Dendritic cells in liver protect against acetaminophen toxicity

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NYU School of Medicine researchers have discovered that dendritic cells in the liver have a protective role against the toxicity of acetaminophen, the widely used over-the-counter pain reliever and fever reducer for adults and children. The study's findings are published in the September issue of the journal *Hepatology*.

The liver is the organ that plays a central role in transforming and filtering chemicals from the body. High-doses of acetaminophen can cause hepatotoxicity, chemical driven liver damage. In fact, accidental and intentional acetaminophen overdose are the most frequent causes of acute liver failure (ALF) in the United States. Acetaminophen related liver failure by intentional or accidental overdose causes 56,000 emergency room visits, 2,600 hospital visits and 450 deaths annually. As a result, this year the FDA mandated drug manufacturers to start limiting the amount of acetaminophen in combination drug products and is currently exploring adding safer dosing instructions to children's acetaminophen products.

In the new study, researchers found an abundance of dendritic cells in the liver can protect the organ from acetaminophen damage while low levels of dendritic cells in the liver are associated with exacerbated liver damage, liver cell and tissue death, known as centrilobular hepatic necrosis, and acute liver failure from acetaminophen.

"Our research results confirm a central role for dendritic cells and their powerful regulation of acetaminophen's toxicity," said George Miller,

MD, senior author of study and assistant professor, Departments of Surgery and Cell Biology at NYU Langone Medical Center. "High levels of dendritic cells have a novel, critical and innate protective role in acetaminophen hepatotoxicity. We now have greater insight into the liver's tolerance of acetaminophen toxicity and dendritic cell regulation of these toxins."

In the study, researchers used acetaminophen-induced hepatic injured mice models to closely examine the protective role of dendritic cells. Dendritic cells are the main antigens in the liver that trigger an immune response and control the liver's tolerance to high doses of invading toxins like acetaminophen. In the experiment all mice were injected with acetaminophen but some mice models were first depleted of dendritic liver cells using a diphtheria toxin while others had their dendritic cell levels bolstered with Flt3L, a protein in the blood previously shown to increase proliferation of dendritic cell levels.

Researchers discovered dendritic cell depletion exacerbates acetaminophen's damage to the liver. The acetaminophen treated mice with depleted dendritic cells had more extensive liver cell and tissue death compared to other mice. Also, these mice died within 48 hours of acetaminophen challenge- whereas death was rare in other mice without dendritic cell depletion. In addition, the study shows dendritic cell expansion successfully diminished the hepatotoxic effects of acetaminophen protecting the liver from damage.

"Understanding the regulatory role of dendritic cells is an important step in the development of immune-therapy for acetaminophen induced liver injury," said Dr. Miller, a member of the NYU Cancer Institute. "Advanced studies are warranted to investigate further the protective role of dendritic cells in humans and their use as a possible new therapeutic target for liver failure prevention in the future."