Hypoxia-inducible factor 1: A biomarker for Acute Respiratory Distress Syndrome?

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Multiple trauma, hemorrhagic shock, and sepsis are most common causes of the acute respiratory distress syndrome (ARDS). ARDS is characterized by severe acute hypoxemia, pulmonary edema resulting from an increased pulmonary capillary permeability, decreased lung compliance, and an increased pulmonary vascular resistance[1,2]. This syndrome is associated with a high mortality rate between 20 and 50%[3]. However, the cellular and molecular bases of ARDS in the setting of trauma hemorrhagic shock (T/HS) are still poorly defined. HS induces excessive production of inflammatory cytokines, which leads systemic inflammation (SIRS), sepsis, and multi-system organ failure[4]. TNF-α plays an important role in the development of SIRS[5]. Pro-inflammatory mediators like TNF-α and IL-1β induces HIF-1α (Hypoxia-inducible Factor-1 alpha) expression in cells[6]. HIF-1 plays a central role in the regulation of myeloid cell-mediated inflammation and infection[7].

HIF-1, a transcription factor, participates in angiogenesis, iron metabolism, glucose metabolism, and cell proliferation/survival. Overexpression of HIF-1 associated with various cancers and diseases[8]. HIF-1, a transcription factor, is a critical mediator in acute lung injury (ALI)[3]. Suter et al. 1992, suggested that elevated level of TNF-α is associated with the development of ARDS in multiple trauma patients[3]. Feinman et al. 2010, reported that HIF-1α is the key regulator of cellular and developmental processes in response to hypoxia[6]. HIF-1α activation was found to be essential for the development and prevention of gut injury. HIF-1α deficiency improved T/HS-induced increase in intestinal permeability, bacterial translocation, and caspase-3 activation[6]. After T/HS, in the ileal mucosa, partial absence of HIF-1α reduced the levels of cyclooxygenase-2, inducible nitric oxide synthase, TNF-α, and IL-1β[6].

HIF-1 is composed of two subunits: HIF-1α and HIF-1β. HIF-1α is synthesized continuously and is destroyed under conditions of normoxia as a result of its ubiquitous degradation by the proteasomes after hydroxylation. HIF-1β is constitutively expressed and unaffected by hypoxia[2]. Regulation of HIF-1 activity is primarily governed by the abundance of the HIF-1α subunit in cells. In hypoxic conditions, HIF-1α is stabilized and is translocated into the nucleus where it dimerizes with HIF-1β[2]. This dimerization transactivates downstream target genes containing HRE (hypoxia-response elements) within their upstream sequences (promoter or enhancer elements). HIF-1 regulates over 70 genes in response to hypoxia in all cells[2].

A previous study reported that HIF-1α act as an adaptive and survival factor for cells undergoing stress or cells exposed to hypoxia, such as that caused by ischemic injury. However, under some conditions, HIF-1α may be associated with apoptotic and inflammatory processes[2]. Even after remaining for two years in ICU, the survivors of ARDS have a lower health-related quality of life and lower functional ability after hospital discharge. The treatment and rehabilitation of ARDS are of great cost, and hence, it remains a disease process of the utmost importance[9]. As HIF-1α is a proven biomarker in septic shock (unpublished data from clinical trials at University of Florida). Thus, HIF-1 may be used as an early predictor of ARDS in the survivors of post-resuscitation trauma haemorrhagic shock. The author feels that this subject needs to be attended.

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References

1. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, et. Incidence and outcomes of acute lung injury. *N Engl J Med.* 2005;353(16):1685-93.
2. Jiang H1, Huang Y, Xu H, Hu R, Li QF. Inhibition of hypoxia inducible factor-1α ameliorates lung injury induced by trauma and hemorrhagic shock in rats. *Acta Pharmacol Sin*. 2012;33(5):635-43
3. Suter PM, Suter S, Girardin E, Roux-Lombard P, Grau GE, Dayer JM. High bronchoalveolar levels of tumor necrosis factor and its inhibitors, interleukin-1, interferon, and elastase, in patients with adult respiratory distress syndrome after trauma, shock, or sepsis. *Am Rev Respir Dis*. 1992;145(5):1016-22.
4. Kumar M, Rao DN, Mohanty S, Selvi A , Bhoi S. Interleukin (IL)-8 is an early predictor of mortality following trauma hemorrhagic shock. *Int. J. Adv. Res. Biol.Sci*. 2015;2(7):12–20.
5. Jaffer U, Wade RG, Gourlay T. Cytokines in the systemic inflammatory response syndrome: a review. *HSR Proc Intensive Care Cardiovasc Anesth*. 2010;2(3):161–175.
6. Feinman R, Deitch EA, Watkins AC, Abungu B, Colorado I, Kannan KB et al. HIF-1 mediates pathogenic inflammatory responses to intestinal ischemia-reperfusion injury. *Am J Physiol Gastrointest Liver Physiol.* 2010;299(4):G833-43.
7. Walmsley SR, Chilvers ER, Whyte MK. Hypoxia. Hypoxia, hypoxia inducible factor and myeloid cell function. *Arthritis Res Ther*. 2009;11(2):219.
8. Ke Q, Costa M. Hypoxia-inducible factor-1 (HIF-1*). Mol Pharmacol*. 2006;70(5):1469-80.
9. Bakowitz M, Bruns B, McCunn M. Acute lung injury and the acute respiratory distress syndrome in the injured patient. *Scand J Trauma Resusc Emerg Med*. 2012;20:54.