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Review Article

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 NFKB [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 glycocalyx 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.

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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 [8,35,36], 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 diffusive 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 neutrophilic 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), lipopolysaccharides (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-kB [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-kB has pivotal roles in inflammatory responses and regulates the innate as well as adaptive immunity of our body [54]. NF-kB inhibits the transcriptional activities of P53, while P53 promotes pro-apoptotic [55,56] and anti-inflammatory responses [7,57]. Thus, P53 and NF-kB 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 stimulating TLR4 receptors. In vivo and in vitro studies revealed that LPS stimulated the activation of NF-kB, and that P53 protects against the LPS-induced ALI by suppressing the activation of NF-kB [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 proteasomal 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/Ref-1), which is an upstream effector 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-1α (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 [60]. 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 lung tissues 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) an effector of P53 [78,79]. MCP-1-induced protein 1 (MCPIP1) is a pivotal downstream target of MCP-1, which causes autophagy in SiO_2 induced pulmonary fibrosis. Activation of P53 regulated the MCPIP1-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 cell-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 $\geq$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 Ca^{2+} concentration, by promoting the transient receptor potential channels and enhancing Ca^{2+} entry [109]. The store operated Ca^{2+} 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-1α [142] which are the major cytokines involved in the COVID-19 related ARDS [143,144].

Various studies reported the antiviral functions of P53 against influenza. The knockdown of P53 inhibited the IFN-α-mediated immune response against the influenza A virus (IAV) [145]. This transcription factor regulates the elevation of the IFN regulatory factor 9 (IRF9) [146] in virus-infected cells [147]. P53 is also involved in the innate immunity due to the transcriptional regulation of TLR3 [148], and interferon regulatory factors (IRFs) [145,149]. P53 deletion delayed the expression of antiviral proteins and impaired the influenza virus clearance from the lungs. In addition, P53 null mice showed decreased monocyte infiltration and defective IAV-specific immune responses of T cells by inhibiting OVA-specific CD8 + T cell proliferation [150].

P53 null mice showed enhanced recruitment of PMNs and inflammatory responses due to LPS. Moreover, P53 overexpression reduced the LPS-induced NF-kB luciferase activity [151]. The mononuclear leukocytes of the patients suffering from community-acquired pneumonia expressed a 15.7 % decrease in P53 levels, and a single one-day treatment increased the expression of P53 by 24.2 % [152].

P53 increased plasminogen activator inhibitor-1 (PAI-1) and inhibited the urokinase-type plasminogen activator (uPA) in alveolar epithelium cells during lung injury [153]. P53 inhibited the replication of poliovirus and vesicular stomatitis virus, and increased the replication of RSV. Indeed, RSV elevated the Akt/MDM2-mediated degradation of P53 to increase the survival of the airway epithelial cells [154]. It was also reported that RSV infection dysregulated the transcriptional activity of P53 and decreased the level of P53 via proteasome-dependent degradation, which in turn induces viral replication [155]. Functional loss of P53 due to RSV infection was correlated to NF-kB activity via the NS-1/NS2-PI3K/Akt pathway [155]. Moreover, P53 induced the expression of toll-like receptor 8 (TLR8), which is associated with RSV infection and enhances the TLR8-mediated immune responses [156].

Pleural effusion is due to fluid accumulation in the pleural space throughout pneumonia, cancer, or congestive heart failure. P53 is overexpressed in pleural effusion and P53 immunostaining can be used as a diagnostic tool for this lung pathology [157]. Randomized trials with 879 patients demonstrated that recombinant human adenovirus-P53 (rAd-P53) in combination with other anticancer agents improved the therapeutic response against malignant pleural effusion (MPE) [158]. A long-term follow-up study with 210 MPE patients revealed that the administration of rAd-P53 had greater therapeutic response than treatment with cisplatin [159].

In pleural mesothelioma, CDK6 phosphorylation is inhibited by the selective CDK4/6 inhibitor palbociclib (PD-0332991). It also increases the phosphorylation of AKT, which can be repressed by upregulation of P53 and P21 [160]. The nuclear TNF receptor associated factor 4 (TRAF4) was also downregulated in malignant pleural effusion, and those effects were related to P53 expression [161].

Tuberculosis (TB) is associated with acute pneumonia [162]. During Mycobacterium (Mtb) infection, M1 macrophages express more P53 than M2 macrophages. Activation of P53 in Mtb-infected M1 macrophages was indirectly regulated by the production of reactive oxygen species, nitric oxide, and inflammatory cytokines [163]. Indeed, induction of P53 by nutlin-3 attenuated the Mtb survival in TB patients. The Mtb secreted virulence factor MptpB inhibited the expression of P53 and enhanced the survival of H37Rv by suppressing the NF-κB and MAPK signal pathways [164]. miR-27b increased the P53-mediated cellular apoptosis and suppressed the NF-kB activity. Bcl-2-associated athanogene 2 (Bag2) in macrophages interacts with P53 to reduce apoptosis, whereas miR-27b directly targets Bag2 and increases P53 activity [165]. The suppression of the epithelial STAT and NF-kB were abolished by the inhibition of Rac1 in Mtb infected AECs [166]. DNA damage-regulated autophagy modulator 1 (DRAM1) silencing resulted in an increased mycobacterium burden [167].

