Keck Researchers Link Mitochondrial Protein to Liver Failure

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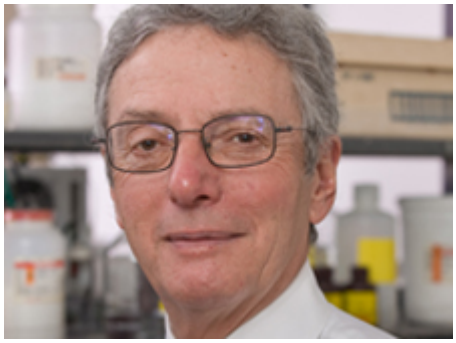

Neil Kalowitz, M.D.
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Popping a Tylenol to ease a headache, or taking a dose of Nyquil at the onset of a cold is such a minor occurrence for most people that it rarely elicits more than a passing thought. Acetaminophen, the primary ingredient in Tylenol and prominent in most cold and cough medicines, usually relieves pain and reduces fever. Once metabolized by the liver, however, this apparently harmless chemical can become the primary cause of drug-induced liver disease and acute liver failure. Researchers at USC's Keck School of Medicine may have found a way to protect the liver from this effect.

Acute Liver Failure

Led by Dr. Neil Kalowitz, the research team investigated a mitochondrial protein in the liver cells of mice. This protein, called Sab or SH3-domain binding protein 5, binds to an enzyme called c-Jun N-terminal kinase or JNK. JNK is linked to cellular stress responses. It regulates both cell protection and cell death, depending on how long it is activated. When the enzyme binds to the Sab protein on the surface of a mitochondrion, it inhibits mitochondrial metabolism. At the same time, the mitochondrion releases chemicals that amplify the enzyme's effects, eventually leading to cell death. When this reaction occurs in the liver, it results in acute liver failure. Acetaminophen is linked to drug-induced liver disease and liver failure through this cascade. Researchers believed at first that, in excess, acetaminophen is broken down into toxic substances that overwhelm liver cells and cause them to die. Later research showed that excess acetaminophen instead contributes to sustained activation of JNK, leading to cellular death as a result of this cascade.

The researchers looked to the important interaction between Sab and JNK for their inspiration. They found that Sab, which is located in the outer membranes of the mitochondria of mouse liver cells, has a direct relationship with JNK.

Methods

The researchers used two different experimental models to confirm that silencing Sab provides dramatic protection against liver toxicity caused by JNK. This included both liver toxicity as a result of excess acetaminophen and liver failure due to infection or other causes.

Why not target JNK instead of Sab? It seems easier to target JNK, but it might not have the hoped-for effects. After all, JNK also plays a role in cellular protection. By confirming that the binding of JNK to Sab leads to cellular death, researchers have found a possible target location for drugs to prevent liver damage without inhibiting cellular protection. Further researcher will look into the exact nature of the interaction between Sab and JNK, as well as investigating the likelihood of a similar interaction occurring in human liver cells.

So Why Care?

The fact that a connection between a single protein and a single enzyme can be linked to liver failure is extraordinary. These researchers have also found that silencing the protein can protect against the damage caused by excess acetaminophen. In this study, the researchers went one step further and found that silencing Sab protected against other forms of liver damage as well. The researchers have located a site that drugs could target to have dramatic effects on liver disease and acute liver failure. If a drug could protect against liver failure, it would help thousands of people, including those who might otherwise have ended up on the transplant list. Equally as important is the implication that an interaction between a protein and an enzyme can cause cellular death, and that inhibiting this interaction protects. There is nothing to say that this interaction does not occur in other cell types. Think, for instance, the impact if such an interaction were to be found to occur in nerve cells, and the number of disease that could be limited or prevented by inhibiting the death of these cells.

Although a small step, this research by Dr. Kalowitz and his team is certainly headed in the right direction. They have confirmed that silencing the Sab protein in the membrane of liver mitochondria stops the JNK feedback that leads to cell death, taking us one step closer to finding a way to protect against liver disease caused by acetaminophen, one of the most common and seemingly harmless drugs.