Researchers uncover cellular mechanism that protects lungs during severe infections

January 9 2015

Dr. Jalees Rehman is an associate professor of medicine and pharmacology, UIC College of Medicine. Credit: Photo: Roberta Dupuis-Devlin

Researchers at the University of Illinois at Chicago have discovered a novel molecular mechanism that tightens the bonds between the cells that line blood vessels to form a leak-proof barrier. The mechanism presents a potential new target to treat acute respiratory distress syndrome (ARDS), an often fatal condition in which fluid leaks out of

blood vessels into the lungs.

UIC researchers, led by Asrar Malik, Schweppe Family Distinguished Professor and head of pharmacology, found they could trigger the cell-tightening mechanism in mice using a small molecule, called Fg4497. Mice that were exposed to an infectious agent that causes fluid to enter the lungs had higher rates of survival and less fluid accumulation than mice not treated with the compound.

The findings are reported in the *Journal of Clinical Investigation*.

ARDS is fatal in approximately half of all cases. The current standard treatment is supportive care, such as artificial ventilation. Few therapies are able to successfully reverse the fluid leakage.

"In ARDS, our body's own immune response becomes a major problem," says Dr. Jalees Rehman, associate professor of pharmacology and medicine in the UIC College of Medicine and one of the lead authors of the study.

As part of the body's normal, healthy immune response to infection, the barrier formed by blood vessel cells temporarily loosens, allowing white blood cells to exit the bloodstream and attack the invading bacteria or virus, Rehman said.

However, in certain cases of severe pneumonia or bloodstream infections, the barrier is not properly restored, he said. Persistent leakiness is especially problematic in the lung. Patients with ARDS are often placed on artificial ventilators and given supplemental oxygen.

"It's a vicious cycle of inflammation and leakiness of the lung blood vessels that is very hard to control," Rehman said. "It's as if the lung is drowning in its body's own fluids. Being able to prevent this by

stabilizing and restoring the integrity of the blood vessel barrier could help save lives."

Rehman and his colleagues study mechanisms that regulate cell-to-cell contacts called adherens junctions. They knew that a molecule called VE-PTP, was important in stabilizing adherens junctions.

In lab experiments with human lung blood vessel cells, the researchers found that low-oxygen conditions induced the expression of the oxygen-sensitive gene regulator HIF2alpha, which in turn increased levels of VE-PTP.

Mice that lacked HIF2alpha had much lower levels of VE-PTP and had much leakier blood vessels than mice that can make HIF2alpha.

They found that if mice exposed to bloodstream infections were given a drug that mimics the effect of low oxygen, levels of HIF2alpha and VE-PTP rose and their blood vessels became less leaky. These mice had significantly higher rates of survival and less fluid in their lungs than mice not given the drug.

"It makes sense that low oxygen would induce this cascade of molecular events leading to the tightening of the barrier," said Rehman. "It seems that the blood vessel cells have their own way of tightening up the barrier when they are in a low oxygen stress situation." As lungs begin to fill with fluid, the blood becomes under-oxygenated, and the cells lining the blood vessels react by tightening the adherens junctions. However, this natural ability to tighten the barrier in response to low oxygen may not occur fast enough in the patients who develop ARDS.

"Our current studies were conducted in mice, but we hope that one day we will be able to take advantage of the body's natural response to low blood oxygen levels with drugs that mimics low oxygen conditions.

These drugs could be given to high-risk patients and hopefully prevent the formation of ARDS by activating the internal protective barrier tightening mechanism," Rehman said.

More information: *Journal of Clinical Investigation*, www.jci.org/articles/view/7770 … f84b5113ab8c080ee17c

Provided by University of Illinois at Chicago