Mycobacterium Bovis BCG induces the survival of infected cells by targeting P53 and inhibiting the TNF-α-induced apoptosis [168]. P53 activated apoptotic signaling pathways are indicators of cellular abnormalities, since they form multinuclear macrophages in BCG infection [169]. Inhibition of P53 and its nuclear translocation by IL-17 impairs apoptosis of the Mtb-infected cells via reduction of caspase-3, Bax, and cytochrome-c release, as well as by increasing Bcl2 [170]. The ethanolic extract of *Pluchea indica* 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.

References

[1] A.M. Puzio-Kuter, The role of p53 in metabolic regulation, Genes Cancer 2 (4) (2011) 385–391.
[2] B. Vergoni, et al., DNA damage and the activation of the p53 pathway mediate alterations in metabolic and secretory functions of adipocytes, Diabetes 65 (10) (2016) 3062–3074.
[3] S. Ros, et al., 6-Phosphofructo-2-kinase/fructose-2,6-biphosphatase 4 is essential for p53-null cancer cells, Oncogene 36 (23) (2017) 3287–3299.

[4] N. Barabutis, A.V. Schally, Antioxidant activity of growth hormone-releasing hormone antagonists in LNCaP human prostate cancer line, Proc. Natl. Acad. Sci. U. S. A. 105 (51) (2008) 20470–20475.
[5] Y. Liang, J. Liu, Z. Feng, The regulation of cellular metabolism by tumor suppressor p53, Cell Biosci. 3 (1) (2013) 9.
[6] M.A. Uddin, N. Barabutis, P53: the endothelium defender, J. Cell. Biochem. 120 (7) (2019) 10952–10955, https://doi.org/10.1002/jcb.28511. In this issue.
[7] N. Barabutis, A.V. Schally, A. Siejka, P53, GHRH, inflammation and cancer, EBioMedicine 37 (2018) 557–562.
[8] N. Mouraret, et al., Activation of lung p53 by Nutlin-3a prevents and reverses experimental pulmonary hypertension, Circulation 127 (16) (2013) 1664–1676.
[9] J. Li, et al., Minocycline protects against NLRP3 inflammasome-induced inflammation and P53-Associated apoptosis in early brain injury after subarachnoid hemorrhage, Mol. Neurobiol. 53 (4) (2016) 2668–2678.
[10] M. Ljungman, Dial 9-1-1 for p53: mechanisms of p53 activation by cellular stress, Neoplasia 2 (3) (2000) 208–225.
[11] K. Bensaad, K.H. Vousden, p53: new roles in metabolism, Trends Cell Biol. 17 (6) (2007) 286–291.
[12] F. Kruiswijk, C.F. Labuschagne, K.H. Vousden, p53 in survival, death and metabolic health: a lifeguard with a licence to kill, Nat. Rev. Mol. Cell Biol. 16 (7) (2015) 393–405.
[13] M. Ren, et al., Transcription factor p73 regulates Th1 differentiation, Nat. Commun. 11 (1) (2020) 1475.
[14] C.J. Koziol-White, R.A. Panettieri Jr., Airway smooth muscle and immunomodulation in acute exacerbations of airway disease, Immunol. Rev. 242 (1) (2011) 178–185.
[15] A. KleinJan, Airway inflammation in asthma: key players beyond the Th2 pathway, Curr. Opin. Pulm. Med. 22 (1) (2016) 46–52.
[16] P.B. Noble, et al., Airway smooth muscle in asthma: linking contraction and mechanotransduction to disease pathogenesis and remodelling, Pulm. Pharmacol. Ther. 29 (2) (2014) 96–107.
[17] J.K. Bentley, M.B. Hershenson, Airway smooth muscle growth in asthma: proliferation, hypertrophy, and migration, Proc. Am. Thorac. Soc. 5 (1) (2008) 89–96.
[18] M.A. Matthay, et al., Acute respiratory distress syndrome, Nat. Rev. Dis. Primers 5 (1) (2019) 18.
[19] T. Okamoto, et al., Gap junction-mediated regulation of endothelial cellular stiffness, Sci. Rep. 7 (1) (2017) 6134.
[20] F. Chang, S. Flavahan, N.A. Flavahan, Superoxide inhibition restores endothelium-dependent dilatation in aging arteries by enhancing impaired adherens junctions, Am. J. Physiol. Heart Circ. Physiol. 314 (4) (2018) H805–H811.
[21] G.B. Singh, et al., High mobility group Box 1 mediates TMAO-Induced endothelial dysfunction, Int. J. Mol. Sci. 20 (14) (2019).
[22] V.A. Malik, et al., GDF15 promotes simultaneous astrocyte remodeling and tight junction strengthening at the blood-brain barrier, J. Neurosci. Res. (2020).
[23] C.F. Natale, et al., Focal adhesion clustering drives endothelial cell morphology on patterned surfaces, J. R. Soc. Interface 16 (158) (2019), p. 20190263.
[24] M.J. Cheng, et al., Targeted intravenous nanoparticle delivery: role of flow and endothelial glycocalyx integrity, Ann. Biomed. Eng. (2020).
