

## Commentary

# Endothelin antagonists: new bullets against lung injury?

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### Abstract

Acute lung injury is a syndrome of inflammation and of increased permeability of the blood-gas barrier. Endothelins are thought to exert proinflammatory effects. Kuklin and colleagues show that the endothelin receptor antagonist tezosentan reduces pulmonary edema in endotoxemic sheep, in parallel with a prevention of protein kinase C- $\alpha$  activation. In turn, the level of some cytokines increased after tezosentan treatment. Whether these contrasting effects of endothelin blockade on inflammatory mechanisms have clinical relevance and whether these agents might benefit patients with acute lung injury is unknown.

In the search for new agents to protect the lung from injury, Kuklin and colleagues [1] report that tezosentan, a non-selective endothelin-1 receptor antagonist, reduces pulmonary edema in endotoxemic sheep, in parallel with a prevention of protein kinase C- $\alpha$  activation.

### Mechanisms of acute lung injury

Acute lung injury (ALI) and its more severe form, acute respiratory distress syndrome (ARDS), are syndromes of acute respiratory failure secondary to permeability, non-cardiogenic, pulmonary edema. Common causes are sepsis, pneumonia, aspiration and trauma. ALI/ARDS is a major cause of morbidity, death and cost in intensive care units [2,3]. Alveolar edema accumulates in ALI/ARDS mainly because the permeability of the capillary (endothelium)-alveolar (epithelium) barrier is increased. This mechanism allows edema formation at normal capillary pressures and greatly increases the rate of edema formation at elevated capillary pressures [2,3]. In addition, pressure elevation in the pulmonary circulation and mechanical stresses applied to the lung (during mechanical ventilation, for example) may cause "stress failure" in lung capillaries and alveoli, as evident in the formation of breaks and discontinuities in the endothelial and epithelial membranes of the blood-gas barrier [4].

The American-European consensus conference on ARDS defined ALI/ARDS as a "syndrome of inflammation and increased permeability". Hence, it is now widely accepted that the pathophysiology of ALI/ARDS is driven by an aggressive inflammatory reaction that damages the alveolo-capillary unit [2,3,5,6]. The inflammatory response includes both cellular and humoral components. After rapid recruitment of leukocytes to the inflamed site, there is activation of mediator cascades including the production of cytokines, chemokines, acute phase proteins, free radicals, complement, coagulation pathway components and focal upregulation of adhesion molecule expression units [5,6]. Several cytokines, such as tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin (IL)-1, IL-6 and IL-8, have been found in bronchoalveolar lavage fluid and plasma of patients with ARDS [3,5]. Inflammatory mediators amplify endothelial injury directly or by recruiting inflammatory cells into the vascular, interstitial and alveolar spaces [3,5].

In addition, some mediators may also alter endothelial permeability by disturbing intracellular signaling pathways. TNF- $\alpha$  and  $\alpha$ -thrombin have been shown to activate protein kinase C-mediated mechanisms that participate in the pulmonary endothelial response to agents involved in lung injury [3,7]. Protein kinase C is a ubiquitously expressed family of kinases that have a key role in regulating multiple cellular activities. Activation of specific protein kinase C isoforms, most probably protein kinase C- $\alpha$ , may cause lung endothelial dysfunction through several mechanisms [1,3,7].

### Endothelins and inflammation

Endothelins are a family of 21-amino-acid isopeptides. Initially described as strong vasoconstrictors, endothelins are now believed also to exert potent proinflammatory effects. For example, transgenic mice overexpressing endothelin-1 release increased amounts of TNF- $\alpha$ , interferon- $\gamma$ , IL-1 and

IL-6 [8]. The endothelin system is activated in clinical lung injury and in various types of experimental lung injury [9], and several endothelin receptor antagonists have been reported to exert protective effects in some models of ALI/ARDS [10]. Endothelins may thus play a pathophysiologic role in ALI/ARDS and promote pulmonary edema by increasing the filtration pressure (as postcapillary vasoconstrictors), and also by increasing capillary permeability (as inflammatory mediators). The results of Kuklin and colleagues [1] are in accordance with this hypothesis and provide further insight into an intracellular effect of endothelin receptor antagonists (i.e. prevention of protein kinase C- $\alpha$  activation).

Endothelin receptor antagonists have been made available recently for clinical use in the treatment of pulmonary arterial hypertension [11]. These drugs may therefore offer new and attractive opportunities for the management of patients with ALI/ARDS, especially because, to date, no pharmacologic agent has been convincingly shown to improve the prognosis of these patients [12]. The data of Kuklin and colleagues [1] suggest that endothelin receptor antagonists might benefit patients with ALI/ARDS.

There is, however, the other side of the coin. As expected from the use of a receptor antagonist, the level of the ligand increased; that is, the plasma concentration of endothelin-1 was elevated after tezosentan treatment [1]. As also expected from the proinflammatory properties of endothelin-1 [8], plasma levels of TNF- $\alpha$  and IL-8 increased after tezosentan treatment [1]. The clinical relevance of these observations is unknown, but production of these cytokines might counteract the benefits expected from endothelin blockade. In other experimental models of ALI/ARDS, endothelin receptor antagonists did not decrease intrapulmonary shunt [13], lung lymph flow or the histologically evaluated degree of parenchymal injury [14], despite a reduction in pulmonary vascular resistance.

## Conclusion

The work of Kuklin and colleagues [1] provides important information on the complex effects of endothelin blockers on inflammatory processes. From a clinical point of view, given the prolific nature of the inflammatory cascade causing ALI/ARDS and the angel/devil effects of endothelin receptor antagonists on inflammatory mechanisms, it is unlikely that these single agents could reverse or terminate such a complex process [12].

## Competing interests

The author(s) declare that they have no competing interests.

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