Involvement of the Rho kinases in mediating sepsis

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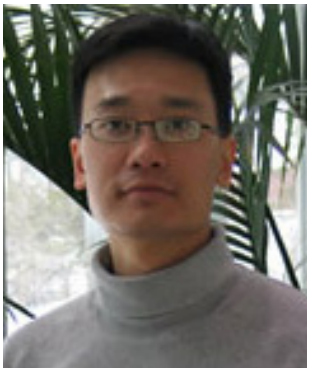

Acute lung injury (ALI) is a serious complication that develops from a variety of conditions that include severe influenza infections, blood transfusions and severe sepsis (1-3). An individual with sepsis is associated with a 40% increased risk of developing ALI over other etiologies that contribute to ALI (4). Acute lung injury manifests itself clinically in a similar manner despite the underlying cause and can be treated in the same way for most of these etiologies (2). ALI is divided up into the following three phases: (I)exudative, (II) proliferative and (III) fibrotic (5). The exudative phase is characterized by cytokine production that increases inflammation in the lung. As well the cytokine production leads to increases in oxidative stress and protease activity (2). There is a rapid onset of respiratory failure leading to arterial hypoxemia that is refractory towards oxygen supplementation (4). The hallmark of the exudative phase is the infiltration of protein rich fluid from the vasculature into the alveolar space. This movement of fluid can lead to alveolar flooding where by the removal of water and protein rich exudate is impaired. This results in decreased lung compliance due to increased viscosity from the protein rich exudates, neutralization of alveolar surfactant and a decrease in the production of surfactant from type II pneumocytes. This leads to an increase in alveolar dead space where gas exchange is impaired (5). In addition to the protein rich fluid accumulation in the alveoli there is an increase in activated neutrophil infiltration. Neutrophil derived elastase has been shown to damage both alveolar epithelial cells and lung endothelial cells (2).

The fibroproliferative phase of ALI occurs by the second week where inflammation persists and there is a rapid proliferation of fibroblasts in the lung in response to damaged epithelial cells as well neovascularization can be detected (2,5).

If the fibroproliferative phase is not resolved then patients will progress to lung fibrosis where epithelial cells are replaced by fibroblasts and increase in extracellular matrix collagen can be detected. This condition can be fatal if it persists.

The characteristic fluid influx seen in the exudative phase of ALI is a result of increased endothelial permeability. In this case the lung capillary endothelial cells no longer functions to form a semi-permeable barrier. Instead intercellular gaps form between the endothelial cells which allows for the passage of protein rich fluid from the vasculature into the interstitium of the lung and the alveolar space. Molecularly this gap formation is mediated by Rho/Rho kinase signaling that affects the cell's cytoskeleton. The Rho family of proteins is comprised of small GTPase proteins which reside inactive in the cytoplasm of endothelial cells. Upon activation Rho members will translocate to the plasma membrane and activate their effector molecule Rho kinase ROCK(6,7). ROCK in turn will phosphorylate its target proteins one of which is the myosin light chain phosphatase. Phosphoylation of this phosphatase results in increased phosphoylation of myosin light chain both by ROCK itself and by the myosin light chain kinase. Together this allows for

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increased activation of myosin light chain and formation of actin myosin interactions. The end result of these interactions is an increase in actomyosin contraction that changes the morphology of the cell through the disruption of cell to cell junctions (8).

The paper by Cinel *et al*. demonstrates that the inhibition of the effector ROCK with the use of a chemical inhibitor Y27632 improves measures of lung damage from septic rats induced by cecal ligation and puncture (CLP) (9). Inhibiting ROCK reduced edema and cellular infiltrates into the lung presumably by preventing the loss of barrier function in the lung endothelial cells. It also shows the protection from neutrophil activation through the reduction in oxidative products seen in the inhibitor treated rats. This paper demonstrates a target that could be used to treat ALI in humans. Complementary to this finding Riento *et al*. have identified an endogenous inhibitor of ROCK I called RhoE/Rnd3 which was found to reduce the phosphorylation and activation of the myosin light chain (10). While Ravindraneth *et al*. identified a partial mechanism for TNF alpha induction of the Rho pathway using a CLP model linking this inflammatory mediator to ALI during sepsis (11). Sepsis produces conditions which produce many activators of the Rho pathway which include thrombin activation, high cytokine production and nitric oxide production (7,12,13). Targeting the Rho pathway could help alleviate the lung injury seen in sepsis in humans. Since the primary treatment for ALI is mechanical ventilation which itself can exacerbate lung injury a treatment that preserves lung function would be beneficial. Better clinical outcomes are associated with preserving lung function or minimizing the time on mechanical ventilation. While the underlying cause of sepsis must be treated the reduction of pulmonary complications induced by sepsis should help improve the outcome of the patient making the development of a therapeutic agent that targets the Rho pathway in lung endothelial cells an important adjunct to sepsis treatment as well as to other causes of ALI. Cinel *et al*. findings have added further support to targeting this central pathway in endothelial cell barrier function.

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References

1. Looney MR. Newly recognized causes of acute lung injury: transfusion of blood products, severe acute respiratory syndrome, and avian influenza. Clin Chest Med 2006;27:591-600; abstract viii.
2. Wheeler AP, Bernard GR. Acute lung injury and the acute respiratory distress syndrome: a clinical review. Lancet 2007;369:1553-64.
3. Toy P, Popovsky MA, Abraham E, Ambruso DR, Holness LG, Kopko PM, et al. Transfusion-related acute lung injury: definition and review. Crit Care Med 2005;33:721-6.
4. Ware LB, Matthay MA. The acute respiratory distress syndrome. N Engl J Med 2000;342:1334-49.
5. Varisco BM. The pharmacology of acute lung injury in sepsis.Adv Pharmacol Sci 2011;2011:254619.
6. Ishizaki T, Maekawa M, Fujisawa K, Okawa K, Iwamatsu A, Fujita A, et al. The small GTP-binding protein Rho binds to and activates a 160 kDa Ser/Thr protein kinase homologous to myotonic dystrophy kinase. EMBO J 1996;15:1885-93.
7. McGown CC, Brown NJ, Hellewell PG, Brookes ZL. ROCK induced inflammation of the microcirculation during endotoxemia mediated by nitric oxide synthase. Microvasc Res 2011;81:281-8.
8. Maekawa M, Ishizaki T, Boku S, Watanabe N, Fujita A, Iwamatsu A, et al. Signaling from Rho to the actin cytoskeleton through protein kinases ROCK and LIM-kinase. Science 1999;285:895-8.
9. Cinel I, Ark M, Dellinger P, Karabacak T, Lulufer T, Cinel L, et al. Involvement of Rho kinase (ROCK) in sepsis-induced acute lung injury. J Thorac Dis 2011;4:30-9.
10. Riento K, Guasch RM, Garg R, Jin B, Ridley AJ. RhoE binds to ROCK I and inhibits downstream signaling. Mol Cell Biol 2003;23:4219-29.
11. Ravindranath TM, Mong PY, Ananthakrishnan R, Li Q, Quadri N, Schmidt AM, et al. Novel role for aldose reductase in mediating acute inflammatory responses in the lung. J Immunol 2009;183:8128-37.
12. Xing J, Birukova AA. ANP attenuates inflammatory signaling and Rho pathway of lung endothelial permeability induced by LPS and TNFalpha. Microvasc Res 2010;79:56-62.
13. Parikh SM, Mammoto T, Schultz A, Yuan HT, Christiani D, Karumanchi SA, et al. Excess circulating angiopoietin-2 may contribute to pulmonary vascular leak in sepsis in humans. PLoS Med 2006;3:e46.