[25] N.F. Couto, et al., OxLDL alterations in endothelial cell membrane dynamics leads to changes in vesicle trafficking and increases cell susceptibility to injury, Biochim. Biophys. Acta Biomembr. 1862 (3) (2020) 183139.
[26] S. Gao, et al., Histidine-rich glycoprotein ameliorates endothelial barrier dysfunction through regulation of NF-kappaB and MAPK signal pathway, Br. J. Pharmacol. 176 (15) (2019) 2808–2824.
[27] L.M. Botros, et al., Bosutinib prevents vascular leakage by reducing focal adhesion turnover and reinforcing junctional integrity, J. Cell. Sci. (2020).
[28] W.J. Brucker, et al., An emerging role for endothelial barrier support therapy for congenital disorders of glycosylation, J. Inherit. Metab. Dis. (2020).
[29] T. Liang, et al., Inhibition of glycogen synthase kinase 3beta improves cognitive function in aged mice by upregulating claudin presences in cerebral endothelial cells, Acta Biochim Biophys Sin (Shanghai) (2020).
[30] K.T. Kubra, et al., P53 versus inflammation: an update, Cell Cycle 19 (2) (2020) 160–162.
[31] N. Barabutis, A. Verin, J.D. Catravas, Regulation of pulmonary endothelial barrier function by kinases, Am. J. Physiol. Lung Cell Mol. Physiol. 311 (5) (2016) L832–L845.
[32] L. Knudsen, M. Ochs, The micromechanics of lung alveoli: structure and function of surfactant and tissue components, Histochem. Cell Biol. 150 (6) (2018) 661–676.
[33] N.R. MacIntyre, Tissue hypoxia: implications for the respiratory clinician, Respir. Care 59 (10) (2014) 1590–1596.
[34] T. Ganz, Does pathological Iron overload impair the function of human lungs? EBioMedicine 20 (2017) 13–14.
[35] S. Mizuno, et al., p53 Gene deficiency promotes hypoxia-induced pulmonary hypertension and vascular remodeling in mice, Am. J. Physiol. Lung Cell Mol. Physiol. 300 (5) (2011) L753–L761.
[36] S. Jacquin, et al., *Inactivation of p53 is sufficient to induce development of pulmonary hypertension in rats*, PLoS One 10 (6) (2015) e0131940.
[37] M.A. Uddin, et al., GHRH antagonists support lung endothelial barrier function, Tissue Barriers 7 (4) (2019) 1669989.
[38] M. Diamond, et al., Acute respiratory distress syndrome (ARDS). StatPearls, Treasure Island (FL), 2020.
[39] N. Barabutis, Unfolded Protein Response in Acute Respiratory Distress Syndrome, Lung 197 (6) (2019) 827–828.
[40] K.M. Kling, et al., Aging exacerbates acute lung injury-induced changes of the air-blood barrier, lung function, and inflammation in the mouse, Am. J. Physiol. Lung Cell Mol. Physiol. 312 (1) (2017) L1–L12.
[41] N. Barabutis, et al., Hydrocortisone and ascorbic acid synergistically prevent and repair lipopolysaccharide-induced pulmonary endothelial barrier dysfunction, Chest 152 (5) (2017) 954–962.
[42] W.Y. Kim, S.B. Hong, Sepsis and acute respiratory distress syndrome: recent update, Tuberc. Respir. Dis. (Seoul) 79 (2) (2016) 53–57.
[43] W.L. Yang, et al., Cold-inducible RNA-binding protein causes endothelial dysfunction via activation of Nlrp3 inflammasome, Sci. Rep. 6 (2016) 26571.
[44] X. Hou, S. Yang, J. Yin, Blocking the REDD1/TXNIP axis ameliorates LPS-induced vascular endothelial cell injury through repressing oxidative stress and apoptosis, Am. J. Physiol., Cell Physiol. 316 (1) (2019) C104–C110.
[45] T. Kishi, et al., Endothelial activation markers as disease activity and damage measures in juvenile dermatomyositis, J. Rheumatol. (2019).
[46] Y. Sun, et al., IFN-gamma and TNF-alpha aggravate endothelial damage caused by CD123-targeted CAR T cell, Onco. Ther. 12 (2019) 4907–4925.
[47] K. Hata, et al., IL-17 stimulates inflammatory responses via NF-kappaB and MAP kinase pathways in human colonic myofibroblasts, Am. J. Physiol. Gastrointest. Liver Physiol. 282 (6) (2002) G1035–44.
[48] M.S. Hayden, S. Ghosh, Regulation of NF-kappaB by TNF family cytokines, Semin. Immunol. 26 (3) (2014) 253–266.
[49] K.V. Ramana, et al., Aldose reductase mediates the lipopolysaccharide-induced release of inflammatory mediators in RAW264.7 murine macrophages, J. Biol. Chem. 281 (44) (2006) 33019–33029.
[50] H. Kim, et al., p53 regulates the transcription of the anti-inflammatory molecule developmental endothelial locus-1 (Del-1), Oncotarget 4 (11) (2013) 1976–1985.
