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Unfolded Protein Response Supports Endothelial Barrier Function

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Abstract

Ongoing efforts are oriented towards the development of novel therapeutic agents to repress lung hyper permeability responses due to inflammation. The endothelial barrier dysfunction due to such events, may eventually lead to severe cardiovascular complications, such as the Acute Respiratory Distress Syndrome. Hsp90 inhibitors are anticancer compounds, associated with strong anti-inflammatory responses in the endothelium. Our latest observations in experimental models of Acute Lung Injury suggest that P53 orchestrates, at least in part, such responses. Remarkably, both Hsp90 inhibition and P53 induction are associated with the activation of the Unfolded Protein Response element. The purpose of the current manuscript, is to introduce the hypotheses that UPR induction protects the vasculature against inflammation.

1. ARDS

1.1 Lung Endothelial Dysfunction: The Cause And Consequence of ARDS

Described over 50 years ago, Acute Respiratory Distress Syndrome (ARDS) remains the major manifestation of the “corrupted” lung homeostasis, destined to cause non-hydrostatic pulmonary edema, respiratory abnormalities and death[1]. ARDS appears in 10 to 86 patients per 100,000 cases. The majority of incidents have been reported in Australia and the United States[2]. The development of that syndrome is due to direct (pneumonia and gastric aspiration); or indirect (sepsis and pancreatitis) lung injury, which in turn results to inflammation and hypoxemia[3]. Indeed, endothelial barrier dysfunction (EBD) manifests ARDS. The disruption of the alveolar-capillary membrane results to lung dysfunction and hyperpermeability responses, which in turn affect the respiratory function [4].

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1.2 Endothelial Hyperpermeability: The Hallmark of Severe Inflammation in the Pulmonary Microvasculature

The endothelium forms a unique barrier between the vascular lumen and the vascular wall[5]. This barrier is a highly metabolic and dynamic unit, essential for the efficient function of the lungs[4]. It is strongly influenced by changes of the cellular redox status due to abnormal increases of reactive oxygen and nitrogen species, malignancies, as well as by diabetic microvascular and macrovascular complications[6]. All those events alter the architecture of junction and adhesion proteins. Irrespective of its diverse etiologies, ARDS leads to increased permeability of the alveolar-capillary barrier, which in turn induce respiratory failure [7]. Since ARDS is associated with thousands of incidents in the USA[8], new pharmacological agents that counteract its severe and lethal outcomes are needed.

1.3 Current Approaches Against ARDS

The therapy for ARDS is focused on preventing lung injury. To maintain viable gas exchange, the mechanical ventilation becomes progressively riskier going from mild to severe (ARDS). Tidal volume, driving pressure, flow, and respiratory rate have been identified as causes of ventilation-induced lung injury[9]. Thus, the patients are given medications to prevent and treat infections, relieve pain and discomfort, prevent blood clots in the legs and lungs, minimize gastric reflux, and sedate [10]. It is clear that the elucidation of the mechanisms that govern vascular barrier function, will propel the development of more efficient and targeted thepapies to support those in need. It is our great hope that the development of novel agents which protect the endothelium against inflammatory insults, will prevent deaths due to ARDS [11]. Thus, intense research on the cellular cascades that supports endothelial barrier function is needed, to discover new approaches for ARDS treatment.

2. P53 and Inflammation

2.1 P53 induces Endothelial Inflammation

P53 has been involved in inflammatory processes. It was demonstrated in HCT116 cancer cells that P53 impairs endothelial function by transcriptionally repressing Kruppel-Like Factor 2 in a histone deacetylase – dependent; and a histone acetyltransferase - independent fashion. P53 leads to inflammatory gene expression and impaired endothelium-dependent vasodilatation, promoting endothelial dysfunction[12]. Furthermore, p53 accumulation and heparanase overexpression in senescent endothelial cells are involved in mediating the increased risk of venous thrombosis with age. Thus, heparanase antagonization, may represent a promising strategy to ameliorate the prothrombotic endothelial phenotype_with age[13]. Mutated P53 is involved in tumor progression[14] via the potentiation of NFκB transcriptional activities[15]. In type 1 diabetic models generated with streptozotocin injection, the endothelial p53 expression was upregulated along with an inhibition in acetylcholine-driven vasodilatation. The genetic disruption of endothelial-cell p53 significantly ameliorated endothelial dysfunction, and in the ischemic vessel p53 level was markedly increased. Conversely, forced expression of endothelial p53 inhibited vessel dilatation, and reduced the blood flow in the ischemic limb. Thus, the authors concluded that the inhibition of endothelial p53 would become a new therapeutic target for vascular

complications related to diabetes[16]. P53 deletion in mice with chronic lung inflammation exerted a protective role towards the lungs, thus it was assumed that p53-triggered senescence promoted lung damage due to inflammation[17].

