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P53 in the impaired lungs

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ABSTRACT

Our laboratory is focused on investigating the supportive role of P53 towards the maintenance of lung homeostasis. Acute lung injury, acute respiratory distress syndrome, chronic obstructive pulmonary disease, pulmonary fibrosis, bronchial asthma, pulmonary arterial hypertension, pneumonia and tuberculosis are respiratory pathologies, associated with dysfunctions of this endothelium defender (P53). Herein we review the evolving role of P53 towards the aforementioned inflammatory disorders, to potentially reveal new therapeutic possibilities in pulmonary disease.

1. Introduction

P53 is a tumor suppressor protein involved in several aspects of human function, partially due to the regulation of glycolysis and oxidative phosphorylation [1]. It represses the glucose transporter 4 [2], which in turn reduces the levels of fructose-2,6-bisphosphate to inhibit glycolysis [3]. Under basal conditions P53 expression levels are relatively low, promoting the expression of several antioxidant genes including sestrins, glutathione peroxidase 1, aldehyde dehydrogenase 4, glutaminase 2, nuclear factor erythroid 2-related factor 2, and parkin [4]. In response to DNA damage, hypoxia, and oxidative stress P53 is stabilized to deliver cellular protection. In case of failure, alternative apoptotic mechanisms are activated to deliver cellular death [5]. This endothelium defender [6] exerts anti-inflammatory responses in the lungs, suggesting its potential therapeutic role in pulmonary inflammatory diseases. Those effects are partially due to its antagonism with NFκB [7].

2. Human pulmonary vasculature

In human lungs, the bronchi are divided into bronchioles, which in turn form the alveoli. Those are the basic functional units, which facilitate the acquisition of oxygen into the bloodstream and remove the carbon dioxide from the blood [8]. This vasculature transfers the entire cardiac output from the right side of the heart and spreads it throughout the alveolar capillaries. Moreover, it provides blood flow to the lungs, in addition to the bronchial circulation [9]. Besides those functions, the lungs support immunological integrity [5,10–13].

The airway smooth muscle (ASM) cells play a major role in regulating airflow through the bronchioles, and exert the ability to contract or dilate the airways to regulate the ventilation of the distal airways [14]. They also sensitive to the surrounding inflammatory signaling milieu [15,16]. Hyper-contractility of those cells may result to asthma [17].

The lung alveolar epithelial and capillary endothelial cells are the regulators of the microvascular permeability in the respiratory gas exchange system. The alveolar epithelial cells (AECs) (type 1 and 2) form a continuous monolayer, and are connected with intercellular tight junctions. Type 2 epithelial cells produce surfactant, which reduces the alveolar surface tension and keep the airspace functional [18]. The type 1 cells participate in the gas exchange between the alveoli and the blood. In case of emergencies, type 2 cells may convert to type 1 cells, so to initiate the alveolar repairing process [18].

The inner lining of the lung alveolar-capillary is composed of endothelial cells, which are linked together with intercellular tight and adherens junctions. The vascular endothelial cell-cell gap or the tight junctions are crucial for controlling the exchange of blood components, gases, fluids, different micro, and macromolecules from the circulatory blood vessels to the alveoli [19–22]. The cellular cytoskeleton and glocalyx regulate the morphology of the metabolically active endothelial cells [23–25]. The endothelium disruption may be due to the cytoskeletal reorganization and pathogen recognition by cellular receptors [26–29]. Lung endothelial hyperpermeability is the cause and consequence of inflammatory lung disease, including ALI or ARDS [30,31]. The heterogeneous fibroblasts in the interstitium regulate extracellular matrix components and contractility to provide structural integrity.
Lung injury activates those endothelial cells [32].

2.1. P53 in the lungs

The alveolar-capillary membrane, also known as the blood-air barrier, separates the circulating blood from flowing air. The optimal exchange of air within the lungs depends on the requisite airflow and blood perfusion throughout their entire area [33]. In the case of ventilation perfusion mismatch, the blood flow locally exceeds airflow or vice versa, affecting the blood oxygenation [34]. P53 participates in vascular homeostasis [5,35,36], and an emerging body of evidence suggest the protective effect of P53 in lung inflammatory reactions [30,37].