[51] S. Chen, et al., Valproic acid attenuates traumatic spinal cord injury-induced inflammation via STAT1 and NF-kappaB pathway dependent of HDAC3, J. Neuroinflammation 15 (1) (2018) 150.
[52] E. McCormack, et al., Synergistic induction of p53 mediated apoptosis by valproic acid and nutlin-3 in acute myeloid leukemia, Leukemia 26 (5) (2012) 910–917.
[53] A.D. Joshi, et al., Histone deacetylase inhibitors prevent pulmonary endothelial hyperpermeability and acute lung injury by regulating heat shock protein 90 function, Am. J. Physiol. Lung Cell Mol. Physiol. 309 (12) (2015) L1410–L1419.
[54] T. Liu, et al., NF-kappaB signaling in inflammation, Signal Transduct. Target. Ther. 2 (2017).
[55] B.J. Aubrey, et al., How does p53 induce apoptosis and how does this relate to p53-mediated tumour suppression? Cell Death Differ. 25 (1) (2018) 104–113.
[56] W.C. Huang, et al., Phosphorylation of CBP by IKKalpha promotes cell growth by switching the binding preference of CBP from p53 to NF-kappaB, Mol. Cell 26 (1) (2007) 75–87.
[57] I. Uehara, N. Tanaka, Role of p53 in the regulation of the inflammatory tumor microenvironment and tumor suppression, Cancers (Basel) 10 (7) (2018).
[58] G. Liu, et al., p53 attenuates lipopolysaccharide-induced NF-kappaB activation and acute lung injury, J. Immunol. 182 (8) (2009) 5063–5071.
[59] M.A. Uddin, K.T. Kubra, N. Barabutis, P53 deficiency potentiates LPS-Induced acute lung injury in vivo, Current Research in Physiology 3 (2020) 30–33.
[60] M.S. Akhter, M.A. Uddin, N. Barabutis, Unfolded protein response regulates P53 expression in the pulmonary endothelium, J. Biochem. Mol. Toxicol. 33 (10) (2019) e22380.
[61] N. Barabutis, et al., Wild-type p53 enhances endothelial barrier function by mediating RAC1 signalling and RhoA inhibition, J. Cell. Mol. Med. 22 (3) (2018) 1792–1804.
[62] M.A. Uddin, et al., P53 supports endothelial barrier function via APE1/Ref1 suppression, Immunobiology 224 (4) (2019) 532–538.
[63] M.S. Akhter, et al., P53-induced reduction of lipid peroxidation supports brain microvascular endothelium integrity, J. Pharmacol. Sci. 141 (1) (2019) 83–85.
[64] M.S. Akhter, M.A. Uddin, N. Barabutis, P53 regulates the redox status of lung endothelial cells, Inflammation 43 (2) (2020) 686–691.
[65] Z. Chen, et al., Costunolide ameliorates lipoteichoic acid-induced acute lung injury via attenuating MAPK signaling pathway, Int. Immunopharmacol. 61 (2018) 283–289.
[66] K.T. Kubra, et al., P53 is subjected to lipoteichoic acid-induced phosphorylation in the lungs, TH Open (2020).
[67] K.T. Kubra, et al., Unfolded protein response in cardiovascular disease, Cell. Signal. 73 (2020) 109699.
[68] N. Barabutis, Unfolded protein response in lung health and disease, Front. Med. (Lausanne) (2020).
[69] N. Barabutis, et al., GHRH antagonists protect against hydrogen peroxide-induced breakdown of brain microvascular endothelium integrity, Horm. Metab. Res. 52 (5) (2020) 336–339.
[70] K.T. Kubra, et al., Hsp90 inhibitors induce the unfolded protein response in bovine and mice lung cells, Cell. Signal. 67 (2020) 109500.
[71] M.A. Uddin, K.T. Kubra, J.J. Sonju, M.S. Akhter, S. Jois, N. Barabutis, Effects of heat shock protein 90 inhibition in the lungs, Medicine in Drug Discovery 6 (2020).
[72] S. Johnson, et al., Radiation induced apoptosis and pulmonary fibrosis: curcumin an effective intervention? Int. J. Radiat. Biol. (2020) 1–9.
[73] R.L. Kusko, et al., Integrated genomics reveals convergent transcriptomic networks underlying chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis, Am. J. Respir. Crit. Care Med. 194 (8) (2016) 948–960.
[74] S. Ghosh, et al., Bleomycin sensitivity of mice expressing dominant-negative p53 in the lung epithelium, Am. J. Respir. Crit. Care Med. 166 (6) (2002) 890–897.
[75] X. Tang, et al., p53 peptide prevents LITAF-induced TNF-alpha-mediated mouse lung lesions and endotoxic shock, Curr. Mol. Med. 11 (6) (2011) 439–452.

[76] S.K. Shetty, et al., p53 and miR-34a feedback promotes lung epithelial injury and pulmonary fibrosis, Am. J. Pathol. 187 (5) (2017) 1016–1034.
[77] Y. Geng, et al., PD-L1 on invasive fibroblasts drives fibrosis in a humanized model of idiopathic pulmonary fibrosis, JCI Insight 4 (6) (2019).
