

Researchers find that a biological 'good guy' has a dark side

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A pair of Oklahoma Medical Research Foundation scientists have discovered that an enzyme previously thought only to be beneficial could, in fact, pose significant danger to developing embryos. The new research could have implications not only for prenatal development but also for treating lymphedema and liver damage resulting from acetaminophen overdose.

Using genetically engineered mouse embryos, OMRF's Courtney Griffin, Ph.D., and Patrick Crosswhite, Ph.D., looked at what would happen if they removed a protein that determines how genes get turned on and off during [blood vessel development](#).

The scientists found a marked increase in the activity of plasmin, an enzyme that is known to help break up blood clots and promote blood vessel development. But in a developing embryo, said Griffin, too much of the enzyme can pose a threat.

"Plasmin has always been seen in a positive light, but we're not finding any beneficial aspects of it in early development," said Griffin. "In fact, excessive plasmin does dangerous things in a growing embryo."

The OMRF researchers also found that liver damage could ensue in embryos when the protein that suppresses plasmin activity—known as CHD4—was absent. Too much plasmin makes liver [blood vessels](#) fragile and prone to bleeding. They also found that excess plasmin could be harmful to the lymph system, an essential part of the immune system, by

breaking down [blood clots](#) that help the lymphatic system function properly.

With this new information, Griffin and Crosswhite will study plasmin behavior later in gestation and in adults. They'll investigate how high concentration of plasmin may contribute to conditions such as lymphedema, a painful lymph disorder marked by swelling in the arms and legs. They'll also look at whether CHD4 continues protecting liver blood vessels from plasmin damage after birth.

More research is needed, said Griffin, but the findings may lead to clinical use of plasmin-blocking compounds after acetaminophen overdose. Acetaminophen is the active ingredient in Tylenol, and overdose is a leading cause of [liver damage](#) in the U.S., resulting in up to 70,000 hospitalizations a year. "Excessive plasmin activity in the liver has been linked to acetaminophen overdose," said Crosswhite, "and we suspect this plasmin may make liver blood vessels dangerously weak."

"This work is innovative and creative, from the results to the interpretation and conclusions," said Rodger McEver, M.D., chair of OMRF's Cardiovascular Biology Research Program. "These scientists were able to show that [plasmin](#) is really important in ways that hadn't been discovered before. It gives us new information and is great basic science, but the data could be clinically relevant to treating acetaminophen toxicity in humans."

The new findings appear in the May 3 issue of the *Journal of Clinical Investigation*.

More information: Patrick L. Crosswhite et al, CHD4-regulated plasmin activation impacts lymphovenous hemostasis and hepatic vascular integrity, *Journal of Clinical Investigation* (2016). [DOI: 10.1172/JCI84652](https://doi.org/10.1172/JCI84652)

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