2.2 P53 Opposes Endothelial Inflammation

P53 has been found to demonstrate an anti-inflammatory role in various tissues and experimental models, partially due to its capacity to suppress NF-κB [18-20]. Mutant rodents lacking P53 were more vulnerable to LPS than the vehicle-treated experimental subjects. However, the induction of P53 due to Nutlin suppressed the production of pro-inflammatory and inflammatory cytokines, and opposed the development of the LPS-inflicted ALI[21]. P53 has been also shown to exert a strong anti-oxidative role both in vivo and in vitro, since it exerted the capacity to reduce ROS accumulation[22]. Studies in knock out mice revealed the protective role of this transcription factor towards Listeria monocytogenes[23]. Furthermore, P53 mediated the release of cytokines in P53 null mice exposed to LPS [24], and has been associated with weak responses against various forms of chemotherapy[25]. P53 deletion in mice intestinal epithelial cells resulted to increased inflammation [26].

2.3 P53 Opposes LPS – inflicted Lung Injury

We have recently shown that “The Endothelium Defender” [27] elicits robust anti - inflammatory activities in the human lung endothelium[14]. P53 protects against the LPS – induced EBD, by I) Disrupting the inflammatory RhoA/MLC2 pathway[28] II) Suppressing the actin - severing activity of cofilin [29] III) Mediating the protective effects of Hsp90 inhibitors in experimental models of ALI[30] IV) Suppressing the deteriorating activities of APE1/Ref1 towards the lung endothelium[30]. Strikingly, both P53 augmentation and Hsp90 inhibition support endothelium integrity and induce the Unfolded Protein Response element (UPR).

3. Unfolded Protein Response

3.1 Hsp90 inhibition and UPR.

The Endoplasmic Reticulum (ER) participates in the biosynthesis and maturation of the majority of intracellular proteins [31]. Cells are constantly monitor and control the misfolded proteins in the ER lumen. When the concentration of those dysfunctional proteins is above a critical threshold, it stimulates the UPR induction[32]. The UPR is composed of IRE1α (inositol-requiring enzyme 1α), PERK (pancreatic endoplasmic reticulum kinase), and ATF6 (activating transcription factor 6). When those ER stress sensors sense increased load of misfolded proteins, they first attempt to restore the protein-folding demand and capacity back into physiological levels[33]. To increase protein folding capacity, UPR increases ER volume and induces the expression of ER chaperones[34]. Further, it accelerates the degradation and removal of the misfolded proteins from the ER lumen. If all those activities succeed, the cells survive and the UPR function returns back to normal [35]. If those adaptive responses are fail to restore the proper protein-folding homeostasis, UPR will be transformed into an alternate signaling state which will actively promote cell death[36]. Thus, the induction of UPR functions towards cellular repair. Since Hsp90

regulates the maturation of proteins, it is strongly involved in the regulation of ER stress [33]. Moreover, Hsp90 inhibition has been associated with both anti - inflammatory activities and UPR activation[23, 32, 33, 37-39].

It has been reported that Hsp90 inhibition by PU-H71 generated ER stress and activated UPR, as evidenced by the XBP1 mRNA splicing and up-regulation of the ER stress markers Grp94, Grp78, ATF4 and CHOP[40]. Indeed, Hsp90 inhibition induced the UPR in myeloma cells. It was suggested that the ability of Hsp90 inhibitors to eliminate myeloma plasma cells is partially due to induction of ER stress with the downstream initiation of all 3 branches of the UPR[37]. Another study reported that the ability of Geldanamycin to stimulate ER stress-dependent transcription depends on its interaction with GRP94. It was suggested that Hsp90 modulates UPR by stabilizing IRE1[41].

Furthermore, the ER chaperone GPR78 which acts as a key sensor of ER stress and activates UPR, has been reported to play a key role in endothelial integrity. This important study by Birukova et al., examined the molecular events triggered by OxPAPC to increase vascular integrity. It was revealed that OxPAPC directly binds GRP78. That binding lead to GRP78 trafficking to caveolin-enriched microdomains on the cell surface, and the consequent activation of sphingosine 1-phosphate receptor 1 and Rac1 GTPase. Those events are essential for cytoskeletal reorganization and EC barrier enhancement [42]. Moreover, it was recently reported that GRP78 translocation to the cell surface and the O-GlcNAcylation of VE Cadherin contribute to ER stress – mediated endothelial permeability[43].