[78] X. Tang, et al., p53 is an important regulator of CCL2 gene expression, Curr. Mol. Med. 12 (8) (2012) 929–943.
[79] H.J. Jin, et al., Senescence-associated MCP-1 secretion is dependent on a decline in BMI1 in human mesenchymal stromal cells, Antioxid. Redox Signal. 24 (9) (2016) 471–485.
[80] H. Liu, et al., Macrophage-derived MCPIP1 mediates silica-induced pulmonary fibrosis via autophagy, Part. Fibre Toxicol. 13 (1) (2016) 55.
[81] C.H. Canan, et al., Characterization of lung inflammation and its impact on macrophage function in aging, J. Leukoc. Biol. 96 (3) (2014) 473–480.
[82] B.R. Grubb, et al., Reduced mucociliary clearance in old mice is associated with a decrease in Muc5b mucin, Am. J. Physiol. Lung Cell Mol. Physiol. 310 (9) (2016) L860–7.
[83] S.J. Snow, et al., Age-related differences in pulmonary effects of acute and subchronic episodic ozone exposures in Brown Norway rats, Inhal. Toxicol. 28 (7) (2016) 313–323.
[84] K. Subramaniam, H. Kumar, M.H. Tawhai, Evidence for age-dependent air-space enlargement contributing to loss of lung tissue elastic recoil pressure and increased shear modulus in older age, J. Appl. Physiol. 123 (1) (2017) 79–87, 1985.
[85] P. Janesch, et al., Age-related changes in the levels and kinetics of pulmonary cytokine and chemokine responses to Streptococcuspneumoniae in mouse pneumonia models, Cytokine 111 (2018) 389–397.
[86] D. Sicard, et al., Aging and anatomical variations in lung tissue stiffness, Am. J. Physiol. Lung Cell Mol. Physiol. 314 (6) (2018) L946–L955.
[87] S.H. van Oostrom, et al., Aging-related trajectories of lung function in the general population-The Doetinchem Cohort Study, PLoS One 13 (5) (2018) e0197250.
[88] A. Mammoto, M. Muyleart, T. Mammoto, LRP5 in age-related changes in vascular and alveolar morphogenesis in the lung, Aging (Albany NY) 11 (1) (2019) 89–103.
[89] X. Chen, et al., Epithelial cell senescence induces pulmonary fibrosis through Nanog-mediated fibroblast activation, Aging (Albany NY) 12 (1) (2019) 242–259.
[90] C. Jiang, et al., Serpine 1 induces alveolar type II cell senescence through activating p53-p21-Rb pathway in fibrotic lung disease, Aging Cell 16 (5) (2017) 1114–1124.
[91] S.D. Pouwels, et al., Susceptibility for cigarette smoke-induced DAMP release and DAMP-induced inflammation in COPD, Am. J. Physiol. Lung Cell Mol. Physiol. 311 (5) (2016) L881–L892.
[92] Y. Chi, et al., Mir-29b mediates the regulation of Nrf2 on airway epithelial remodeling and Th1/Th2 differentiation in COPD rats, Saudi J. Biol. Sci. 26 (8) (2019) 1915–1921.
[93] B. He, et al., Melatonin protects against COPD by attenuating apoptosis and endoplasmic reticulum stress via upregulating SIRT1 expression in rats, Can. J. Physiol. Pharmacol. 97 (5) (2019) 386–391.
[94] Z.H. Zheng, et al., Upregulation of miR-675-5p induced by lncRNA H19 was associated with tumor progression and development by targeting tumor suppressor p53 in non-small cell lung cancer, J. Cell. Biochem. 120 (11) (2019) 18724–18735.
[95] H. Yang, et al., Acetylation of HDAC1 and degradation of SIRT1 form a positive feedback loop to regulate p53 acetylation during heat-shock stress, Cell Death Dis. 6 (2015) e1747.
[96] A.R. Gomes, et al., Sirtuin1 (SIRT1) in the acetylation of downstream target proteins, Methods Mol. Biol. 1436 (2016) 169–188.
[97] M. Suzuki, A. Ikeda, J.D. Bartlett, Sirt1 overexpression suppresses fluoride-induced p53 acetylation to alleviate fluoride toxicity in ameloblasts responsible for enamel formation, Arch. Toxicol. 92 (3) (2018) 1283–1293.
[98] C. Gu, et al., Sirtuin 1 activator SRT1720 protects against lung injury via reduction of type II alveolar epithelial cells apoptosis in emphysema, COPD 12 (4) (2015) 444–452.
[99] H. Li, et al., Quercetin is the active component of Yang-Yin-Qing-Fei-Tang to induce apoptosis in non-small cell lung Cancer, Am J Chin Med 47 (4) (2019) 879–893.
[100] A. Sagiv, et al., p53 in bronchial club cells facilitates chronic lung inflammation by promoting senescence, Cell Rep. 22 (13) (2018) 3468–3479.
[101] M.M. Gouda, et al., Changes in the expression level of IL-17A and p53-fibrinolytic system in smokers with or without COPD, Mol. Biol. Rep. 45 (6) (2018) 2835–2841.
[102] S. Mizuno, et al., p53 signaling pathway polymorphisms associated with emphysematous changes in patients with COPD, Chest 152 (1) (2017) 58–69.
