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Unfolded protein response in the COVID-19 context

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ABSTRACT

The unfolded protein response (UPR) maintains cellular homeostasis by regulating key elements of cellular growth and defense. Recent evidence suggests that this mechanism affects the vascular barrier function, by modulating lung endothelial permeability. Dysregulation of this barrier contributes in the irreversible outcomes of the SARS-CoV-2 - inflicted acute respiratory distress syndrome (ARDS). Thus, it is highly probable that the targeted activation of those UPR components in charge of repairing the destructed lung endothelium of the COVID-19 patients, may deliver a promising therapeutic possibility for those subjected to the devastating outcomes of the ongoing pandemic.

COVID-19

The current pandemic destructs social interactions, deteriorates the fabric of our society, and spreads insecurity in the population. The available medical countermeasures do not suffice to save those in urgent need, and the development of novel therapeutic approaches to oppose the SARS-CoV-2 is of the highest priority, especially to the elderly. Lung endothelial barrier dysfunction contributes to the lethal outcomes of the COVID-19 - related ARDS [1]. The rapid restoration of the endothelium structure will most probably assist in recovering the normal respiratory functions of the hospitalized patients, and will oppose the lung endothelium hyper-permeability due to the SARS-CoV-2 - induced cytokine storm. Hence, it will either prevent or restore the abnormal accumulation of the protein-rich edema within the interstitium and alveolus [2].

Unfolded protein response (UPR)

Our research is focused on delineating the molecular cascades regulating the structure and function of the lung microvasculature. Identifying the molecular targets able to dynamically capacitate the repair of the severely inflamed endothelium, will reveal new approaches towards the development of efficient therapies against the SARS-CoV-2 - inflicted ARDS. We focus on the properties of the UPR, which has been previously associated with tissue maintenance and recovery [3].

This highly conserved molecular machinery acts upon increases of endoplasmic reticulum stress, to orchestrate meticulous responses to cellular threats. It is consisted of the activating transcription factor 6 (ATF6), the protein kinase RNA-like endoplasmic reticulum kinase (PERK); and the inositol-requiring enzyme-1α (IRE1α) [4]. A mild activation of the UPR components, is capable of propelling tissue repairing processes [5]. When such protective processes are not feasible due to extensive or irreversible damage, alternate pathways may dictate the cellular elimination [5]. Thus, UPR may serve as a potential target for pharmacological intervention in those undergoing respiratory dysfunctions during the late stages of COVID-19.

In support of our hypothesis, we have recently revealed that the UPR suppressor Kifunensine compromises the function of the lung microvasculature. Bovine pulmonary artery endothelial cells treated with this mannosidase inhibitor exerted hyper-permeability responses [6]. Heat shock protein 90 (Hsp90) inhibitors are UPR inducers [7,8]. It was recently reported that Luminespib (AUY-922), an advanced Hsp90 inhibitor, counteracts the Kifunensine-Induced lung endothelial barrier dysfunction [9]. Those observations provide first evidence that UPR modulation serves as a crucial regulator of vascular function [9]. AUY-922 has been associated with P53 induction, both in vivo and in vitro [10].

UPR and P53

P53 is a tumor suppressor protein and a powerful mediator of several anti-inflammatory drugs, including the growth hormone releasing hormone antagonists [11,12] and Hsp90 inhibitors [13,14]. UPR crosstalks with P53. UPR induction by brefeldin A, dithiothreitol, and thapsigargin induced P53. On the other hand, the UPR suppressors N-acetyl cysteine, Kifunensine, and ATP-competitive IRE1α kinase-inhibiting RNase attenuator reduced its expression levels [15]. P53 has been associated with strong anti-inflammatory responses in several human tissues, including the lungs [16]. Those properties are partially due to anti-oxidant properties of that tumor suppressor [17].

P53 also participates in the regulation of the actin cytoskeleton, by affecting the Rho family of kinases [18]. It endorses cofilin deactivation, by mediating the Rac 1 – triggered formation of cortical actin. On

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the other hand, P53 suppresses the RhoA – mediated formation of the F actin stress fibers (increased permeability) by inducing P190RhoGAP [19]. In vivo, P53 null mice exerted stronger LPS-induced inflammatory responses in the lungs compared to the wild type counteracts, as reflected in the expression of major inflammatory mediators (e.g. IL-1α, IL-1β) [20].

Conclusion

A highly targeted pharmacologic intervention inwards the intrinsic capacity of our endothelium to self-repair, will most probably oppose the devastating outcomes of COVID-19. UPR manipulation serves that purpose, since recent evidence suggest that it is a powerful endothelial regulator, able to repair the pulmonary vascular barrier [9]. Such measures might be used in a prophylactic manner to the medical personnel and employees routinely exposed to SARS-CoV-2. Future studies on genetically modified mice which do not express or overexpress PERK, ATF6 or IRE1α will delineate the exact UPR components involved in those tissue repairing processes, as well as the extent of the P53 involvement in the corresponding events.

Declaration of Competing Interest

None declared.

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