2.2. ALI and ARDS

Acute lung injury (ALI) and its most severe form, the acute respiratory distress syndrome (ARDS) are potentially lethal inflammatory conditions. ARDS is characterized by poor oxygenation, pulmonary infiltrates, hyaline membrane formation, epithelial cell hyperplasia, capillary endothelial injury, atelectasis, as well as diffuse alveolar damage [18]. There are 64–78 cases of ARDS per 100,000 persons in the United States, associated with unacceptable high mortality rates (27–45%) [38]. The ARDS survivors suffer from declined cognitive ability, depression, post-traumatic stress disorder, and persistent skeletal-muscle weakness [39]. Elderly patients with ARDS demonstrate higher alveolar neutrophil infiltration, lung inflammation, disrupted air-blood barrier, and altered pulmonary functions compared to the younger patients [40].

Sepsis is a life-threading condition which may result in multiple organ dysfunction syndrome [41]. ARDS is developed in cases of severe sepsis [42]. The damaged endothelium releases cytokines and circulating endothelial cells to increase the expression of cell surface adhesion molecules [43–46].

The increased permeability of the alveolar-capillary endothelium to blood components and fluids is the hallmark of ARDS progression [18]. Developmental endothelial locus-1 (Del-1); also known as Edil3; is an endothelial-derived anti-inflammatory agent that is down-regulated by many inflammatory stimuli such as tumor necrosis factor α (TNF-α), lipo polysaccharides (LPS), and interleukin-17 (IL-17) [47–49]. The histone deacetylase (HDAC) inhibitors such as valproic acid and butyric acid activate P53 and Del-1 mRNA levels and inhibit NF-κB [50–53]. Activated P53 directly binds to the upstream fragment of Del-1 via the P53REs and induces the Del-1 transcriptional activity [50].

NF-κB has pivotal roles in inflammatory responses and regulates the innate as well as adaptive immunity of our body [54]. NF-κB inhibits the transcriptional activities of P53, while P53 promotes pro-apoptotic [55,56] and anti-inflammatory responses [7,57]. Thus, P53 and NF-κB oppose each other functions in the lungs [7,56]. Lipopolysaccharides (LPS), a component of the outer membrane of gram-negative bacteria, and induce inflammatory responses by stimulatingTLR4 receptors. In vivo and in vitro studies revealed that LPS stimulated the activation of NF-κB, and that P53 protects against the LPS-induced ALI by suppressing the activation of NF-κB [58]. P53 null mice potentiate the LPS-induced acute lung injury and inflammatory responses [59]. LPS-induced upregulation of MDM2, an E3 ubiquitin ligase, promotes the proapoptotic degradation of P53. Heat shock protein 90 (Hsp90) inhibitors suppressed the LPS-induced phosphorylation and degradation of P53, protecting against lung endothelial barrier dysfunction [60].

Hsp90 inhibitors have also induced the expression levels of P53; which in turn enhances the endothelial barrier function via activation of the Rac1 signaling [61]. Rac1/p21-activated kinase 1 (Pak1)/LIM domain kinase 1 (LIMK1) signaling regulates cofilin activity, and activation of Rac1 suppresses the actin-severing activity of cofilin. The human apurinic/apyrimidinic endonuclease 1/redox factor-1 (APE1/Ref1), which is an upstream effecter of VEGF; negatively affects the Rac1 pathway. P53 attenuated the inflammatory effects of APE1/Ref1 and enhanced the endothelial barrier function by suppressing APE1/Ref1 in the lung endothelium [62].

Induction of P53 suppressed the generation of reactive oxygen species and lipid peroxidation, supporting the endothelial barrier integrity [63,64]. Lipoteichoic acid (LTA) is a cellular toxic agent derived from gram-positive bacteria. LTA-induced ALI serves as an experimental model to mimic gram-positive bacteria-induced lung injury [65]. LTA induced P53 phosphorylation, thus reduced the levels of P53 in pulmonary microvascular endothelial cells [66].

Unfolded protein response (UPR) is a molecular machinery consisting of the activating transcription factor 6 (ATF6), the protein kinase RNA-like ER kinase (PERK), and the inositol-requiring enzyme-1 (IRE1α). It ensures proper protein folding and maturation [67]. Several studies have reported the involvement of UPR in lung health and disease [68]. UPR directly regulates the expression levels of P53 in the lung endothelium [66]. Recent studies suggested that the endothelial barrier enhancing effects of Hsp90 inhibitors and growth hormone-releasing hormone (GHRH) antagonists might be associated with UPR mediated P53 expression [69–71]. GHRH antagonist induces the expression of P53 and suppresses the major inflammatory extracellular signal-regulated kinases 1/2 (ERK1/2), Janus kinase 2 (JAK2), and signal transducer and activator of transcription 3 (STAT3) pathways in lung microvascular endothelial cells which express GHRH receptors [37].