[103] S. Chrusciel, et al., Lack of transcription factor p53 exacerbates elastase-induced emphysema in mice, Am. J. Respir. Cell Mol. Biol. 54 (2) (2016) 188–199.
[104] F. Xu, et al., PM2.5 exposure induces alveolar epithelial cell apoptosis and causes emphysema through p53/Siva-1, Eur. Rev. Med. Pharmacol. Sci. 24 (7) (2020) 3943–3950.
[105] Y.H. Kim, et al., Dried yeast extracts curtails pulmonary oxidative stress, inflammation and tissue destruction in a model of experimental emphysema, Antioxidants Basel (Basel) 8 (9) (2019).
[106] N. Galie, et al., 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT), Eur. Heart J. 37 (1) (2016) 67–119.
[107] J.W. Barnes, et al., O-GlcNAc transferase regulates angiogenesis in idiopathic pulmonary arterial hypertension, Int. J. Mol. Sci. 20 (24) (2019).
[108] Z. Wang, et al., Divergent changes of p53 in pulmonary arterial endothelial and smooth muscle cells involved in the development of pulmonary hypertension, Am. J. Physiol. Lung Cell Mol. Physiol. 316 (1) (2019) L216–L228.
[109] X. He, et al., Hypoxia selectively upregulates cation channels and increases cytosolic [Ca(2+)] in pulmonary, but not coronary, arterial smooth muscle cells, Am. J. Physiol., Cell Physiol. 314 (4) (2018) C504–C517.
[110] M.K. Ball, et al., Regulation of hypoxia-induced pulmonary hypertension by vascular smooth muscle hypoxia-inducible factor-1alpha, Am. J. Respir. Crit. Care Med. 189 (3) (2014) 314–324.
[111] I. Fijalkowska, et al., Hypoxia inducible-factor1alpha regulates the metabolic shift of pulmonary hypertensive endothelial cells, Am. J. Pathol. 176 (3) (2010) 1130–1138.
[112] Z. Deng, et al., Familial primary pulmonary hypertension (gene PPH1) is caused by mutations in the bone morphogenetic protein receptor-II gene, Am. J. Hum. Genet. 67 (3) (2000) 737–744.
[113] P.P.H.C. International, et al., Heterozygous germline mutations in BMPR2, encoding a TGF-beta receptor, cause familial primary pulmonary hypertension, Nat. Genet. 26 (1) (2000) 81–84.
[114] I. Diebold, et al., BMPR2 preserves mitochondrial function and DNA during reoxygenation to promote endothelial cell survival and reverse pulmonary hypertension, Cell Metab. 21 (4) (2015) 596–608.
[115] N.V. Guevara, et al., The absence of p53 accelerates atherosclerosis by increasing cell proliferation in vivo, Nat. Med. 5 (3) (1999) 335–339.
[116] R.Y. Cao, et al., Effects of p53-knockout in vascular smooth muscle cells on atherosclerosis in mice, PLoS One 12 (3) (2017) e0175061.
[117] Z. Sun, et al., Long non-coding RNA MEG3 downregulation triggers human pulmonary artery smooth muscle cell proliferation and migration via the p53 signaling pathway, Cell. Physiol. Biochem. 42 (6) (2017) 2569–2581.
[118] Y. Liu, et al., Baicalin inhibits proliferation and promotes apoptosis of vascular smooth muscle cells by regulating the MEG3/p53 pathway following treatment with oxLDL, Int. J. Mol. Med. 43 (2) (2019) 901–913.
[119] S. Mukhopadhyay, et al., Myeloid p53 regulates macrophage polarization and venous thrombus resolution by inflammatory vascular remodeling in mice, Blood 129 (24) (2017) 3245–3255.
[120] A. Papi, et al., Asthma, Lancet 391 (10122) (2018) 783–800.
[121] I. Mahmutovic Persson, et al., IL-1beta mediates lung neutrophilia and IL-33 expression in a mouse model of viral-induced asthma exacerbation, Respir. Res. 19 (1) (2018) 16.
[122] M.D. Wellenstein, et al., Loss of p53 triggers WNT-dependent systemic inflammation to drive breast cancer metastasis, Nature 572 (7770) (2019) 538–542.
[123] V. Ubertini, et al., Mutant p53 gains new function in promoting inflammatory signals by repression of the secreted interleukin-1 receptor antagonist, Oncogene 34 (19) (2015) 2493–2504.
[124] G. Geng, et al., KIF3A knockdown sensitizes bronchial epithelia to apoptosis and aggravates airway inflammation in asthma, Biomed. Pharmacother. 97 (2018) 1349–1355.
[125] S. Isik, et al., Sinomenine ameliorates the airway remodelling, apoptosis of airway epithelial cells, and Th2 immune response in a murine model of chronic asthma, Allergol. Immunopathol. (Madr) 46 (1) (2018) 67–75.
[126] E. Ermakova, et al., Lactose binding to human galectin-7 (p53-induced gene 1) induces long-range effects through the protein resulting in increased dimer stability and evidence for positive cooperativity, Glycobiology 23 (5) (2013) 508–523.
