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Study shows main cell type in the liver has key role in defending against some viruses

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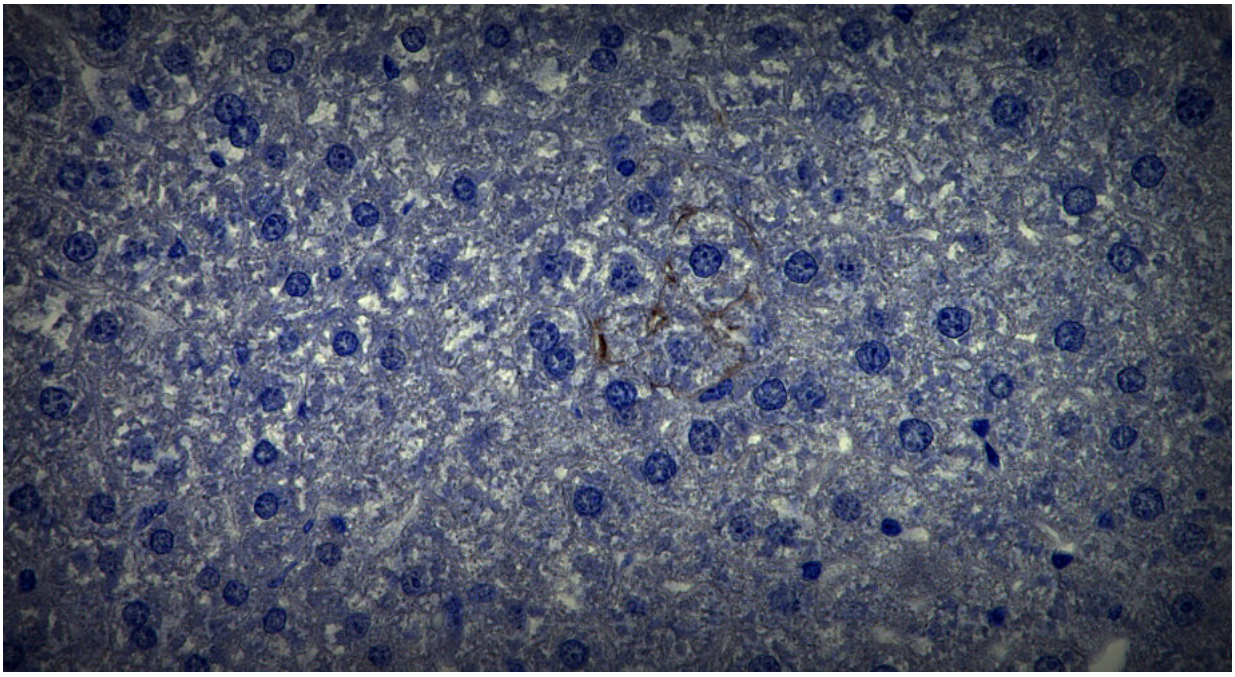

Through experiments involving modified versions of liver cells known as “hepatocytes” (pictured), scientists showed that these cells likely absorb viruses in the body to slow their spread. Credit: Whitton laboratory at Scripps Research

Scientists at Scripps Research have uncovered an important disease-fighting role for cells called hepatocytes, which constitute most of the liver. The discovery could potentially be harnessed to develop new medicines for viral illnesses.

According to the new study, which appears in *Communications Biology,* hepatocytes help control infections from common viruses called coxsackieviruses, and probably defend against many other viruses as well. The findings suggest these liver cells, long known for their role in deactivating chemical toxins in the blood, should also be viewed as a significant element of the immune system—an element that future drugs might be able to enhance to strengthen the body's defense against emergent viruses.

"Hepatocytes may have evolved the ability to absorb and silence a variety of different viruses, to slow their spread in the body and reduce infection-related illness," says Taishi Kimura, Ph.D., postdoctoral research associate at Scripps Research and first author of the study.

Kimura worked on the study while in the laboratory of J. Lindsay Whitton, MD, Ph.D., professor in the Department of Immunology and Microbiology at Scripps Research and senior author of the study.

