Commentary

Understanding the roles of the transcription factors nuclear factor-κB and hypoxia-inducible factor-1α in lung injury

Katherine Craig[1] and Delbert Dorscheid[2]

[1]Visiting Scientist, Critical Care Medicine, St, Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada
[2]Assistant Professor, Critical Care Medicine, St, Paul's Hospital, University of British Columbia, Vancouver, British Columbia, Canada

Correspondence: Delbert Dorscheid, ddorscheid@mrl.ubc.ca

Published online: 8 October 2002 *Critical Care* 2002, **6**:471-472 (DOI 10.1186/cc1834)
This article is online at http://ccforum.com/content/6/6/471

Abstract

The role of oxidative stress in regulating transcription factors and specific gene responses in critical illness is a new and emerging area. A better understanding of the proinflammatory oxidant stimuli of reactive oxygen species generation and how this generates the clinical phenotype of acute lung injury by regulating gene expression may allow the development of new therapeutic strategies. In his review John Haddad describes the present data and role for transcription factors nuclear factor-κB and hypoxia-inducible factor-1α in acute lung injury.

Keywords hypoxia, hypoxia-inducible factor-1α, lung injury, nuclear factor-κ, oxidative stress

In this and the next issue of *Critical Care*, John Haddad [1,2] presents a comprehensive review on the contributions of transcription factors to lung injury. The topic is large and ever changing, and the complete coverage of nuclear factor-κB (NF-κB) and hypoxia-inducible factor (HIF)-1α is spread over two issues. In critical care approximately 80% of patients with sepsis develop an acute lung injury [3]. The majority of these patients progress to the point at which they require intubation and mechanical ventilation, with an associated high mortality. Recent studies [4] have demonstrated that low tidal volume (6 ml/kg) ventilation strategies dramatically reduce this mortality. However, many other clinical trials of various treatments have failed at either reducing the lung injury or accelerating the healing to the end-point of reduced mortality [5].

In this age of genomics and proteomics we continue to explore the association of gene and environment. With respect to lung injury, we need to identify and understand the mechanisms that predispose patients to the excessive inflammation resulting from an overactive innate immune response that characterizes sepsis and lung injury. These include stimuli, signal transduction (receptors, enzyme cascades, transcription factors), gene(s) response and the measured clinical phenotype. John Haddad [1,2], in his two-part review, identifies many 'clinical stimuli' in cell culture, animal model and patient studies representing an oxidative stress that can generate a response via NF-κB or HIF-1α dependent signalling.

Nuclear factor-κB: response to stimuli

NF-κB was originally described in B lymphocytes [6], but it is now recognized as a member of the Rel family of transcription factors and is a critical response element in many cytokine-dependent events or inflammatory conditions [7]. As a result of this link, NF-κB has become a major target for new therapeutic approaches in such clinical disease states as asthma, cancer, arthritis, and cardiovascular and neurodegenerative conditions. Haddad [1,2] discusses the roles of critical care conditions such as hyperoxia, haemorrhage and resuscitation; the 'stress response' to illness (interleukin-6, interleukin-8, tumour necrosis factor, RANTES [regulated upon activation, normal T cell expressed and secreted]); and mechanical ventilation and ischaemia/reperfusion. In all of these conditions free radical production can activate NF-κB. These dynamic variations in

HIF = hypoxia-inducible factor; NF-κB = nuclear factor-κB; VEGF = vascular endothelial growth factor.

cellular redox or oxidative stress, if in disequilibrium, may regulate gene expression and lead to apoptosis (cell death without inflammation), inflammation and lung injury.

Hypoxia-inducible factor-1α: role in hypoxaemia-initiated lung injury

The master regulatory element of hypoxic conditions and adapting oxidative stresses to gene expression is HIF-1α [8–10]. HIF-1 consists of two subunits. HIF-1α, a DNA-binding protein, has increased stability and binding in hypoxic conditions and is degraded rapidly in normoxia. The accumulation of the α-subunits allows for αβ heterodimer formation and translocation into the nucleus during hypoxia. This process leads to selective upregulation of genes whose products are involved in hypoxia and inflammatory lung injury. These include erythropoietin, vascular endothelial growth factor (VEGF) and glucose transporter [9–11]. Work by Haddad [12,13] has demonstrated that proinflammatory cytokines also activate HIF-1α stability and DNA binding. This effect was most profound in hypoxic conditions and was, in fact, greater than that in hypoxaemia alone. It is felt that HIF-1α, via its action on VEGF expression, is directly related to lung injury by endothelial barrier dysfunction mediated by VEGF and recognized clinically as increased pulmonary vascular permeability. Haddad [1,2] discusses in detail how hypoxia and inflammatory stimuli initiate many signalling cascades via HIF-1α to generate a response phenotype to these oxidative stresses.

