binding of a viral RNA to RIG-I, the ATPase activity of RIG-I is stimulated to induce a three-dimensional structural change and oligomerization of RIG-I, which binds to mitochondrial antiviral signaling protein to activate IFN production. It was found that overexpression of SeP mRNA inhibited the ATPase activity important in the RIG-I activation steps: oligomerization of RIG-I and RIG-I localization to mitochondria. SeP mRNA, by binding to and interacting with the regulatory domain (RD) of RIG-I protein that specifically recognizes and captures viral RNA, inhibited the three-dimensional structural change necessary for RIG-I activation, and

negatively regulated innate immunity.

Thus the present study has elucidated the regulation mechanism of innate immunity by SeP mRNA via RIG-I, one of the antiviral immune regulation mechanisms in the liver.

Since chronic hepatitis C and type 2 diabetes are high in morbidity worldwide, they must be treated as early as possible. In this study, we investigated the clinical relationship between HCV infection and type 2 diabetes, focusing on SeP, an inducer of insulin resistance. RIG-I protein was thought only to recognize RNAs of pathogens invading cells thus protecting against pathogens, but not to act on host RNAs. So far, very few host mRNAs have been reported acting like SeP mRNA, which functions as a 'decoy' to bind RIG-I thus repressing its functions. This information is important for understanding immune tolerance in the liver and autoimmune diseases. The study is expected to lead to further investigations of host RNAs regulating RIG-I and to the development of clinical application targeting such mRNAs, such as nucleic acid medicine.

The study is published in *Cell Host & Microbe*.

More information: *Cell Host & Microbe* (2019). [DOI: 10.1016/j.chom.2019.02.015](https://doi.org/10.1016/j.chom.2019.02.015)

Provided by Kanazawa University

Citation: Discovery of a host mRNA that inhibits immune functions of antiviral protein RIG-I (2019, April 10) retrieved 30 January 2023 from <https://medicalxpress.com/news/2019-04-discovery-host-mrna-inhibits-immune.html>

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