

Rho kinases (ROCKs) in sepsis-induced acute lung injury

Ravin Narain

Department of Chemical and Materials Engineering, Faculty of Engineering, University of Alberta, Canada

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Sepsis is a life-threatening syndrome which develops through the systemic inflammatory response to infection or extensive tissue damage and is manifested by varying degrees of hypotension, coagulopathy, and multiorgan dysfunction. Sepsis is the systemic response to infection and the host responds by producing mediators and proinflammatory cytokines (1-3). Although triggering the inflammatory response is generally considered as protective against pathogenic threats, the interplay between the signaling pathways that are induced or suppressed during sepsis may harm the host.

The complex molecular crosstalk between the various components of the cellular response network highlights the difficulty in identifying a single driving force responsible for sepsis. In addition for being triggered by an overwhelming initial response, sepsis is also characterized by hyperactivation of cellular immunity. Neutrophils, macrophages, lymphocytes and other immune cells produce and respond to the proinflammatory cytokine release. These cytokines include TNF- α , interleukin (IL)-1, IL-6 and secondary mediators (oxygen and nitrogen species) that further enhance the misregulated inflammatory network (1-3). During the early stages of sepsis, the complement system is a defense mechanism involved in clearing the pathogenic organisms and cellular debris. However, the complement activation enhances cytokine and chemokine secretion, and promotes reactive oxygen species (ROS) that ultimately lead to injury at the late stage. Another level of the complexity correlated with sepsis is misregulating the homeostatic systems including the fibrinolysis and coagulation pathways. Hyperactivation of these cascades results in disseminated intravascular coagulation (DIC), depletion of coagulation factors and platelets, and as consequences decreasing the flow rate and hydrostatic pressure of the blood. These conditions will progressively develop to hypoperfusion, hypoxia, ischemia and ultimately multiple organ failure and death (4,5).

Although this dynamic response is a key component of complex conditions associated with sepsis, recent studies have proposed other molecular mechanisms to explain the substantial heterogeneity that exists in sepsis patients. For example, sepsis-induced apoptosis does not only impair the cellular function of immune and non-immune cells, but may also contribute to both immunosuppression and multiple organ failure that characterize severe septic patients (6,7). The fine-tuning coordination between the release of proinflammatory mediators and the regulatory anti-inflammatory molecules which is believed to mediate the immunosuppression is a critical factor in determining the magnitude of early injury phase and subsequent risk of complications. While some septic patient die during the early hyperinflammatory stage, high death

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Corresponding to: Ravin Narain, PhD, Associate Professor. Department of Chemical and Materials Engineering, Faculty of Engineering, University of Alberta, 116 st and 85 Ave, Edmonton, AB, T6G 2G6, Canada. Tel: 780 492 1736 or 780 492 6101; 780 492 6715 (lab); Fax: 780 492 2881. Email: narain@ualberta.ca.

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rates have been also reported in patients displaying prolonged immunosuppression (2,3,8).

Rho-kinases (ROCKs) belong to a family of serine/threonine proteins that were first identified as downstream effectors of Rho GTPases signaling. Stimulation of the G-protein-coupled receptors results in activation of RhoA through recruitment and activation of Rho-GEF. Binding of activated RhoA to the Rho-binding domain (RBD) of ROCKs induces conformational changes at the carboxyl terminus and the activation of the kinase domain. ROCKs play central roles in regulating diverse physiological and pathological responses including cellular proliferation, metabolism, migration, and apoptosis through control of the cytoskeleton assembly and cell contraction (9-11). In response to apoptotic signals, cells undergo significant changes including contraction, membrane blebbing, and fragmentation of apoptotic cells into apoptotic bodies. These events have been shown to be driven by ROCK-mediated actin-myosin contraction. It has demonstrated that caspase 3-mediated ROCK1 activation is essential for the formation of membrane blebbing of apoptotic cells through myosin light chain (MLC) phosphorylation and actomyosin contraction. Furthermore, ROCK activation is also required for apoptotic nuclear disintegration and residing of fragmented DNA into blebs and apoptotic bodies. Recently, it has been shown that Rho/ROCK signaling also contributed in the clearance of apoptotic cells through the regulation of actin cytoskeleton (12-15).

Using different targeting approaches, recent evidence has indicated that blockade of intrinsic and extrinsic aspects of apoptosis improves the survival of animal models of sepsis (16,17). Acute lung injury (ALI) is clearly identified as a serious and frequent complication of human sepsis in critically ill ICU patients. According to the Acute Lung Injury Verification of Epidemiology (ALIVE) report, ALI affects approximately 7% of ICU patients, and approximately 54% of these patients develop full-blown acute respiratory distress syndrome (ARDS) ARDS within 24 h. Several mechanisms have been proposed to explain the impaired lung function during sepsis including reactive oxygen/nitrogen species and apoptosis (18,19).

Currently, studies are being performed to study the complex condition of sepsis and to design potential therapies. In this issue of the Journal of Thoracic Disease, Cinel *et al.* add another layer to this picture by providing novel data in relation to the functionality of ROCK in sepsis induced-ALI (20). The authors demonstrate the activation of ROCKs in aCLP model of sepsis and they have found evidence for oxidative and nitrosative stress. This condition was associated with caspase-3 activation, accumulation of positive TUNEL cells, edema and inflammation of lungs along with histopathological features of lung injury. Interestingly, the dependency of lung injury parameters on ROCKs was altered by treatment with Y-27632 (a selective ROCK inhibitor). This findings suggest that these kinases are

involved in the development of sepsis-induced ALI. In addition, this work identifies ROCK as a candidate for therapeutic targeting. ROCK represents an attractive target for the treatment of several pathological conditions including; cancer, kidney failure, asthma, glaucoma, osteoporosis, and insulin resistance. Of considerable interest is the recent experimental and clinical data which validates ROCK inhibitors (Fasudil) for the treatment of cardiovascular diseases (21).

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