Whitton and his lab have long studied coxsackieviruses, a family of polio-like viruses that spread via the fecal-oral route and can cause a broad array of symptoms including fever, sore throat, rash, diarrhea, meningitis, pancreatitis and inflammation of the heart muscle. The viruses are named for the New York town of Coxsackie, where virus specimens were initially isolated from patients in the late 1940s.

Recently Kimura and research assistant Claudia Flynn observed that mice experience significant liver damage, including damage to and deaths of hepatocytes, when infected with a type of coxsackievirus called coxsackievirus B3 (CVB3).

Hepatocytes, along with many other cell types, express a cell-surface protein called "coxsackievirus-adenovirus receptor" or CAR, which CVB3 uses to get into cells. So Kimura and Flynn genetically engineered

mice whose hepatocytes—but no other cell types—lack CAR, and thus could not be infected by CVB3. Unsurprisingly, when these mutant mice were infected with CVB3, their hepatocytes were spared significant damage.

However, the CVB3 infection hit these mutant mice much harder on the whole, compared with non-mutant siblings. The mutants with protected hepatocytes swiftly showed high blood levels of virus, lost more weight, developed complications such as heart inflammation and were much more likely to die from the infection.

These findings showed that ordinary hepatocytes, when they are able to be infected by CVB3, help protect the rest of the body from the virus. In further experiments, the team found more support for this idea, observing that when hepatocytes absorb CVB3, they quickly shut down the virus's replication using an immune protein called IRF1. Although the infected hepatocytes are damaged by taking up the virus, the liver itself does not show the strong inflammation that is seen in other virus-infected organs, such as the heart and pancreas.

Virus researchers have known that other, much-less numerous cell types in the liver—such as so-called Kupffer cells—can trap and neutralize viruses that are circulating in the blood. Hepatocytes had not been thought to do this, but the study shows that they do.

Given the large size of the liver, hepatocytes constitute a major cell type in the body. To the researchers, it seems unlikely that this major cell type has evolved to defend against only one family of viruses. More likely, they say, it acts broadly, like an antiviral "sponge," soaking up any of a variety of virus types from the bloodstream early in infection, to help slow and limit the infection in the rest of the body. Hepatocytes that absorb viruses in this way may be damaged or die, the researchers add, but the harm to the liver is perhaps only temporary.

"Hepatocytes have an extraordinary capacity for regeneration, and this may be an adaptation that has more to do with their antiviral role than with their better-known role against toxins," Whitton says. "Toxins may not have been enough of a threat during animal evolution to create pressure for such an adaptation, but viruses probably have been."

Whitton and Kimura also note that other common viruses, including the SARS-CoV-2 coronavirus that causes COVID-19, can cause modest and often temporary liver damage, much like that observed for CVB3. This again hints that hepatocytes' defensive role may extend far beyond coxsackieviruses. Though Whitton is retiring this year, Kimura intends to continue this line of research into whether—and how—hepatocytes defend against SARS-CoV-2 and other viruses.

"The protein IRF1, which hepatocytes use to silence CVB3, works by activating a broad set of antiviral genes, and it may be that each of these antiviral genes is adapted to silence a different set of viruses," Whitton says.

By actively taking up virus that is circulating in the blood, hepatocytes may also serve as a first-alert mechanism that helps activate other immune system elements, Kimura says. In principle, Kimura adds, future drug treatments might enhance hepatocytes' uptake of viruses to limit serious infections when no other option is available, such as with new human-infecting viruses.

"This hepatocyte response might turn out to be a key element of the human immune response against emergent viruses," he says.

"Hepatocytes trap and silence coxsackieviruses, protecting against systemic disease in mice" was authored by Taishi Kimura, Claudia Flynn and J. Lindsay Whitton.

More information: Taishi Kimura et al, Hepatocytes trap and silence coxsackieviruses, protecting against systemic disease in mice, *Communications Biology* (2020). DOI: 10.1038/s42003-020-01303-7

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