3.2 Inflammation and UPR

3.2.1 UPR activation induces Inflammation—The harmful effects of the robust endothelium UPR activation, will inevitably cause cellular death[44-49]. Moreover, a robust UPR activation has been shown to be associated with homocysteinemia, hyperlipidimia, high glucose, insulin resistance, disturbed blood flow, pulmonary hypertension part through the activation of ER stress.[49, 50]. A study on the role of the UPR mediators in angiogenesis revealed a critical role for ATF6 and PERK in VEGF-mediated signaling. The activation of PERK and ATF6, but not IRE1α, was important for the VEGF-mediated anti-apoptotic pathway that also involved mTORC2- dependent Ser473 phosphorylation of AKT. VEGF activation did not lead to CHOP induction, but instead ensured a pro-survival advantage by maintaining a high level of AKT phosphorylation[51].

3.2.2 UPR activation Opposes Inflammation—However, a recent emerging body of evidence suggests that UPR propels dynamic anti–inflammatory responses. It was recently suggested that the IRE1α in intestinal epithelial cells is essential for protecting against colitis, and revealed that it functions to maintain the intestinal epithelial homeostasis and oppose inflammation due to bowel diseases[52]. Remarkably, the transfection of human pulmonary artery endothelial cells with siRNA for BiP (the ER Hsp70) abrogated endothelial permeability[51]. Furthermore, the LDL–induced inflammatory responses in human mesangial cells were reduced after IRE1alpha silencing. Pretreatment of those cells with the UPR inductor Tunicamycin significantly reduced the elevation of the LDL – induced pro - inflammatory cytokines[53].

It was suggested that CHOP deficiency results in elevated LPS - induced inflammation and kidney injury[54]. The investigators revealed that CHOP mice developed more severe AKI after LPS injection, thus in that case the UPR activation exerted a protective role against AKI. Moreover, mild endoplasmic reticulum stress ameliorates LPS - induced neuroinflammation and cognitive impairment via regulation of microglial polarization[55]. Interestingly, a subcytotoxic dose of subtilase cytotoxin prevented LPS - induced inflammatory responses, depending on its capacity to induce the UPR.

Pretreatment of a mouse macrophage cell line, RAW264.7, with a subcytotoxic dose of SubAB-triggered UPR and inhibited LPS-induced MCP-1 and TNF-a production associated with inhibition of NF-kB activation. SubAA272B, a SubAB active site mutant that cannot induce UPR, did not show such effects[56].

Although ER stress triggers activation of NF-kB in the early phase, these results indicate a possibility that a subsequent UPR has the potential to inhibit activation of NF-KB in a later phase. The mechanisms involved in those events have not been fully elucidated, but there are several possibilities. ER stress-induced UPR may inhibit NF-KB by downregulating TRAF2 (TNF receptor-associated factor 2) and/or the induction of C/EBPs (CCAAT/enhancer-binding proteins) and A20[57]. Interestingly, the proteasome inhibitor MF132 inhibits NF-KB by MG132 through ER stress-mediated induction of the liver activating protein and the liver enriched inhibitory protein[58]. In summary, the previously mentioned data support the underappreciated role of UPR induction against inflammation.

3.3. The Reciprocal Regulation between P53 and UPR.

There is a limited body of reports devoted on the “cross talking” between P53 and UPR in the endothelium. Most of the published reports are in malignant experimental models. In cancer cells, it was revealed that P53 negatively regulates IRE1α expression [59]. In breast cancer cells (MCF7), ER stress induced p53 expression via NF-κB Activation[60]. In 3T3 fibroblasts and prostate cancer cells, ER stress induced p53 degradation via the phosphorylation of P53 at serine S315 and S376[61]. Interestingly, in HCT116 human colorectal carcinoma $p53^{+/+}$ cells, treatment with the ER stress-inducing agent thapsigargin caused a rapid drop in total p53 levels, while it induced CHOP levels[62]. In human and canine osteosarcoma cells, it was suggested that P53, UPR and ER stress form a regulatory loop, and that P53 may suppresses UPR. These studies were not supported by “in vivo” observations [63]. Our group has recently demonstrated that UPR regulates P53 expression in the pulmonary endothelium[64]. This study reports the first evidence that both UPR and P53 operate towards the regulation of lung endothelium integrity. Indeed, future efforts will elucidate the exact components of the UPR machinery in charge of those molecular events.

4. Conclusions

A robust and prolonged UPR induction has been associated with severe inflammatory responses, often associated with lethal outcomes. The present assay suggests that a mild UPR induction is probably associated with protective effects in the vascular endothelium, and may serve as an attractive target towards the development of new therapies against ARDS.

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