

Cell death, a potential therapeutic target in acute lung injury and acute respiratory distress syndrome?

Editorial

Acute lung injury and acute respiratory distress syndrome (ALI/ARDS) are the severe pulmonary illnesses. These illnesses severally impact on public health in the United States, the morbidity and mortality of the illnesses remains high in 30-40%. In 1967, a progressive respiratory failure with high short-term mortality was described as a “respiratory distress syndrome”. This subset of patient’s features with severe pulmonary dysfunction typically showed non-cardiogenic pulmonary edema, severe hypoxemia, and difficulty breathing. Since then, through several decades’ endeavor of the basic and clinical pulmonary investigators, remarkable progress has been made in defining the illness, in elucidating the pathogenesis, in establishing diagnostic criteria, and in developing therapeutic approaches.

The etiology of the ALI/ARDS involves in a vast range of diseases including infectious and non-infectious diseases. Viral infection, bacterial pneumonia, and sepsis are the major infectious causes. More than 70% of the ALI/ARDS cases are reported to be the patients with infectious pulmonary diseases. Most of the bacterial strain isolated from those patients is multi-drug resistant. Opportunistic bacterial *Pseudomonas aeruginosa* is responsible for 30% of death in nosocomial infectious patients. Interestingly, the etiologic non-infectious causes of ALI/ARDS comprise trauma, aspiration, pancreatitis, and other non-infectious diseases.

Given the fact of the diverse etiologic causes and most of the infectious pathogens are multi-drug resistant, no effective cure has been developed. As a supportive therapeutic approach, small amount ventilation has been developed and implemented to relief the symptoms such as hypoxemia in ALI/ARDS patients. However, the effectiveness of the approach in overall is limited that only partly reduces the mortality of ALI/ARDS patients. Therefore, exploration of other non-antibiotic therapeutic approaches is a practical need.

The pathology of ALI/ARDS in the rapidly progressive stage is characterized as alveolar barrier damage and dysfunction that clinically results in hypoxia. Clinical and experimental studies have identified substantial inflammatory cell infiltration, cytokine secretion, increased permeability pulmonary edema, and alveolar epithelial cell death in human ALI/ARDS lung samples. These pathological changes are similar to that of bacterial pneumonia, perhaps in a more severe content. Notably, epidemiologic studies revealed that only 10% of the pneumonia patients develop into ARDS, suggesting an existence of a critic turning point in the development of the illness. After achieving the turning point, structural damage of the lung tissue should be pathologically irreversible that accelerates the illness progressing into ARDS. Clinical studies have reported substantial alveolar epithelial cell death in ALI/ARDS patient lungs. The cell death is characterized as a mixture of necrosis and apoptosis. In consistent with these observations, molecular biological studies demonstrated an increased level of cell death markers such as activated caspases accompanied

Volume 3 Issue 2 - 2016

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Received: March 10, 2016 | **Published:** March 24, 2016

by a reduced level of survival signals. Substantial alveolar epithelial cell death may be the critical turning point in the pathogenesis of ALI/ARDS.

Therefore, it is reasonable to develop molecular approaches against alveolar epithelial cell death that may contribute to the cure of the illness. Cell death is a major player in the pathogenesis of many diseases. Long-term attempts have been made to develop pharmaceutical approaches against cell death. Several small molecules have shown anti-cell death effects. Such cell death inhibitors include “DEVD”, a tetra-peptide selectively inhibits apoptotic executive Caspase-3 enzymatic activity. DEVD inhibits apoptosis effectively in cell models. Unexpectedly, Caspase-3 peptide inhibitor showed marginal effects in animal models, suggesting that the strategy of targeting cell death at cell death executive level is actually less effective or practically infeasible. Therefore, new strategies need to be tested in fighting against cell death. From the view of molecular biology, irreversible enzymatic cascade results in cell death. In apoptosis, the culminated death signal has been enlarged through the enzymatic reactions. Conceivably, more and more substrate is stepwise needed downstream the signal transduction. The availability of these cell death executives is under stringent control in healthy living cells. As a major way to increase their availability, prompt gene expression of cell death executives should be critical in this process. Thus, an alternative strategy is to develop pharmaceutical approaches to target cell death at gene transcription level.

Such attempt has been thrown in reality. In such, a recent publication reported to control the cell death at epigenetic level in pneumonia animal models. Epigenetics modulates chromatin structure that controls DNA accessibility. One such readout is activation or repression of gene transcription. Mounting evidence show that epigenetic markers such as histone modification enzymes involve in cell death. For example, knockdown of histone acetylation enzyme p300 in living cells results in cell death. Imaginably, other histone modification enzymes may also contribute to the cell death and survival. As a matter of fact, many epigenetic markers are deregulated

in the protein level in ALI/ARDS lung tissues. Morf411, a component of Sin3A deacetyltransferase complex, is among the deregulated molecules in human pneumonia lung tissues. Small molecule targeting Morf411 shows protective effects in pneumonia animal models. There is a long way from bench top to bedside. However, these attempts may shed lights on non-antibiotic approaches against ALI/ARDS.

This work was supported partly by a National Institutes of Health R01 grant HL125345 and an American Heart Association Award 12SDG12040330 to CZ.

Acknowledgements

None.

Conflict of interest

The author declares no conflict of interest.