Conclusion

Understanding the molecular signalling that couples oxidative stresses via NF-κB or HIF-1α to acute lung injury should generate new therapeutic options. Haddad [1,2] discusses the rationale for the use of tyloxapol to reduce proinflammatory cytokines, N-acetyl cysteine (a glutathione precursor) to reduce neutrophil-associated alveolitis in chronic conditions such as cystic fibrosis, and the use of pyrrolidine dithiocarbamate in transplantation to reduce neutrophil-associated oxidant lung injury. Two new compounds, isohelenin and lisofylline, a phosphodiesterase inhibitor, are described as being able to reduce proinflammatory cytokines and ameliorate oxidant lung injury in animal models. As exciting as this emerging field is, with its predictable contribution to future 'bench to bedside' discussions, a more complete mechanistic understanding and future clinical trials will assist in the realization of improved treatment and reduced mortality from oxidant-mediated lung injury.

Competing interests

None declared.

References

1. Haddad JJ: **Basic science review: Redox and oxygen-sensitive transcription factors in the regulation of oxidant-mediated lung injury: role for nuclear factor-κB.** *Crit Care* 2002, **6**:481-490.
2. Haddad JJ: **Basic science review: Redox and oxygen-sensitive transcription factors in the regulation of oxidant-mediated lung injury: role for hypoxia-inducible factor-1α.** *Crit Care* 2003, **7**:in press.
3. Fein AM, Calalang-Colucci MG. **Acute lung injury and acute respiratory distress syndrome in sepsis and septic shock.** *Crit Care Clin* 2000, **2**:289-317.
4. The Acute Respiratory Distress Syndrome Network. **Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome.** *N Engl J Med* 2000, **342**:1301-1308.
5. Conner BD, Bernard GR. **Acute respiratory distress syndrome. Potential pharmacologic interventions.** *Clin Chest Med* 2000, **3**:563-587.
6. Pugin J, Dunn I, Jolliet P, Tassaux D, Magnenat JL, Nicod LP, Chevrolet JC: **Activation of human macrophages by mechanical ventilation *in vitro*.** *Am J Physiol* 1998, **275**:L1040-L1050.
7. Leeper-Woodford SK, Detmer K: **Acute hypoxia increases alveolar macrophage tumor necrosis factor activity and alters NF-κB expression.** *Am J Physiol* 1999, **276**:L909-L916.
8. Wond HR, Ryan M, Wispe JR: **Stress response decreases NF-κB nuclear translocation and increases IκB-α expression in A549 cells.** *J Clin Invest*, **99**:2423-2428.
9. Lentsch AB, Shanley TP, Sarma V, Ward PA: ***In vitro* suppression of NF-κB and preservation of IκB-α by interleukin-13.** *J Clin Invest* 1997, **100**:2443-2448.
10. Lentsch AB, Czermak BJ, Bless NM, Ward PA: **NF-κB activation during IgG immune complex-induced lung injury: requirements for TNF-α and IL-1β but not complement.** *Am J Pathol* 1998, **152**:1327-1336.
11. Lentsch AB, Czermak BJ, Jordan JA, Ward PA: **Regulation of acute lung inflammatory injury by endogenous IL-13.** *J Immunol* 1999, **162**:1071-1076.
12. Haddad JJ, Land SC: **A non-hypoxic, ROS-sensitive pathway mediates TNF-alpha-dependent regulation of HIF-1alpha.** *FEBS Lett* 2001, **505**:269-274.
13. Haddad JJ: **Recombinant human interleukin (IL)-1beta-mediated regulation of hypoxia-inducible factor-1alpha (HIF-1alpha) stabilization, nuclear translocation and activation requires an antioxidant/reactive oxygen species (ROS)-sensitive mechanism.** *Eur Cytochine Netw* 2002, in press.