2.3. Pulmonary fibrosis

Pulmonary fibrosis is associated with extracellular matrix deposition, inflammation, alveolar fibrosis and destruction. This condition leads to serious health complications including pulmonary hypertension, heart failure, respiratory failure, and lung cancer. The only available medical countermeasures are oxygen therapy and pulmonary rehabilitation [72].

Patients with idiopathic pulmonary fibrosis (IPF) and non-specific interstitial pneumonia (NSIP) express increased levels of P53 in their lungs and epithelial cells. Integrated genomics revealed the activation of the P53-hypoxia pathway in both the IPF and COPD, as well as the differential splicing of PDGFA (platelet-derived growth factor subunit A) [73]. Mice expressing dominant-negative P53 were more susceptible to bleomycin-induced lung injury, fibrosis, and collagen deposition [74]. P53 was shown to prevent the TNF-α-induced endotoxic shock in mice [75]. Overexpression of miR-34a increased the P53, plasminogen activator inhibitor-1 (PAI-1), and apoptosis [76]. Explant lung tissues from IPF lung fibroblast expressed increased programmed death-ligand 1 (PD-L1) related to IPF invasiveness. P53 silencing of the lung fibroblasts of IPF patients upregulated the PD-L1 expression and vice versa.

Interestingly, lung fibroblast growth and adhesion were promoted due to P53 suppression, and were inhibited by the absence of CD274 (PD-L1) [77]. Fibroblasts and macrophages express monocyte chemotactic protein-1 (MCP-1) and MCP-1-induced protein 1 (MCP1P1) is a pivotal downstream target of MCP-1, which causes autophagy in SiO2 induced pulmonary fibrosis. Activation of P53 regulated the MCP1P1-mediated autophagy and apoptosis [80].

Aged lungs are prone to infectious diseases due to decreased mucociliary clearance, impaired innate and adaptive immunity [81–88]. In mouse pneumonia models, the cytokines and chemokine levels were higher in aged mice [85]. The peripheral airway and lung parenchymal cells sustained inflammatory symptoms, the major characteristic of age-related COPD and IPF. Targeting cellular senescence may delay pulmonary fibrosis [89]. The senescence of AECs type II was induced by PAI-1 (serpine 1) in IPF lungs via the activation of the p53-p21-Rb pathway [90]. Oxidative stress and ROS generation triggered pulmonary fibrosis. P53 modulates the redox status of lung cells, since induction of P53 by nutlin-3a and Hsp90 inhibitors suppressed ROS generation [64].
3. COPD

Chronic obstructive pulmonary disease (COPD) is a lung disease associated with chronic airway inflammation, which limits the airflow in the lungs. The underlying mechanisms responsible for the development of COPD involve inflammation, apoptosis, and airway epithelial remodeling [91–93]. It was reported that 80 % of lung cancer patients suffer from COPD [94].

Sirtuin-1 and sirtuin-6 protect against COPD. Suppression of sirtuin-1 potentiates the possibility of lung cancer in COPD patients, since it inhibits the K-RAS-driven lung adenocarcinomas. Sirtuin-1 also activates the transcription factor peroxisome proliferator-activated receptor-gamma coactivator (PGC) 1α and inhibits the P53-induced cellular senescence. Restoration of sirtuin-1 and sirtuin-6 in the airway epithelial cells of COPD patients suppressed the expression of P53, P16, and P21, indicating cellular senescence. P53 acetylation enhances cell cycle arrest, cellular senescence, and apoptosis. Suppression of the sirtuin-1 stimulated P53 acetylation [95–97]. Thus, sirtuin-1 may be involved in COPD by mediating the P53-mediated cellular senescence. Others have demonstrated that the pharmacological activator of SIRT1 protected against the AECII apoptosis by downregulating P53 [98]. Since AEC type 2 cells may proliferate and differentiate to AEC type 1, it exerts a vital role in alveolar homeostasis and lung epithelium repair [18].

