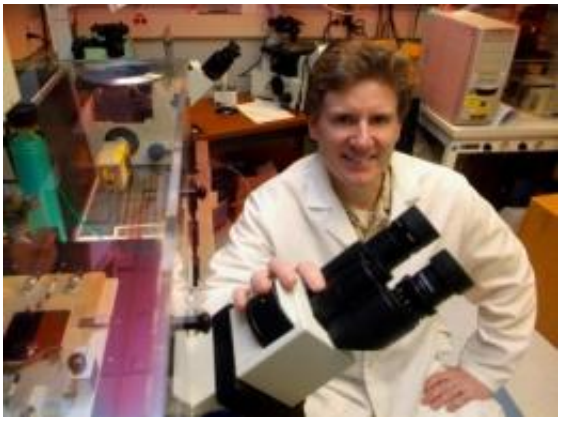
Better treatment sought for acute lung injury

August 22 2011



Dr. Stephen Black, cell and molecular physiologist at Georgia Health Sciences University, is leading a major research initiative to find better ways to treat acute lung injury. Credit: Phil Jones/GHSU photographer

Patients can essentially drown in their own fluids when trauma and infection prompt blood vessels to leak, flooding millions of air sacs in their lungs.

"Once you get an acute lung injury, you will either survive or die based on who you are," Dr. Stephen Black, a cell and molecular physiologist at Georgia Health Sciences University.

He is Program Director on an $11.3 million National Institutes of Health grant enabling a research team at GHSU's Vascular Biology Center to try to improve patient odds by identifying key, destructive events over the first hours and days of injury and developing a cocktail of therapies to

block them.

Nearly a half century of experience with acute lung injury has yielded no effective treatment for a malady that occurs in about 150,000 people annually in the United States, killing about one-third of patients and leaving others with scarred, at-risk lungs, Black said.

Potential therapies the GHSU team is exploring include HSP90 inhibitors already in use for cancer. HSP90 is a molecular chaperone that helps cancer cells survive and evidence suggests its inhibitors can block the barrier dysfunction and resulting vascular leakage of acute lung injury. Conversely, the researchers also are looking at adenosine agonists that appear to ramp up barrier protection as well as development of novel drugs to keep vessels from leaking. They aim to move forward with clinical trials by the end of the five-year grant.

Culprits in acute lung injury include the mechanical ventilators that provide oxygen support but also pummel fragile air sacs. Other instigators are common bacterial infections that cause maladies such as pneumonia, severe trauma that induces shock, multiple transfusions, burns and meconium aspiration, when newborns inhale waste products. These conditions commonly require a ventilator, which can compound the damage. In fact, the only real progress in acute lung injury in the past 40-plus years has been decreasing ventilator settings when possible to reduce the resulting trauma, Black said.

Healthy blood vessels are effectively impenetrable with tightly knit endothelial cells leaving no room for escape. But researchers have shown trauma and infection disrupt the usual balance of key proteins called RhoA and Rac1 causing cells to move apart. This enables the liquid part of the blood, called plasma, and later blood proteins, to escape into adjacent air sacs. Ironically the lungs' excess capacity often precludes diagnosis until significant damage is done and breathing is impaired.

"Our idea is to put the balance back," Black said of Rac1, which protects the integrity of the endothelial barrier, and RhoA, which disrupts it.

Dr. John Catravas, vascular biologist and a Project Leader on the grant, thinks one cause of elevated Rho levels is the well-intended inflammation following trauma or infection when white blood cells rally to clean up the mess. "The problem in some people who die with acute lung injury is, after the invading organism is eliminated, the white cells remain and start consuming their tissue," Catravas said. Lingering white cells release proinflammatory cytokines and reactive oxygen species that stimulate Rho activity. Catravas has evidence that HSP90 inhibitors can block the function of these white cells. "Obviously you would not want to block HSP90 while the invading organism is active," he noted. Rather Catravas wants to better understand the role of HSP90 in acute lung injury and identify when intervention with an inhibitor is most beneficial.

Dr. David Fulton, Interim Director of the Vascular Biology Center, is Project Leader on studies focusing on gram positive toxins from pneumonia. Published research has demonstrated that these toxins bind to the innermost layer of endothelial cells within pulmonary blood vessels, giving calcium unfettered access inside cells and promoting gaps and leaks in the protective endothelial cell layer. Normally, calcium levels are tightly regulated inside the cells. Fulton and collaborators have found that left unchecked, gram positive toxins can activate protein kinase C. Together with the large calcium influx, this compromises the activity of the enzyme nitric oxide synthase, which produces the protective molecule, nitric oxide. This prompts nitric oxide synthase to produce more of the powerful oxidant peroxynitrate. The resulting imbalance of nitric oxide and peroxynitrate throws off the balance of Rac and Rho in favor of blood vessels that leak into the lungs. Fulton wants to design new therapies to restore the balance of products produced by nitric oxide synthase.

In the case of sick patients, that may mean, at least for a while, reducing Rho and "goosing up" Rac to tighten and restore the barrier, Black said. His project focuses on the impact on this critical balance of lipopolysaccharide, a major component of the outer membrane of gram-negative bacteria that can prompt a strong immune response. He's shown infection with the bacterium causes elevation of an endogenous inhibitor of nitric oxide synthase resulting in increased production of peroxynitrate as well as increased levels of protein nitration. These changes again set Rac and Rho up for dramatic change in their activity. Patents are pending on novel peptides that may prevent nitration of Rac and Rho and ideally the leaky blood vessels that can result.

Dr. Alexander D. Verin, Director of Research for Pulmonary and Critical Care Medicine at GHSU, is exploring the ability of the natural compound adenosine – already used to treat abnormal heart rhythms – to "goose up" Rac activity. In response to infection with lipopolysaccharide, he's shown adenosine rapidly increases Rac activity and attenuates leakiness. Now he'll learn more about how it works in both mouse models of acute lung injury and human endothelial cells.

GHSU researchers are the first to culture endothelial cells of the tiny human blood vessels for use in the studies. "When you get sick, these are the cells that get damaged," Catravas noted. Previous studies have looked at leakiness in larger vessels. GHSU Cardiothoracic Surgeon Vijay Patel – who treats the consequences of altering lung physiology with a ventilator or infection - is providing researchers with lung tissue removed during surgery. Researchers also are using mouse models of gram positive and gram negative-induced acute lung injury.

Provided by Georgia Health Sciences University