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# The Gtpase Rab1 is Required for NLRP3 Inflamma some Activation and Inflammatory Lung Injury

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## Abstract

**Rationale:** Uncontrolled inflammatory response in sepsis predominantly contributes to development of multi-organ failure and lethality. However, the cellular and molecular mechanisms for excessive production and release of proinflammatory cytokines are not clearly defined. The purpose of this study is to determine the role of the GTPase Ras-related protein in brain (Rab)1a in regulating the nucleotide binding domain-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome activation and lung inflammatory injury during sepsis.

**Methodology:** Human alveolar macrophages were isolated from septic patients. Cecal ligation and puncture was performed to assess lung inflammation. Genetic manipulation of Rab1 expression in murine bone marrow-derived macrophages was conducted by electroporation.

**Findings:** Rab1a activity was elevated in alveolar macrophages from septic patients and positively associated with severity of sepsis and respiratory dysfunction. In alveolar macrophage-depleted mice challenged with cecal ligation and puncture, pulmonary transplantation of Rab1a-inactivated macrophages by expression of dominant negative mutant Rab1 N124I plasmid dramatically reduced the release of interleukin (IL)-1β and IL-18, neutrophil count in bronchoalveolar lavage fluid, and inflammatory lung injury. Expression of Rab1 N124I plasmid in bone-marrow-derived macrophages prevented the release of IL-1β and IL-18, NLRP3 inflammasome activation, production of pro-IL-1β and pro-IL-18, and attenuated Toll-like receptor 4 surface expression and nuclear factor-κB activation induced by bacterial lipopolysaccharides and ATP compared with control cells.

**Conclusion & Significance:** Inhibition of Rab1a activity in macrophages resulting in the suppression of NLRP3 inflammasome activation is a promising target for the treatment of patients with sepsis.

## Biograph :

Guochang Hu is an Associate Professor of Departments of Anesthesiology and Pharmacology at the University of Illinois at Chicago. Over the past 15 years, his research has focused on acute lung injury, innate immunity and inflammation, and vascular endothelial permeability. He has established a record of successful and productive research in the areas highly relevant to lung inflammatory injury. He is currently serving as a scientific reviewer of more than 40 journals. He also has served as a grant reviewer for the National Institutes of Health and American Heart Association. He has received numerous teaching and research awards including a Young Investigator Award from the American Heart Association.

Lijun Wang is the Chairman of Department of Critical Care Medicine of the Affiliated Hospital of Southern Medical University, China. He has his expertise in the field of critical care medicine, especially in the management of critical maternal near-miss. He has constructed a network including consultation and transfer of critical patients between tertiary referral center and Grade-II hospitals.