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Unfolded Protein Response: A Regulator of the Endothelial Barrier

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Abstract

Recent evidence suggest that the endothelial barrier function is enhanced by the mild activation of the unfolded protein response (UPR), which aims to suppress abnormal increases of endoplasmic reticulum stress. Heat shock protein 90 inhibitors and growth hormone releasing hormone antagonists exert the capacity to activate this multifaceted cellular mechanism (UPR). Thus, investigations on the signalling network involved in those events, may deliver exciting opportunities in diseases related to endothelial barrier dysfunction. The diverse spectrum of those pathologies include sepsis and Acute Respiratory Distress Syndrome (ARDS).

Keywords

Inflammation; Acute Lung Injury; Acute Respiratory Distress Syndrome; Sepsis; P53

Acute Respiratory Distress Syndrome as well as sepsis are considered to be both a cause and consequence of endothelial barrier dysfunction [1]. The current pandemic (COVID-19) fueled Herculean efforts of the medical and research community to introduce and apply novel therapeutic interventions in the affected population. Our group in interested on delineating the molecular mechanisms involved in lung endothelial responses against inflammatory agents. Those agents include toxins of both gram-positive (lipoteichoic acid) [2] and gram-negative (lipopolysaccharides) bacteria [3].

Our in vivo and in vitro observations suggest that P53 protects against the lipopolysaccharides (LPS)-triggered endothelial hyperpermeability [4]. Super P53 mice which globally overexpress this endothelial defender (P53) [5] were more resilient to LPS than the wild-type counteracts [6]. The opposite effects were observed in P53 null mice,

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which presented aggregated LPS-induced inflammatory responses, as compared to their wild-type littermates [7]. P53 is induced by Growth Hormone Releasing Hormone (GHRH) antagonists in a diverse variety of tissues, while GHRH exerts the opposite effects. Thus, it reduces P53 [8]. The primary production site of GHRH is the hypothalamus. GHRH stimulate the synthesis of growth hormone from the anterior pituitary gland. However, this hypothalamic hormone (GHRH) and its receptors have been strongly involved in other processes, including tumorigenesis [8].

P53 is targeted by the unfolded protein response (UPR), which aims to suppress robust increases of endoplasmic reticulum stress [9]. In bovine pulmonary artery endothelial cells (BPAEC), activation of UPR due to brefeldin, dithiothreitol, or thapsigargin resulted in increased P53 expression. However, pharmacologic UPR suppression (N-acetyl cysteine, Kifunensine, and ATP-competitive IRE1α kinase-inhibiting RNase attenuator) reduced P53. Hence, we decided to investigate the effects of heat shock protein (Hsp) 90 inhibitors and growth hormone releasing hormone (GHRH) antagonists)) in UPR [10], as well as the effects of UPR modulation in the endothelial permeability.

In BPAEC and human lung pulmonary endothelial cells the Hsp90 inhibitors Tanespimycin (17-AAG), Luminespib (AUY-922) and 17-DMAG induced UPR, as reflected in the activation of the corresponding UPR branches. Those are the protein kinase RNA-like ER kinase (PERK), activating transcription factor 6 (ATF6), and the inositol-requiring enzyme-1α (IRE1α). Those compounds suppress the activated Hsp90, thus inhibit the progression of robust inflammatory cascades, mediated by the Hsp90 client proteins [11]. Similar results were obtained in vivo [12, 13], as well as after treatment of endothelial cells with GHRH antagonists [14]. Those peptides have already been associated with the suppression of the reactive oxygen species [15], exert anti-inflammatory effects in the lungs [16, 17]; and oppose the LPS-induced vascular dysfunction [18].

To assess the effects of UPR suppression in endothelial permeability, we measured the transendothelial resistance of endothelial monolayers after exposure to the UPR suppressor Kifunensine, a mannosidases inhibitor. That compound triggered hyperpermeability responses in a time-dependent manner, which involved the modulation of key cytoskeletal components [19]. Those Kifunensine-induced effects were counteracted by both AUY-922 [20] and GHRH antagonists [14], initially developed to fight cancers [8].

To the best of our knowledge, the effects of UPR in the lung barrier regulation are largely unknown. Our recent works have attempted to elucidate certain aspects of those interrelations. The delineation of the pathways involved in the UPR-mediated endothelial regulation may lead to new therapeutic avenues towards sepsis, ARDS, as well as the ARDS related to COVID-19.

GHRH antagonists and Hsp90 inhibitors enhance the tissue barrier function and induce UPR, suggesting their potential to counteract endothelial hyper-permeability responses. Further studies on characterizing the exact interrelations between UPR, GHRH and Hsp90 would be of great benefit in the fight against endothelial dysfunction. The generation of

endothelial specific mutants which do not express ATF6, PERK or IRE1α would deliver novel information in that regard. This is the goal of our future efforts.

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Highlights

- GHRH antagonists induce UPR
- Hsp90 inhibitors induce UPR
- UPR enhances endothelial barrier function
- Discovering the exact interrelations of GHRH and Hsp90 in the UPR context may deliver new therapies against ARDS and sepsis.