A study in non-small cell lung cancer (NSCLC) patients with COPD indicated that P53 is the downstream target of miR-675. P53 was downregulated due to increased miR-675 levels [94]. Other studies have indicated that increased P53 activity suppresses the COPD in NSCLC [99]. Tobacco smoking is a leading cause of COPD, and contributes to neuromuscular respiratory failure. Rats exposed to chronic tobacco expressed more P53 and P21 levels in their diaphragm [32]. The bronchial club-specific deletion of P53 abolished the lung inflammation following acute and chronic exposure to LPS [100]. Induction of P53 in smoking-induced COPD increased PAI-1, which is a downstream target of P53-induced inflammation. Moreover, AECs death occurred due to the interaction of IL-17A and P53 in the fibrinolytic system during smoking-induced COPD [101].

Emphysema is a form of COPD, and P53 plays a pivotal role in the protection against emphysema. The changes in the emphysematous conditions are associated with the polymorphism of P53 and MDM2 [102], and lack of P53 in mice promotes the elastase-induced emphysema [103]. AECs apoptosis and emphysema were induced by the P53 and siva-1 (apoptosis regulatory protein) signaling pathways [104]. Quercetin-induced inflammation in the emphysematous lung were associated with suppression of the NF-kB signaling [105], as well as with P53 and caspase activation [99].

3.1. Pulmonary arterial hypertension

The elevation of pulmonary vascular resistance results in pulmonary arterial hypertension (PAH), characterized by mean pulmonary arterial pressure (PAP) of ≥25 mmHg at resting conditions [106]. PAH is the consequence of pulmonary vascular remodeling, heart failure, blood clots, atherosclerosis, HIV, inherited heart defect, pulmonary fibrosis, liver diseases, adverse effect of drugs, arthritis, and other autoimmune diseases. Higher PAP causes dilution of the right ventricle and heart failure. It also affects the proliferation of smooth muscle cells. The vascular wall becomes thicker, and plexiform lesions are formed [107].

In the case of hypoxia-induced pulmonary hypertension, P53 is increased in the pulmonary arterial endothelial cells (PAECs) but it is decreased in the pulmonary arterial smooth muscle cells (PASMCs). This decrease is associated with increased HIF-1α levels of the smooth muscle cells [108].

The rapid accumulation of HIF-1α in the nucleus of PASMCs contributes in the elevation of the cytosolic Ca²⁺ concentration, by promoting the transient receptor potential channels and enhancing Ca²⁺ entry [109]. The store operated Ca²⁺ entry (SOCE) and PASMCs proliferation are associated with lung tissue remodeling. In P53 KO mice, it was demonstrated an acceleration of the the hypoxia-induced pulmonary arterial hypertension as well as vascular remodeling [35]. In chronic hypoxia, HIF-1α in smooth muscle cells contributed to vascular remodeling and hypertension [110]. The experimental PH-induced increase in P53 caused apoptosis of the PAECs and pulmonary vasoconstriction [108].

The bone morphogenetic protein receptor (BMPR) 2 protects against mitochondrial dysfunction, which is related to clinical and experimental pulmonary hypertension (PH) [111]. Mutations in the BMPR2 gene causes pulmonary arterial endothelial cells dysfunction and inherited pulmonary hypertension [112,113]. Studies employing transgenic mice and PPAEC with deletion of BMPR2 in EC reported that P53 and PGC1α are associated with altered BMPR2 in pulmonary artery endothelial cells [114].

Pulmonary artery atherosclerosis is potentiated by increased cellular proliferation due to the absence of P53 [115]. Atherosclerosis is the result of vascular inflammation. P53 deficiency affected the vascular smooth muscle cell migration and proliferation, an indication of atherosclerotic lesion formation [116].

The long noncoding RNA-maternally expressed gene 3 (MEG3) is a vital regulator of PAH. Downregulation of MEG3 promoted pulmonary artery smooth muscle cell proliferation and migration [117]. P53 exerted a protective role in oxidized low-density lipoprotein-induced atherosclerotic plaque formation and PAH [118]. Moreover, in a monocrotaline-induced PH model P53 protected against PH [36]. In mice, P53 augmentation by its pharmacological agonist quinacrine was shown to regulate macrophage polarization and venous thrombus resolution. P53 inhibition resulted to the opposite effects [119].

