# Possible treatment target found for main cause of severe liver disease in kids

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Unexpected discovery of a new molecular signature for a destructive and often lethal pediatric liver disease may lead to a new therapeutic target for the hard-to-treat condition.

In a study that included human livers and a mouse model of biliary atresia, researchers report in the November Journal of Clinical Investigation that not all children with biliary atresia share the same disease process. Some patients have a second molecular conductor of disease called Th2 (T helper cell 2) immune system.

Biliary atresia is disease that destroys the bile ducts in and near the liver in the first few months of life. Driven by an overly aggressive immune system response after birth, the condition is the most common cause of severe pediatric liver disease. The ducts, which normally carry bile from the liver and gall bladder to the intestines, become blocked over time. Even with treatment, which can include surgery, children often need a liver transplant within two years of birth.

Despite the need for better therapies, progress has been hampered by a limited knowledge of biological processes driving the disease, according to Jorge Bezerra, MD, principal study investigator and a researcher/physician in the division of Gastroenterology, Hepatology and Nutrition at Cincinnati Children's Hospital Medical Center.

"Our findings add a new dimension to the understanding of biliary atresia," Bezerra said. "They provide a potential target for new therapies and have implications for clinical trials. Now, depending on the molecular signature of a child's disease, we can develop new strategies to also target the Th2 immune system with anti-inflammatory agents."

Bezerra said physicians have learned in clinical trials that not all children with biliary atresia respond in similar fashion to the same treatment protocols. The current study may help explain why.

Until now, only molecular signals from the Th1 cytokines had been linked consistently to the biochemical processes that cause biliary injury. Th cytokines, also referred to as T-helper cells, are part of the immune system. They send molecular signals to help initiate and maximize the body's immune system response. In biliary atresia, that response can go into overdrive and become too aggressive, piling on damage to the bile ducts and the liver.

Despite the prevalence of Th1 detection in children with the disease, there have been reports that some biliary atresia patients exhibit low levels of Th1. This led Bezerra and his colleagues to look for Th1-independent drivers.

They tested their hypothesis with genetically modified newborn mice that lack the ability to mount a Th1-modulated immune response. The mice were infected with rhesus rotavirus Type A, which can cause severe inflammation of the bile ducts if infections occur soon after birth. This prompted an almost immediate and robust immune response involving Th2 cytokines.

The mice developed damaged bile ducts, duct obstructions within seven days and then full atresia (blockage) shortly thereafter. The researchers then depleted a Th2 molecule known as Interleukin 13 and noted a reduction in tissue infiltration by immune cells. It also maintained the integrity of bile duct tissues and prevented obstructions from occurring.

Bezerra examined the blood of children with biliary atresia and found that some of them exhibit high levels of Th2 cytokines. This, coupled with the current study findings, demonstrate "a compatibility between Th2 and the onset of biliary atresia, and suggest that patient subgrouping in future clinical trials should account for differences in Th2 status,"

he said.

The current study was funded in part by grants from the National Institutes of Health and the Digestive Disease Research Core Center in Cincinnati. It follows a study from Bezerra and colleagues published Sept. 29 in Science Translational Medicine, which points to how immune system dendritic cells trigger the initial immune response in a mouse model of biliary atresia.

The September study reported that dendritic cells - which process and transmit signals from the surfaces of tissues to recruit other immune system components - activated natural killer cells in the immune system. This activation set off a cascade of hyperactive immune response in the newborn mice, worsening the disease.

Researchers were able to disable the process be depleting or blocking the signaling activity of plasmacytoid dendritic cells and Interleukin 15. This prevented injury of the bile ducts and shut down the disease process. Bezerra cautioned that more research is needed before determining whether blocking this process may have therapeutic benefit in humans.

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