MEDICAL PROPHYLAXIS TO MITIGATE CHEMICAL THREATS

Regulation Of Actin Depolymerization Resulting From Lung Injury

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Abstract
Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) result from the inhalation of a variety of different agents; and upon exposure to these toxins, a proinflammatory signaling pathway is activated, which then leads to actin filament depolymerization. Consequently, in alveoli, the breakdown of actin filaments results in the epithelial fluid barrier weakening and becoming leaky. Using a mouse model, we have demonstrated that delivery of a constitutively active form of a protein involved in the signaling pathway (V12Rac1) prevents actin-dependent barrier loss and protects mice from exposure to the sulfur mustard analog, CEES. To prepare V12Rac1 for therapeutic administration, we produced it using different constructs and confirmed that the GTP-binding site of the purified protein remained intact using a fluorescence-based assay. We are developing this assay into a screening platform for compounds that will achieve the same level of activity as the mutant Rac1 in order to identify potential chemical treatments.

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