J Anesth (2007) 21:122–123
DOI 10.1007/s00540-006-0475-9

Journal of Anesthesia

Three-step research strategies for ARDS: new target molecules—ACE2, HMGB1, and HSP47

Hideo Iwasaka

Oita University, Faculty of Medicine, Department of Brain and Nerve Science, Anesthesiology and Intensive Care Unit, 1-1 Idaigaoka, Hasama-machi, Oita 879-5593, Japan

H. Iwasaka

The acute respiratory distress syndrome (ARDS) is a common, devastating clinical syndrome of acute lung injury that affects both medical and surgical patients. This syndrome is often progressive, and is characterized by distinct stages with different clinical, histopathological, and radiographic manifestations. I consider that these stages consist of three different phases, an acute and exudative phase, an exacerbatory inflammatory phase, and the last phase, fibrosing alveolitis. An improved understanding of the pathogenesis of ARDS has led to the assessment of several novel treatment strategies. Therefore, I believe that we have to investigate the strategies that hasten the resolution of ARDS according to the three different phases.

Address correspondence to: H. Iwasaka
Received: October 19, 2006

First-step strategy, targeting angiotensin-converting enzyme (ACE2) in the acute phase

Angiotensin-converting enzyme 2 (ACE2), which has recently been identified as a negative regulator of the renin-angiotensin (RA) system and as a potential receptor for severe acute respiratory syndrome (SARS) virus, is expressed in lungs [1]. ACE2 negatively regulates the RA system by inactivating angiotensin II. The activated RA system promotes the pathogenesis of lung edemas and impairs lung function in the acute phase of ARDS. I tried using an angiotensin II receptor type 1 (AT1) antagonist for the purpose of inactivating the RA system in an endotoxin-treated rat model. The AT1 antagonist improved the histological lung edema and protected against the downregulation of ACE2 in lung tissue.

Second-step strategy, targeting the high mobility group box 1 (HMGB1) molecule in the exacerbatory phase

High mobility group box 1 (HMGB1), in addition to its role as a transcriptional regulatory factor, has recently been identified as a late mediator of endotoxin lethality [2]. HMGB1 has been demonstrated to be a long-searched-for nuclear danger signal that is passively released by necrotic, as opposed to apoptotic, cells that will induce inflammation. Lipopolysaccharide (LPS)-induced acute lung injury was almost completely resolved by treatment with two antibodies [that for HMGB1 and its receptor, receptor for advanced glycation endproducts (RAGE)] and the use of a newly developed extracorporeal column, an "HMGB1 absorber". These results demonstrate that the specific inhibition and absorption of endogenous HMGB1 therapeutically reverses the lethality of established sepsis-induced lung injury, indicating that HMGB1 inhibitors and this absorber could be used in a clinically relevant therapeutic

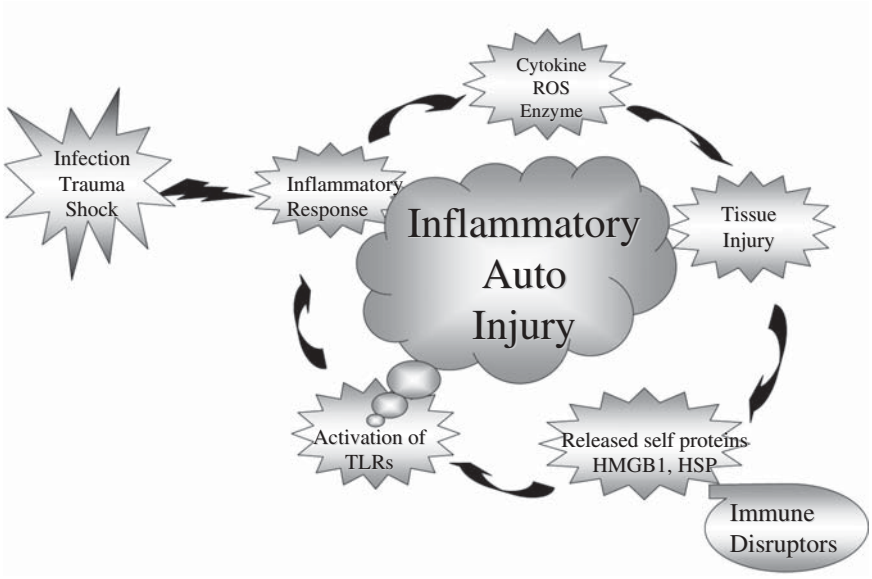

Fig. 1. The concept of inflammatory autoinjury is shown as a pernicious inflammatory cycle. After the onset of inflammation, injured tissue releases endogenous intracellular proteins, such as HMGB1 and several HSPs, which work as immune disruptors. These proteins interact with toll-like receptors, which activate the inflammatory response. *ROS*, radical oxygen species; *HMGB1*, high mobility group box 1; *HSP*, soluble heat shock protein; *TLRs*, toll-like receptors

window that is significantly wider than that for other known cytokines.

Third-step strategy, targeting heat shock protein (HSP)47 in the fibrosing phase

Heat shock protein (HSP)47 is a procollagen/collagen specific molecular chaperone protein and essential for the early stages of collagen biosynthesis [3]. The formation of collagenous fibrous tissue is a vital part of the process of fibrosing alveolitis. The expression of HSP47 has been reported to increase in parallel with the expression of collagens during the progression of various fibrosis models. We attempted to attenuate pulmonary collagen accumulation by inhibiting the overexpression of HSP47 with antisense oligonucleotides in an experimental pulmonary fibrosis model induced with bleomycin. The administration of HSP47 antisense oligonucleotides markedly suppressed the increased production of collagens and attenuated the histologic manifestations of the disease.

Like any form of inflammation, acute lung injury and ARDS represent a complex process in which multiple pathways can propagate or inhibit the lung injury. The most common risk factor for ARDS was reported to be severe sepsis with a suspected pulmonary source, followed by severe sepsis with a suspected nonpulmonary source. Inflammation itself can migrate to various organs as do spreading cancer cells. Therefore, improving our understanding of the pathogenesis of ARDS and devising new strategies for treating ARDS in the exacerbatory phase are important, because almost all ARDS patients are admitted to intensive care units during this period. In this period, inflammation can be exacerbated not only by infective organisms but also by endogenous proteins released from injured tissues. We call this the pernicious inflammatory cycle of inflammatory autoinjury (see Fig. 1).

The above three-step research strategies used from the onset of lung injury to the end-stage of ARDS have led to the assessment of novel clinical treatment strategies.

References

1. Imai Y, Kubo K, Rao S, Huan Yi, Guo F, Guan B, Yang P, Sarao R, Wada T, Leong-Poi H, Crackower MA, Fukamizu A, Hui CC, Hein L, Uhlig S, Slutsky AS, Jiang C, Penninger JM (2005) Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 436:112–116
2. Wang H, Bloom O, Zhang M, Vishnubhakat JM, Ombrellino M, Che J, Frazier A, Yang H, Ivanova S, Borovikova L, Manogue KR, Faist E, Abraham E, Andersson J, Andersson U, Molina PE, Abumrad NN, Sama A, Tracey KJ (1999) HMG-1 as a late mediator of endotoxin lethality in mice. Science 285:248–251
3. Nagata K, Saga S, Yamada KM (1988) Characterization of a novel transformation-sensitive heat-shock protein (HSP47) that binds to collagen. Biochem Biophys Res Commun 153:428–434