Naturally occurring lipid blocks RSV infection in lungs

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Researchers at National Jewish Health have discovered that a naturally occurring lipid in the lung can prevent RSV infection and inhibit spread of the virus after an infection is established. RSV is the major cause of hospitalization for children in the first two years of life, and is increasingly recognized as a dangerous pathogen in adults with chronic lung diseases, the elderly, and immunocompromised individuals. Currently, there is no effective vaccine for the virus.

The findings, published in the December 21, 2009, issue of The Proceedings of the National Academy of Sciences, also help explain how the lipid, known as POPG, helps the lung tolerate a daily barrage of inhaled inflammatory irritants.

"Our findings demonstrate that POPG is a potent antiviral agent both as a prophylactic and after infection has occurred," said Dennis Voelker, PhD, Professor of Medicine at National Jewish Health. "While these are still early studies, several characteristics of POPG make me believe that it has real potential as both an antiviral and anti-inflammatory treatment."

POPG (palmitoyl-oleoyl-phosphatidylglycerol) is one of several lipids in the fluid that lines the air sacs of the lungs. Other lipids and proteins in this surfactant fluid are known to prevent collapse of the air sacs and to contribute to innate immunity. Until now, however, POPG's function has been unknown. Previous research, published by the Voelker team this fall, showed that POPG reduces inflammation in the lung and suggested

that it might play a role in RSV infection.

In the current research, Voelker and his colleagues showed in cell-culture studies that inoculation with POPG before RSV exposure prevents RSV infection, as well as cell death and inflammation associated with RSV infection. In mice, prophylactic intranasal inoculation with POPG, reduced the RSV infection-rate by a factor of 1,700, and prevented the infiltration of inflammatory cells into the lung that can cause tissue damage.

The researchers also showed that application of POPG to cells in culture after a viral infection is established dramatically arrests the spread of infection to neighboring uninfected cells.

"Our findings suggest that supplemental POPG may have significant potential for preventing RSV infections in vulnerable human populations, and treating infections after they become established," wrote the authors in their paper.

The researchers demonstrate that POPG works by binding to RSV, thus preventing it from binding to receptors on cell surfaces.

Previous research by the Voelker team revealed that POPG also binds to CD14 and MD2, cell-surface molecules that detect bacterial endotoxin and initiate inflammatory responses. The POPG binding to CD14 and MD2 suppresses the inflammatory response to endotoxin. The suppression of inflammation by POPG helps explain how healthy people can routinely inhale low environmental levels of endotoxin without mounting a robust inflammatory immune response. In essence, POPG sets a high tolerance threshold for endotoxin in the lung, thereby preventing chronic inflammation. It also suggests that supplemental POPG may be helpful in damping down the inflammatory response and the "cytokine storm" that accompanies severe bacterial infections and

sepsis.

While molecules that look promising in cell-culture and mouse studies often fail to translate into therapeutic treatment in humans, Voelker and his colleagues are optimistic about POPG's chances for success, for a few reasons. For one, POPG occurs naturally in the lungs. The researchers have also administered massive doses to mice with no apparent ill effects. POPG also has been safely administered to millions of premature infants as part of a lipid mixture to protect their lungs. It is also a small molecule that is easily synthesized and is chemically stable.

The researchers next plan to evaluate POPG's effectiveness against other pathogens, including influenza.

Provided by National Jewish Medical and Research Center

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