[127] J. Tian, et al., Galectin-7 overexpression destroy airway epithelial barrier in transgenic mice, Integr. Zool. (2020).
[128] X. Sun, W. Zhang, Silencing of Gal-7 inhibits TGF-beta1-induced apoptosis of human airway epithelial cells through JNK signaling pathway, Exp. Cell Res. 375 (2) (2019) 100–105.
[129] K. Beyfuss, et al., The role of p53 in determining mitochondrial adaptations to endurance training in skeletal muscle, Sci. Rep. 8 (1) (2018) 14710.
[130] Y.Y. Lee, et al., Mitochondrial nucleoid remodeling and biogenesis are regulated by the p53-p21(WAF1)-PKCzeta pathway in p16(INK4a)-silenced cells, Aging (Albany NY) 12 (8) (2020) 6700–6732.
[131] T. Trian, et al., Selective dysfunction of p53 for mitochondrial biogenesis induces cellular proliferation in bronchial smooth muscle from asthmatic patients, J. Allergy Clin. Immunol. 137 (6) (2016) 1717–1726, e13.
[132] L. Yuan, et al., ITGB4 deficiency induces senescence of airway epithelial cells through p53 activation, FEBS J. 286 (6) (2019) 1191–1203.
[133] P. Wang, et al., Phosphatase wild-type p53-induced phosphatase 1 controls the development of TH9 cells and allergic airway inflammation, J. Allergy Clin. Immunol. 141 (6) (2018) 2168–2181.
[134] J. Shloush, et al., Structural and functional comparison of the RING domains of two p53 E3 ligases, Mdm2 and Pirh2, J. Biol. Chem. 286 (6) (2011) 4796–4808.
[135] Y. Ma-Lauer, et al., p53 down-regulates SARS coronavirus replication and is targeted by the SARS-unique domain and PLpro via E3 ubiquitin ligase RCHY1, Proc Natl Acad Sci U S A 113 (35) (2016) E5192–201.
[136] N. Singh, A. Bharara Singh, S2 subunit of SARS-nCoV-2 interacts with tumor suppressor protein p53 and BRCA: an in silico study, Transl. Oncol. 13 (10) (2020) 100814.
[137] Z. Hao, et al., Tumor suppressor p53 inhibits porcine epidemic diarrhea virus infection via interferon-mediated antiviral immunity, Mol. Immunol. 108 (2019) 68–74.

[138] X. Deng, et al., Analysis of coronavirus temperature-sensitive mutants reveals an interplay between the macrodomain and papain-like protease impacting replication and pathogenesis, J. Virol. 93 (12) (2019).
[139] X. Deng, et al., Structure-guided mutagenesis alters deubiquitinating activity and attenuates pathogenesis of a murine coronavirus, J. Virol. 94 (11) (2020).
[140] L. Wang, W. Hu, C. Fan, Structural and biochemical characterization of SADS-CoV papain-like protease 2, Protein Sci. 29 (5) (2020) 1228–1241.
[141] L. Yuan, et al., p53 degradation by a coronavirus papain-like protease suppresses type I interferon signaling, J. Biol. Chem. 290 (5) (2015) 3172–3182.
[142] C.D. Wiley, et al., Small-molecule MDM2 antagonists attenuate the senescence-associated secretory phenotype, Sci. Rep. 8 (1) (2018) 2410.
[143] C. Huang, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506.
[144] Q. Ye, B. Wang, J. Mao, The pathogenesis and treatment of the `Cytokine Storm' in COVID-19, J. Infect. 80 (6) (2020) 607–613.
[145] Z. Zhu, et al., Type I interferon-mediated immune response against influenza A virus is attenuated in the absence of p53, Biochem. Biophys. Res. Commun. 454 (1) (2014) 189–195.
[146] H.H. Feng, et al., Foot-and-mouth disease virus induces lysosomal degradation of NME1 to impair p53-regulated interferon-inducible antiviral genes expression, Cell Death Dis. 9 (9) (2018) 885.
[147] S. Smith, et al., MicroRNA-302d targets IRF9 to regulate the IFN-induced gene expression in SLE, J. Autoimmun. 79 (2017) 105–111.
[148] D. Menendez, et al., Ligand dependent restoration of human TLR3 signaling and death in p53 mutant cells, Oncotarget 7 (38) (2016) 61630–61642.
[149] S.M. Dong, et al., Hypermethylation of the interferon regulatory factor 5 promoter in Epstein-Barr virus-associated gastric carcinoma, J. Microbiol. 53 (1) (2015) 70–76.
[150] C. Munoz-Fontela, et al., p53 serves as a host antiviral factor that enhances innate and adaptive immune responses to influenza A virus, J. Immunol. 187 (12) (2011) 6428–6436.
[151] J.H. Madenspacher, et al., p53 integrates host defense and cell fate during bacterial pneumonia, J. Exp. Med. 210 (5) (2013) 891–904.
[152] A. Andrey, V.A. Khadartsevb, S.S. Bondarb, T.V. Nikiforovc IV, The state of intracellular molecular regulators during the reconvalescence of community-acquired pneumonia under the influence of microwaves at 1 GHz, Integr. Med. Int. 4 (2017) 171–180.
