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COMMENTARY

P53 in acute respiratory distress syndrome

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Abstract

P53 is a tumor suppressor protein, associated with strong anti-inflammatory activities. Recent evidence suggest that this transcription factor counteracts lung inflammatory diseases, including the lethal acute respiratory distress syndrome. Herein we provide a brief discussion on the relevant topic.

Keywords Inflammation · Acute lung injury · Unfolded protein response · Heat shock proteins

The severities of the acute respiratory distress syndrome (ARDS), including the ARDS related to COVID-19, are associated with thousands of deaths worldwide. The current therapeutic approaches do not suffice to reduce the unacceptably high mortality rates of that lethal disorder. Hence, intense efforts are oriented towards the development of efficient medical countermeasures. Since lung endothelial hyper-permeability due to the "cytokine storm" is both a cause and consequence of ARDS, the elucidation of the mechanisms involved in the regulation of the lung endothelium is of the utmost need. Delineation of the molecular signaling governing the vascular barrier function may deliver new and exciting therapeutic possibilities for those patients in need [1].

P53 is an anti-inflammatory transcription factor, which devises cellular responses against a diverse variety of environmental stimuli. Indeed, it is subjected to a reciprocal regulation with the nuclear factor-kappa B (NF-κB). The exact nature of those interrelations has been recently described in a recent exceptional study by Carra et al. [2]. The proficient investigators explored the great depths of the tumoral P53/NF-κB network and released their own perspectives in the corresponding field [2].

P53 counteracts stress by promoting cell death, senescence, or cell cycle arrest by utilizing oxidative phosphorylation. NF-κB initiates immune responses by aerobic glycolysis [3]. The activation of one of those proteins results in the deactivation of the other, hence inhibition of NF-κB results in the activation of P53 functions [4]. Chronic infections by mycoplasma as well as NF-κB-activating peptides reduce P53, contributing to the progression of malignant transformations [5]. P53 is required for the repression of NF-κB by the glucocorticoid receptor [6], and P53 deficiency in mice was shown to potentiate the LPS-induced inflammation [7]. Moreover, P53 inhibits inflammation by antagonizing NF-κB [8].

The anti-inflammatory activities of P53 in human pathophysiology are not limited to cancer tissues. Indeed, it appears that this transcription factor exerts the capacity to protect against the LPS-induced lung endothelial hyper-permeability, by suppressing the inflammatory RhoA/MLC2 pathway, thus reducing the formation of the F-actin fibers [9]. Further studies revealed that P53 enhances endothelial barrier function by suppressing the actin-severing activity of cofilin, as well as by mediating the opposing activities of Rac1/RhoA both in vitro and in mutant mice overexpressing P53 [10].

Cofilin is the downstream target of the Rac1/p21-activated kinase/LIMK axis [11, 12], and has been associated with hyper-permeability responses [13]. Activation of this molecular cascade by P53 inducers (i.e. Hsp90 inhibitors) phosphorylates, hence deactivates, cofilin [10]. On the other hand, this endothelial defender (P53) [14] suppresses the RhoA pathway via p190RhoGAP induction. This is a Rho family GTPase-activating protein which regulates actin stress fiber dynamics via hydrolysis of Rho-GTP, and it is a suppressor of the RhoA/MLC2 pathway [15].

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The phosphorylation of P53 is modulated by both LPS and Hsp90 inhibitors, indicating that activated (phospho) P53 is involved in lung hyper-permeability responses [16]. Furthermore, studies in bovine lung microvascular cells indicated that the protective effects of P53 are associated with the suppression of the inflammatory apyrimidinic endonuclease 1/redox factor-1 (APE1/Ref1) [17]; and the reduction of the reactive oxygen species [18]. APE1/Ref-1 is a redox signalling factor, which regulates the DNA binding activities of NF-κB and hypoxia-inducible transcription factor 1α [19]. Thus, it exerts a major role in promoting inflammation and serves as a therapeutic target in human disease [20].

Interestingly, this endothelium defender (P53) [14] has been shown to be a direct target of the unfolded protein response (UPR) [21, 22]. UPR acts to restore impaired functions of damaged tissues [23], including the lungs [24, 25] and affects P53 levels in a positive manner. In lung bovine cells the UPR inductors Brefeldin A, dithiothreitol, and thapsigargin induced P53, while the UPR inhibitors N-acetyl cysteine, kifunensine, and ATP-competitive IRE1α kinase-inhibiting RNase attenuator produced the opposite effects. Hence P53 may mediate, or even initiate, UPR-mediated responses towards the maintenance of lung homeostasis [26].

This multifaceted maestro (P53) is strongly involved in the protective effects of Hsp90 inhibitors and GHRH antagonists in the lung microvasculature [27, 28]. Those anti-cancer and anti-inflammatory agents induce UPR both in vivo and in vitro. Hence, the existence of a new molecular network in the context of P53/UPR/Hsp90 [29], which operates towards the repair of the severely inflamed lungs, is highly possible [30, 31]. Pharmacological "fine-tuning" of that meticulously orchestrated network, may deliver novel ways to restore respiratory functions in the hospitalized ARDS patients.

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