New therapy protects lungs from runaway inflammation

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A novel anti-inflammatory therapy designed by Vanderbilt University Medical Center investigators prevents acute lung injury in mice exposed to an inflammation-causing toxin, the researchers report in the journal *Molecular Therapy*.

The new therapy may offer a way to protect the lungs from the "runaway inflammation" that can accompany bacterial or viral pneumonia, said Jacek Hawiger, M.D., Ph.D., the leader of the research team that has pioneered the new approach.

"Lung inflammation is an extremely perplexing problem," noted Hawiger, chair of the Department of Microbiology & Immunology.

The immune system sometimes overreacts to lung infection and produces excessive concentrations of inflammatory signals (cytokines and chemokines), which can damage the fine architecture of the lungs and lead to life-threatening acute respiratory distress syndrome (ARDS). Such damage is most likely when pneumonia has both viral and bacterial causes - for example from combined influenza and Staphylococcus aureus infections.

"We believe that in addition to controlling the infection with antibacterial and antiviral agents, we need therapies that reduce this inflammation-induced collateral damage to the lung tissue," Hawiger said. "This would allow both faster clearance of the infecting organisms and faster healing of the lung."

Several years ago, Hawiger and colleagues began searching for new targets for anti-inflammatory therapy. They reasoned that a protein called NF-kappa-B - the "master regulator" of genes that encode mediators of inflammation - might make a good target.

The researchers knew that NF-kappa-B moves from the cell cytoplasm to the nucleus (where it is active) in response to cellular injury or microbial agents, and they decided to try to block this nuclear translocation.

They designed a small protein fragment - a peptide - that mimicked the nuclear transport "signal," hoping that it would compete with, and block, NF-kappa-B's movement to the nucleus. To get the peptide into cells, the team took advantage of the cellular mechanism that proteins use to cross membranes and engineered a membrane-crossing motif onto the therapeutic peptide.

"To our delight, we found that this peptide crossed the cell membrane and stopped NF-kappa-B in its tracks, blocking it from going to the nucleus in response to conditions which cause inflammation," Hawiger said.

It turned out that the inhibitor worked even more broadly than the researchers expected. The peptide blocks a "shuttle" that ferries not only NF-kappa-B to the nucleus, but also a group of additional stress-responsive proteins. The nuclear shuttle protein represents a new intracellular target for anti-inflammatory therapy, Hawiger said.

The researchers tested the effectiveness of this cell-penetrating peptide therapy against inflammation in a mouse model of acute lung injury.

They exposed mice to staphylococcal enterotoxin B (SEB), an immunotoxin produced by methicillin-resistant S. aureus (MRSA). SEB

generates a "storm" of inflammatory signals that damages the lungs and causes ARDS and multiple organ dysfunction. Airborne SEB caused fatal ARDS in non-human primates.

Treatment of SEB-exposed mice with the nuclear transport inhibitor suppressed the inflammatory storm in the lungs. Inflammatory cells, whose numbers increase 2.5-fold after SEB exposure, remained normal in peptide-treated mice. Peptide therapy also suppressed the levels of chemokines and cytokines and prevented injury to the lung's blood vessels.

"It's very reassuring to us that this single agent, which targets the nuclear import shuttle, suppressed the production of all of these harmful mediators of excessive inflammation," Hawiger said.

The investigators are pursuing pre-clinical studies of the peptide therapy with hopes that it will lead to improved adjunctive therapies for life-threatening pneumonia caused by multiple germs.

Source: Vanderbilt University Medical Center