3.2. Asthma

Airway obstruction due to allergens, air pollutants, viruses; and the contraction of the airway smooth muscle cells is the major clinical manifestation of asthma. Rhinitis and rhinosinusitis are common comorbidities of this bronchial hyperresponsive disease. Usual bronchial asthma is managed by bronchodilators, steroids, and anti-inflammatory agents [120]. Asthma results from the accumulation of excessive IL-1β and neutrophils [121]. The serum level of IL-1β were associated with P53 expression [122]. Mutant P53 induces IL-1β by inhibiting secreted interleukin-1 receptor antagonist (sIL-1Ra) [123]. Other studies have demonstrated increased cellular apoptosis in the bronchial epithelial cells of patients with asthma [124,125].

Galectins are carbohydrate-binding proteins that bind specifically to beta-galactosides to mediate inflammation and immune responses. Galectin-7 was induced by P53 [126,127]. Increased expression of galectin-7 initiated asthma due to airway epithelial apoptosis and injury. Suppression of galectin-7 by siRNA inhibited the activation of the JNK pathway and attenuated the TGF-β1-induced apoptosis in the airway epithelial cells [128].

P53 regulates mitochondrial homeostasis and biogenesis [129,130]. Asthmatic patients exert an increased expression of P53 in BSM and decreased Mdm2/P53 interaction, due to phosphorylation of P53 at Ser20. Lentiviral transduction of P53 in asthmatic patients suggested that P53 is not completely functional in asthmatic patients, and P53 dysfunction in mitochondrial biogenesis promotes BSM cell proliferation [131].

Integrin β4 (ITGB4), the structural component of airway epithelial cells, is downregulated in asthmatic patients upon inflammatory stimulation. Activation of P53 induces senescence of airway epithelial cells by suppressing ITGB4 [132], P53 induced phosphatase 1 (Wip1), which is involved in the pathogenesis of allergic airway inflammation. Inhibition of this phosphatase ameliorates the progression of the allergic airway inflammation by inhibiting IL-9 transcription [133].
3.3. P53, influenza and pneumonia

Viral infections downregulate P53 to sabotage the innate host response. Ring-finger and CHY zinc-finger domain-containing 1 (RCHY1), is an E3 ubiquitin ligase involved in the proteasomal degradation of P53 [134]. The application of high-throughput screening revealed that RCHY1 and calcium/calmodulin-dependent protein kinase II delta (CAMK2D) is an important interacting element of the SARS-CoV (severe acute respiratory syndrome coronavirus) unique domain (SUD). P53 was shown to inhibit the replication of SARS-CoV [135].

Bioinformatic analysis suggested that the S2 subunit of SARS-CoV-2 strongly interacts with P53, breast cancer type 1 susceptibility protein (BRCA-1), and breast cancer type 2 susceptibility protein (BRCA-2) [136]. P53 transactivates interferon regulatory factor 7 (IRF7) to regulate the expression of IFNα and IFNβ. Overexpression of P53 in porcine epidemic diarrhea virus (PEDV) infection, a pathogen from the coronavirus family, negatively regulates viral replication [137]. Other studies suggested that papain-like proteases (PLPs) may serve as a potential therapeutic target for viral infections [138-140]. Human coronavirus - induced activation of PLPs suppressed P53 activity and inhibited the IFN-dependent antiviral activity [141].

SARS-CoV and MERS-CoV (middle east respiratory syndrome coronavirus) affect the MDM2/P53 feedback loop, suggesting that SARS-CoV-2 may reduce the immune response by inducing MDM2 (P53 suppressor). Moreover, Nutlin 3a and MI-63 suppressed the IL-6 and IL-1β expression of toll-like receptor 8 (TLR8), which is associated with RSV [142] and other antitubercular drugs exhibited anti-tuberculosis and anti-inflammatory effects by P53-mediated apoptosis [171,172].

4. Conclusions

P53 deficiency has been associated with severe respiratory disorders [173,174]. Thus, pharmacological interventions which induce the intracellular abundance of that protein in the lungs, may deliver novel therapeutic possibilities in human disease. The anticancer and anti-inflammatory agents Hsp90 inhibitors [175] and GHRH antagonists [176,177] are holding the potential to serve towards that purpose, since they affect P53 levels [30,178].

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Declaration of Competing Interest

No conflicts of interest, financial or otherwise, are declared by the authors.

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