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...
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 tyl oxaprol 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.

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