Age-related hepatitis B infection and the gut microbiome

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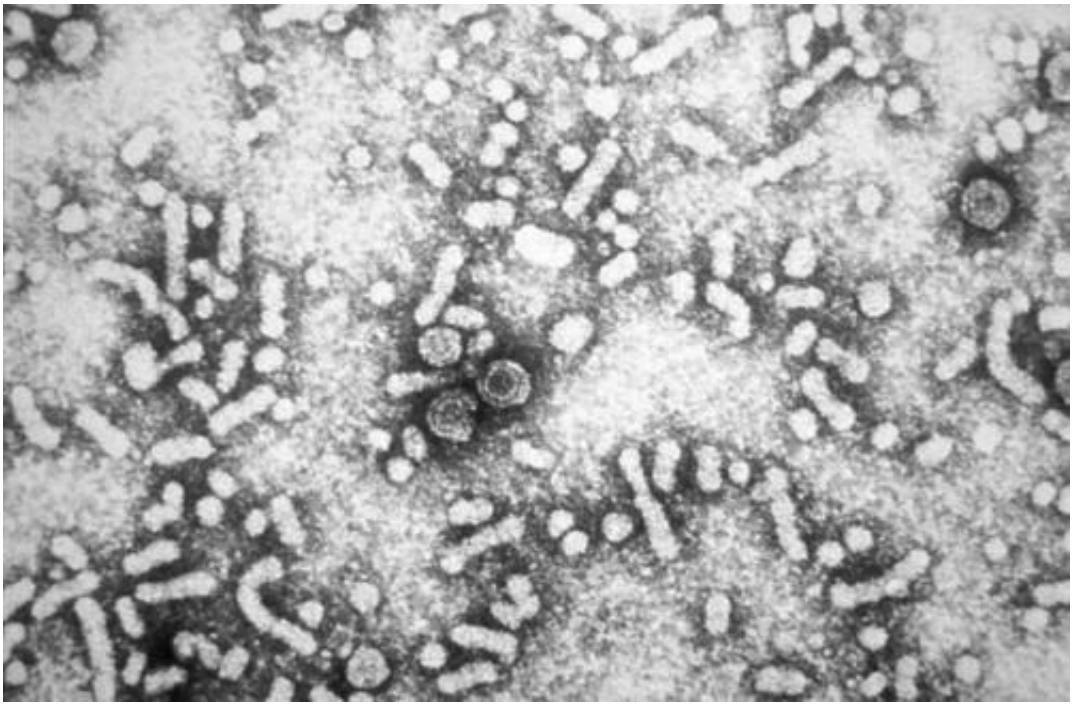

Electron micrograph of hepatitis B virus. Credit: Centers for Disease Control and Prevention

(Medical Xpress)—The hepatitis B virus (HBV), which affects the liver, behaves differently in different people depending on genetics and the age the person is when infected. Ninety-five percent of adults who contract hepatitis B clear the virus after several weeks. However, 90 percent of neonates and 30 percent of children under the age of five develop chronic hepatitis B, which can lead to liver damage.

A new study by Han-Hsuan Chou and Wei-Hung Chien from the College of Medicine at Taiwan University shows that the development of the gut microbiome may explain why babies and young children tend to get chronic hepatitis B compared to adults.

Human beings live in a symbiotic relationship with bacteria that reside in and on our bodies. These bacteria and their respective environments are known as the microbiome. The microbiota living in the gut has been of particular interest recently because studies indicate a correlation between the composition of the gut microbiota and certain diseases that affect the immune system.

In this study, Chou and Chien used mouse models to investigate how the gut microbiota changes with age, whether the composition of the gut microbiota affects expulsion of HBV, and how gut microbiota the genetics of liver immunity are related. They used a particular mouse model that is known to mimic several of the features of hepatitis B infection in humans, including age dependency and genetic effects.

Chou and Chien used three different genetic strains of mice and found that, at six weeks old, HBV lingered more in some strains than others, indicating that there is some genetic component to how long the HBV remains in the body. However, in all of the strains, there was an overall pattern that showed adult mice clearing the virus while young mice did not. The adult mice, which were infected at twelve weeks old, cleared the virus after only five weeks. Most of the young mice were still infected after 26 weeks, showing that age of infection takes prominence over genetics factors in fighting HBV.

Chou and Chien then wanted to look at the composition of the gut microbiota to see if there was a correlation between composition and response to HBV. They focused their microbiota studies on the genetic strain of mice that had the greatest disparity between the young mice and

the adult mice.

To investigate the effects of the microbiota, they treated some of the adult mice with a well-established antibiotic regimen. They left the other adult mice untreated as a control, and did not treat any of the young mice with antibiotics. The untreated mice had a gut microbiota profile that went through substantial changes between six and eight weeks of age, but stabilized after nine weeks. This shows the timeframe for the mouse gut microbiome to stabilize.

In the mice treated with antibiotics, the gut microbiota was nearly undetectable during treatment, but was measurable four days after treatment ended. Notably, four weeks after the antibiotic treatment ended, the gut microbiota composition did not return to levels similar to the untreated adult mice.

Each of these groups, the mice treated with antibiotics and the mice without, were infected with HBV and monitored. Chou and Chien found that in the adult mice without antibiotics, HBV levels were undetectable after six weeks. In the adult mice with antibiotics, 60 percent showed HBV still present after six weeks. In the young mice, 90 percent showed HBV present after six weeks. After six months, 53 percent of the antibiotic mice and 80 percent of the young mice remained infected with HBV. These results indicate that the gut microbiota composition plays an important role in the liver's immune response to HBV. This was confirmed by additional tests showing that disrupting the microbiome inhibited antibody production.

Finally, Chou and Chien investigated how the gut affects the liver immune response of the mice. They found that the gut microbiota composition likely affects the signaling pathway that activates the TLR4 gene. In mutant mice, in which this signaling pathway is disrupted, all mice, regardless of age, were able to clear the HBV after eight weeks

and showed the presence of antibodies.

The results of this study show that the gut microbiota composition plays a role in liver immune response to HBV. Younger mice may be more vulnerable to developing chronic hepatitis B because their gut microbiome has not yet stabilized. Adults, whose gut microbiome has stabilized, were more likely to develop acute hepatitis B; however, adult mice, whose microbiome was disrupted from antibiotics, responded to HBV infection similarly to young mice.

These studies provide helpful clues for investigating prevention and treatment of hepatitis B infection.

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