Researchers find novel way to prevent drug-induced liver injury

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Massachusetts General Hospital (MGH) investigators have developed a novel strategy to protect the liver from drug-induced injury and improve associated drug safety. In their report receiving advance online publication in the journal *Nature Biotechnology,* the team reports that inhibition of a type of cell-to-cell communication can protect against the damage caused by liver-toxic drugs such as acetaminophen.

"Our findings suggest that this therapy could be a clinically viable strategy for treating patients with drug-induced liver injury," says Suraj Patel, PhD, of the MGH Department of Surgery, the paper's lead author. "This work also has the potential to change the way drugs are developed and formulated, which could improve drug safety by providing medications with reduced risk of liver toxicity."

Developing, approving and prescribing a drug requires that the therapeutic benefits be weighed against any potential toxicities. Liver toxicity limits the development of many therapeutic compounds and presents major challenges to both clinical medicine and to the pharmaceutical industry. Drug-induced liver injury is the most common cause of acute liver failure in the U.S. and is also the most frequent reason for abandoning drugs early in development or withdrawing them from the market. Since no pharmaceutical strategies currently exist for preventing drug-induced liver injury, treatment options are limited to discontinuing the offending drug, supportive care and transplantation for end-stage liver failure.

Gap junctions are hollow channels that connect neighboring cells and allow direct intercellular communication between coupled cells. In the heart, gap junctions are known to propagate the electrical activity required for contraction, but their role in the liver is poorly defined. Recent work by the MGH team and others has shown that assemblies of intercellular gap junctions spread immune signals from injured liver cells to surrounding undamaged cells, amplifying overall inflammation and injury. The current study was designed to discover the potential of targeting liver-specific gap junctions to limit drug-induced liver injury.

The researchers first used a strain of genetically mutated mice that lack a particular liver-specific gap junction. The mice were administered various liver-toxic drugs, such as the commonly used medicine acetaminophen. Overdoses of acetaminophen, which is best known under the brand name Tylenol, are the most frequent cause of drug-induced liver injury. Compared to normal mice, those lacking liver gap junctions were protected against liver damage, inflammation and death caused by administration of liver-toxic drugs.

The team then identified a small-molecule inhibitor of liver gap junctions that, when given with or even after the toxic drugs, protected the livers of normal mice against any injury and prevented their death. Additionally, cell culture experiments indicated that blocking gap junctions limited the spread through liver cells of damaging free radicals and oxidative stress, suggesting a possible mechanism for the observed protection.

"This finding is very exciting and potentially very powerful from a number of basic science and clinical application standpoints, which we are continuing to explore," says Martin Yarmush, MD, PhD, director of the MGH Center for Engineering in Medicine and senior author of the study. "However, before we can think about applying this approach to patients, we need to know more about any off-target effects of these gap

junction inhibitors and better understand the long-term ramifications of temporarily blocking liver-specific gap junction channels."

A patent related to the work has been filed by Partners Healthcare, and an early stage biotechnology company, Heprotech Inc., was recently established to develop this new technology further. "The findings from this work suggest a novel drug development strategy in which therapeutically effective but potentially liver-toxic compounds could be co-formulated with selective gap junction inhibitors to improve their safety," explains Patel, a co-founder of Heprotech along with Yarmush. "We look forward to helping commercialize this new technology, with the ultimate goal of developing liver-safe pharmaceuticals and better treatments for drug-induced liver injury."

Provided by Massachusetts General Hospital