Lung (2019) 197:827–828
https://doi.org/10.1007/s00408-019-00279-4

LETTER TO THE EDITOR

Unfolded Protein Response in Acute Respiratory Distress Syndrome

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Received: 26 September 2019 / Accepted: 30 September 2019 / Published online: 11 October 2019

The endothelial layer of the lung microvasculature regulates the traffic of blood fluid, electrolytes, and proteins crosswise the vascular wall. Inflammatory stimuli partner with multifarious messengers to reform the junction and adhesion proteins of the cytoskeleton, which in turn causes endothelial anomalies. Endothelial barrier dysfunction (EBD) due to lung injury increases the permeability across the endothelial and epithelial barriers of the lung and produces an influx of protein-rich edema fluid, endothelial hyperpermeability, and pulmonary dysfunction. ARDS represents the manifestation of severe EBD complications in hospitalized individuals. It is associated with non-hydrostatic pulmonary edema and respiratory abnormalities, often associated with lethal outcomes. Indeed, the unacceptable high mortality rates of ARDS suggest that the exploration of new therapeutic avenues towards this syndrome is an urgent need. The discovery of the molecular components that regulate vascular permeability and the development of agents that enhance the endothelial integrity may lead to new therapies against ARDS [1].

Cells monitor the amount of misfolded protein in the endoplasmic reticulum (ER). The accumulation of those proteins above a critical threshold activates the unfolded protein response (UPR), which attempts to eliminate the undesirable misfolded proteins. This signal transduction pathway is initiated by the inositol-requiring enzyme 1α (IRE1a), the pancreatic endoplasmic reticulum kinase (PERK), and the activating transcription factor 6 (ATF6). If those responses fail to restore the functional protein-folding homeostasis, UPR will promote cellular execution. The severe and persistent UPR activation in the endothelium results in ER stress and major cardiovascular dysfunctions. However, recent studies support that UPR exerts the potential to fight lung inflammation [2].

Hsp90 is a molecular chaperone which stabilizes multifarious client proteins in charge of cellular responses to a plethora of stimuli. The inhibition of this protein affects the conformation of the Hsp90-clients complexes, and deteriorates the function of the corresponding proteins. Since the activated Hsp90 accelerates the maturation of inflammatory mediators, it promotes the establishment of disease states. Hsp90 inhibitors are being developed to enter clinical trials, and have been reported to induce UPR. In bovine pulmonary arterial endothelial cells, UPR regulates P53 expression in a positive manner [2].

P53 induction counteracts the LPS-triggered endothelial hyperpermeability, and regulates the release of inflammatory cytokines in mice with tissue-specific P53 deletion. In contrast, lack of P53 in mice exposed to LPS exerted a protective role against lung tissue destruction restricted to bronchiolar exocrine cells. Recent endeavors to expose new therapeutic avenues towards ARDS revealed that Hsp90 inhibitors recruit P53 to oppose the LPS-induced EBD by modulating the Rac1/RhoA pathways. Thus, P53 and Hsp90 inhibitors partner to support endothelium integrity. Both elements have been previously shown to induce UPR [2].

In this study, we propose an alternatively theurapeutical strategy towards ARDS, based on a highly selective and targeted UPR manipulation. However, we shall always take into account that both "keepers" (P53, UPR) may be transformed to phenomenal killers in case that are not stochastically targeted (Fig. 1). Thus, future endeavors shall focus on delineating the mechanisms transducing the protective actions of UPR in the lung vasculature. Moreover, the efficacy of promising anti-inflammatory compounds such as growth hormone releasing hormone (GHRH) antagonists shall be tested towards those protective effects [3].

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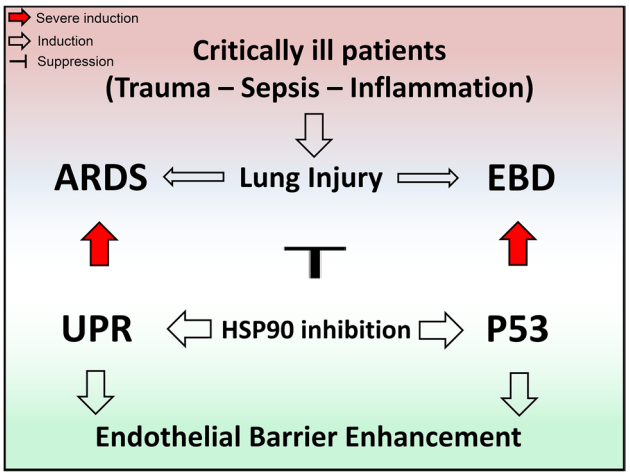

Fig. 1 Graphical abstract of the interrelations among Hsp90, and P53 and UPR in the pathophysiology of the lung. Endothelial barrier dysfunction (EBD) due to direct and indirect lung injury is the hallmark of the acute respiratory distress syndrome (ARDS). Heat shock protein 90 (Hsp90) inhibition induces P53 and triggers the unfolded protein response (UPR) induction, supporting the endothelial barrier integrity. However, a severe induction of UPR or P53 may cause EBD-induced ARDS due to cellular death. The exact interrelations between P53, UPR, and Hsp90 in the human pulmonary microvasculature are under investigation

Funding Dr. Barabutis' is supported by the R&D, Research Competitiveness Subprogram (RCS) of the Louisiana Board of Regents through the Board of Regents Support Fund (LEQSF(2019-22)-RD-A-26), as well as by the NIGMS/NIH (5 P20GM103424-15, 3 P20GM103424-15S1).

Compliance with Ethical Standards

Conflict of interest All authors declare that have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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