

Novel therapeutic use of protein kinase RNA-like endoplasmic reticulum kinase (PERK) inhibitor for acute lung injury treatment

Brief Description

Mitigating lung injury and lung inflammation through PERK pathway inhibition

Inventor

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STATE OF DEVELOPMENT

Proof-of-concept and *in vivo* testing

INTELLECTUAL PROPERTY

Provisional pending

DESIRED PARTNERSHIPS

- License
- Co-development

APPLICATIONS

- Acute lung injury
- Ventilator-induced lung injury
- Acute respiratory distress syndrome
- Lung inflammation

Problem

Acute lung injury, induced by long-term treatment with a mechanical ventilator, and acute respiratory distress syndrome (ARDS) affects 190,000 patients per year in the United States, with associated mortality of 35-40%. The highest numbers of deaths are in patients with sepsis, pneumonia, or aspiration. ARDS is characterized by sudden breathlessness within hours to days of an inciting event, including trauma, sepsis, drug overdose, blood transfusion, and aspiration. ARDS is a life-threatening condition caused by widespread inflammation of the lungs that can lead to multisystem organ failure. Currently, there is no specific therapy for acute lung injury or lung inflammation, and adjunctive strategies that modulate the deleterious effects of mechanical ventilation are needed.

Solution

During lung injury, the Margulies lab has discovered, *in vitro* with a rat epithelial stretch model and *in vivo* with ventilated rats and pigs, that protein kinase RNA-like endoplasmic reticulum kinase (PERK) inhibition reduces the activation of the integrated stress response (ISR) signaling pathway that is induced upon mechanical stretch. Upon mechanical stretch, PERK is phosphorylated and initiates the signaling cascade. PERK inhibition in the ISR pathway improves mechanical stretch-induced epithelial monolayer permeability, mitigating mechanical stretch-induced cell death and tight junction dissociation. Inhibiting the ISR pathway *in vivo* may reduce acute lung injury during large tidal volume ventilation. This work represents the first implication of the PERK pathway in lung injury, as well as a new use of a commercially available PERK inhibitor previously connected with cancer and neurodegenerative diseases, and diseases with activated unfolded protein response pathways.

Advantages

- Use commercially available PERK inhibitor for alternate indication to treat lung injury and inflammation
- New method of use for existing compound
- Safety previously tested in humans
- Potential therapeutic where one does not exist for this condition

LEARN MORE

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