Changes in Plasma Gelsolin Concentration During Acute Oxidant Lung Injury in Mice

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Abstract. Oxidant stress may contribute to acute lung injury under some circumstances. The rapid depletion of plasma gelsolin following major trauma in patients who subsequently develop respiratory distress suggests that this actin-scavenging protein might protect against delayed pulmonary complications. The specific aim of these experiments was to explore the temporal and quantitative relationship between gelsolin levels and lung damage. Gelsolin levels were measured in three murine models of oxidant injury: immunotargeting of pulmonary endothelium with an H2O2-generating enzyme; continuous exposure to >95% O2; and single high-dose thoracic radiation. The degree of lung injury was inversely related to gelsolin levels in mice treated with glucose oxidase-conjugated antibodies against platelet endothelial cell adhesion molecule-1 (p < 0.0001). By 60–72 hours of hyperoxic exposure, gelsolin levels had dropped precipitously in all mice who sustained major lung damage (p < 0.0001), establishing a quantitative association between gelsolin concentration and hyperoxic lung injury (r = −0.72; 95% confidence interval: −0.81 to −0.59). Gelsolin levels modestly but progressively fell in irradiated mice over the 3 days following treatment (p = 0.012) despite the development of only microscopic lung damage during this timeframe. These findings are consistent with the hypothesis that gelsolin depletion is involved in the pathogenesis of acute oxidant lung injury.

Key words: Gelsolin—Hyperxia—Lung injury—Actin

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Introduction

The acute respiratory distress syndrome (ARDS) is a common and devastating cause of morbidity and mortality in patients experiencing major trauma, undergoing bone marrow transplantation (BMT), and suffering from sepsis, visceral abscesses, necrotizing pancreatitis, ischemic bowel disease, and profound hypotension from any cause [10, 18, 35, 36]. Although the precipitating conditions have been well described [10, 18, 36], the molecular pathophysiology of ARDS has yet to be unraveled [27, 35]. There are accumulating data to suggest that intracellular contents leaked from dying cells contribute to acute lung injury [9, 11, 14, 17, 19–21, 24, 33]. Circulating actin may be directly toxic to pulmonary endothelium [11] and can obstruct the microcirculation of the lungs [17]. Actin-scavenging proteins appear to counteract the pathophysiological consequences of actin released into the circulation but the capacity of this defense system can be overwhelmed by massive tissue injury [14, 20, 21]. Gelsolin and Gc-globulin (vitamin D-binding protein) function as plasma actin sequestering proteins [19]. After binding actin, the complexes are quickly cleared from the circulation [14, 21], thus protecting the host from further damage.

Reduced plasma gelsolin concentrations have been described in acute lung injury of diverse etiologies [9, 17, 20, 22, 24]. Circulating gelsolin levels are lower in patients with established ARDS than in healthy adults or patients with uncomplicated bacterial pneumonia [20]. In our recent study of 65 patients who had sustained traumatic injuries, 10 of the 13 patients (77%) with gelsolin levels greater than two standard deviations (SD) below the normal mean at the time of admission required prolonged mechanical ventilation, developed ARDS, and/or died during the ensuing hospitalization [24]. Patients who develop idiopathic pneumonitis following BMT have significantly lower plasma gelsolin levels than similar transplant recipients who experience uneventful recoveries [9]. The only experimental model to date correlating gelsolin depletion and acute lung injury involved oleic acid-induced lung injury in rats [33].

Given that gelsolin is a highly conserved constituent of mammalian plasma, we hypothesized that depletion of plasma gelsolin may have a permissive role in the propagation of acute lung injury. Treatment of mice exposed to 95% O2 with recombinant gelsolin modestly diminished the acute inflammatory response and degree of lung injury [5]. In this study, the quantitative and temporal relationships between decreasing plasma gelsolin levels and increasing lung damage were evaluated in three distinct murine models of oxidant lung injury: an artificial model whereby mice are treated systemically with a pro-oxidant enzyme conjugated to antibodies against endothelial cell antigens, and two more physiological and clinically relevant models involving hyperoxic exposure and thoracic irradiation.

Glucose oxidase (GOX) is a relatively stable enzyme that generates H2O2 from glucose and can be attached to antibodies directed against highly expressed endothelial surface antigens, such as platelet endothelial cell adhesion molecule-1 (PECAM) and thrombomodulin (TM) [26]. Intravenously injected GOX-conjugated anti-PECAM antibodies accumulate in the lung, are transported intracel-