[153] B. Puthusseri, et al., Regulation of p53-mediated changes in the uPA-fibrinolytic system and in lung injury by loss of surfactant protein C expression in alveolar epithelial cells, Am. J. Physiol. Lung Cell Mol. Physiol. 312 (6) (2017) L783–L796.
[154] D.J. Groskreutz, et al., Respiratory syncytial virus decreases p53 protein to prolong survival of airway epithelial cells, J. Immunol. 179 (5) (2007) 2741–2747.
[155] D. Machado, et al., Role of p53/NF-kappaB functional balance in respiratory syncytial virus-induced inflammation response, J. Gen. Virol. 99 (4) (2018) 489–500.
[156] D. Menendez, et al., p53-responsive TLR8 SNP enhances human innate immune response to respiratory syncytial virus, J. Clin. Invest. 129 (11) (2019) 4875–4884.
[157] W.M. Soh, M.L. Yeong, K.P. Wong, Malignant granular cell tumour of the mediastinum, Malays. J. Pathol. 36 (2) (2014) 149–151.
[158] R. Biaoxue, et al., Evaluation of efficacy and safety for recombinant human adenovirus-p53 in the control of the malignant pleural effusions via thoracic perfusion, Sci. Rep. 6 (2016) 39355.
[159] K.L. Li, et al., Efficacy of recombinant adenoviral human p53 gene in the treatment of lung cancer-mediated pleural effusion, Oncol. Lett. 9 (5) (2015) 2193–2198.
[160] M.A. Bonelli, et al., Combined inhibition of CDK4/6 and PI3K/AKT/mTOR pathways induces a synergistic anti-tumor effect in malignant pleural mesothelioma cells, Neoplasia 19 (8) (2017) 637–648.
[161] Z.J. Zhao, et al., Expression, correlation, and prognostic value of TRAF2 and TRAF4 expression in malignant plural effusion cells in human breast cancer, Diagn. Cytopathol. 43 (11) (2015) 897–903.
[162] M. Wei, et al., Pneumonia caused by Mycobacterium tuberculosis, Microbes Infect. (2020).
[163] Y.J. Lim, et al., M1 macrophage dependent-p53 regulates the intracellular survival of mycobacteria, Apoptosis 25 (1-2) (2020) 42–55.
[164] L. Fan, et al., MptpB promotes mycobacteria survival by inhibiting the expression of inflammatory mediators and cell apoptosis in macrophages, Front. Cell. Infect. Microbiol. 8 (2018) 171.
[165] S. Liang, et al., MicroRNA-27b modulates inflammatory response and apoptosis during Mycobacterium tuberculosis infection, J. Immunol. 200 (10) (2018) 3506–3518.
[166] N. Alaridah, et al., Mycobacteria manipulate G-Protein-Coupled receptors to increase mucosal Rac1 expression in the lungs, J. Innate Immun. 9 (3) (2017) 318–329.
[167] M. van der Vaart, et al., The DNA damage-regulated autophagy modulator DRAM1 links mycobacterial recognition via TLR-MYD88 to autophagic defense [corrected], Cell Host Microbe 15 (6) (2014) 753–767.
[168] S. Holla, et al., Mycobacterium bovis BCG promotes tumor cell survival from tumor necrosis factor-alpha-induced apoptosis, Mol. Cancer 13 (2014) 210.
[169] D.A. Il'in, S.A. Arkhipov, V.A. Shkurupy, In vitro study of cytophysiological characteristics of multinuclear macrophages from intact and BCG-Infected mice, Bull. Exp. Biol. Med. 160 (5) (2016) 668–671.
[170] A. Cruz, et al., IL-17A promotes intracellular growth of Mycobacterium by inhibiting apoptosis of infected macrophages, Front. Immunol. 6 (2015) 498.
[171] E.D. Bazhanova, D.S. Sukhanov, D.L. Teplyi, Pathways of apoptosis regulation in hepatocytes induced by first-line antitubercular drugs, Bull. Exp. Biol. Med. 158 (5) (2015) 650–653.
[172] C.L. Kao, et al., Ethanolic extracts of Pluchea indica induce apoptosis and antiproliferation effects in human nasopharyngeal carcinoma cells, Molecules 20 (6) (2015) 11508–11523.
[173] N. Barabutis, Regulation of lung endothelial permeability by NEK kinases, IUBMB Life 72 (4) (2020) 801–804.
[174] M.S. Akhter, et al., *Kifunensine compromises lung endothelial barrier function*, Microvasc. Res. (2020) 104051.
[175] N. Barabutis, Heat shock protein 90 inhibition in the inflamed lungs, Cell Stress Chaperones 25 (2) (2020) 195–197.
[176] N. Barabutis, A glimpse at growth hormone-releasing hormone cosmos, Clin. Exp. Pharmacol. Physiol. 47 (9) (2020) 1632–1634.
[177] N. Barabutis, A. Siejka, The highly interrelated GHRH, p53, and Hsp90 universe, Cell Biol. Int. 44 (8) (2020) 1558–1563.
[178] N. Barabutis, P53 in lung vascular barrier dysfunction, Vasc Biol 2 (1) (2020) E1–E2.