Targeting blood vessels, immune system may offer way to stop infection-caused inflammation

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Treating virulent influenza, sepsis, and other potentially deadly infections long has focused on looking for ways to kill viruses and bacteria. But new research from the University of Utah and Utah State University shows that modulating the body's own overeager inflammatory response to infection may help save more lives.

In a study published March 17 in *Science Translational Medicine*, researchers led by U of U cardiologist Dean Y. Li, M.D., Ph.D., professor of internal medicine and director of the Molecular Medicine Program, shows that protecting blood vessels from hyper-inflammatory response to infection reduced mortality rates in mouse models of avian flu and sepsis by as much as 50 percent. Specifically, the researchers identified a protein signaling pathway, Robo4, that when activated prevents inflammation from weakening blood vessels, which causes them to leak and can result in life-threatening organ damage.

The findings raise the possibility of new broad-range therapies that could be rapidly implemented by public health agencies to fight both viral and bacterial infections, such as pandemic influenza and sepsis, and even potentially deadly human-made biological agents that could cause widespread illness and death, according to Li. Such therapies would be given along with antibiotics, antivirals, and other drugs.

"By blocking the ill effects of inflammation on the host or patient by

stabilizing blood vessels, we have identified an entirely different strategy to treat these infections," Li said. "In essence, we've shown that rather than attacking the pathogen, we can target the host to help it to fight infections."

While this study proves the concept of controlling the effects of inflammation to fight the effects of serious infection, developing therapies for people will take years.

Inflammation is a powerful weapon in the body's immune system; without this inflammation, patients would not be able to fight infection. But it's also a double-edged sword. When Biochemical mediators, called cytokines, are released in massive quantities as part of the inflammatory response, they can destabilize blood vessels, resulting in leakage, tissue edema (swelling), and in extreme cases, organ failure and death. For example, a severe infection such as that of the 1918 pandemic flu, can cause life-threatening lung damage when alveoli become inflamed and fill with fluid, a condition known as lung edema. Similarly, sepsis can damage organs such as the kidneys by weakening blood vessels and allowing fluid to leak into the kidney tissue, impairing its vital functions.

Although it will take much more work to determine if Robo4 can be manipulated to block inflammation in sepsis, influenza, and other infections, the protein's signaling pathway appears to be ideal for stabilizing the endothelial cells that line blood vessels, according to Guy A. Zimmerman, M.D., a U of U professor of internal medicine who investigates inflammation and sepsis. "For this reason, the Robo4 pathway may be more effective and less likely to have negative side-effects than some of the approaches and drugs that have been tried in the past," said Zimmerman, a co-author on the study.

Targeting the pathogens that cause influenza and sepsis has been the primary strategy to fight those infections. While this has been successful,

it also has limitations because pathogens can evolve quickly to develop resistance to antibiotics and antiviral medications. A second approach has been to dampen a patient's immune system response to infection. However, past approaches led to poor outcomes in patients, in part because they sometimes increased the sick individual's susceptibility to a second, "opportunistic" infection.

Protecting the host from its own inflammatory response to infection offers a potential strategy to reduce the mortality rate from many different types of serious infections. In the mouse models of this study, the mortality rate for some sepsis and avian flu infections approached 90 percent when left untreated. By protecting blood vessels through activating Robo4, mortality was reduced in some cases to almost half.

Dale L. Barnard, Ph.D., a virus specialist and research associate professor at the Institute for Antiviral Research in the Department of Animal, Dairy and Veterinary Sciences at Utah State University, said the study opens a potentially exciting approach to treating virulent viral-caused infections such as pandemic H1N1 and the highly infectious avian flu. "It may be even a more effective approach if it were to be used in combination with antiviral drug therapy, perhaps allowing the antiviral drug to be used at concentrations below those which would induce drug resistance or allow the drug to be administered for shorter periods of time," said Barnard, also a co-author on the study.

Li's study of Robo4 as an agent for mitigating the effects of inflammation grew from his research into blood vessel formation. In 2003, he cloned Robo4 and showed that it inhibits uncontrolled blood vessel growth, thereby stabilizing vessels and preventing leakage. Robo4 is activated by another protein, called Slit.

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