CLINICAL-MORPHOLOGICAL STUDY OF LUNG DISEASES IN BASIC TREATMENT WITH THE USE OF ANTIOXIDANTS OF DIFFERENT ORIGIN AND WITHOUT

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Annotation. The purpose of the work is to analyze contemporary views on the morphological changes of lung tissue in inflammatory disease in the clinical and experimental conditions and results of correction by using the antioxidants. The analysis is based in a review if foreign articles for 2014-2019, using the scientometric databases PubMed, Web of Science and Google Scholar. According to the latest data from WHO and WORLD HEALTH RANKINGS 5-year mortality rate of such disease as COPD typically ranges from 40% to 70%, depending on disease severity, while the 2-year mortality rate for people with severe COPD is about 50%. We know that almost 90% of COPD deaths occur in low- and middle-income countries such as Ukraine. Thereby mortality rate from lung tissue diseases in Ukraine is 11.11%. These diseases often accompanied by inflammation and oxidative stress. The last can cause mitochondrial dysfunction, dynamic changes and mitophagy impairment, which leads to increase the number of superoxide anions, hydrogen peroxide etc., inflammatory responses and cellular senescence. They all play important roles in the pathogenesis of chronic lung diseases, such as chronic obstructive pulmonary disease, pulmonary fibrosis and bronchopulmonary dysplasia. Many studies in vitro approved the role of antioxidants in the decreasing of the degree of morphological changes: inflammatory cells infiltration and alveolar edema, permeability and inflammation. In vivo disease development is mainly related to the many conditions, but closely to its severity and possible combination with other diseases. Thereby treatment of such diseases by using e.g. leaves extract of different herbs can be prescribe to ameliorate the level of reactive oxygen species and decrease the possible cell injure made by anti-inflammatory medicines.

Keywords: reactive oxygen species, antioxidants, acute lung injury.
combination with an mtROS scavenger [1, 34]. Indeed, the levels of Parkin are reduced in lung tissues of COPD patients compared with those of non-smokers and smokers [1, 12, 34], which further confirms the impairment of mitophagy in COPD. Other authors admitted that severe stress derived from high concentrations of cigarette smoke induces necroptosis (i.e. necrosis and apoptosis), which is mediated by PINK1-induced mitophagy [20, 34]. To attenuate the changes of lung tissue after impact of cigarettes smoke and decrease the oxidative stress Ahmad Husari and co-authors (2016) used supplementation of pomegranate juice (PJ) [11]. One month of sublimation of PJ resulted in limited destruction of the normal alveolar architecture and decreased level of TNF-α; third month of sublimation reversed the emphysemaus changes noted histologically and attenuated the increase in linear intercept distance [11]. The in vitro study showed that PJ supplementation significantly suppressed CS-induced reactive oxygen species (ROS) [11]. Another study admitted the role of Atorvastatin and Simvastatin in enhancing mouse lung repair after CS induced lung tissue injury. Pinho-Ribeiro V. and co-authors observed that morphologically changes of lung tissue and noted the same pattern of total cell numbers was observed in macrophages, but not in neutrophils, which were higher in CS [25].

Mechanical ventilation (MV) as a method of breath support in COPD closely involved in developing ventilator-induced lung injury (VILI). Last is characterized by a disruption of the alveolar-capillary barrier which increases permeability, thus causing edema, inflammatory leukocyte infiltration (mainly neutrophils), and hemorrhage [30]. As follows, the correction of ROS and mtROS level in COPD opens the new ways of increasing patient's life level. Bixin induces the expression of nuclear factor-erythroid-related factor 2 (NRF2) and its downstream targets in lung tissues of Nrf2+/+ mice. More importantly, bixin pretreatment restored normal lung morphology and alleviated MV-induced inflammation and oxidative stress, these effects seem to be dependent on NFRF2 signaling since Nrf2−/− mice did not benefit from bixin pretreatment [30]. Although the use of direct antioxidants, like N-acetyl cysteine (NAC), has some degree of beneficial effects but Shasha Tao and co-authors suggested that activating the body's own defensive responses through upregulation of the NRF2 pathway in combination with low tidal ventilator strategies will result in greater benefits for the patients [30, 23]. Another histological study revealed that inflammatory cells infiltration and alveolar edema, permeability and inflammation induced by ventilation were significantly severe in VILI as compared to other groups treated by curcumin. In addition, curcumin ameliorates level of tumor necrosis factor (TNF)-α and NF-κB activity which were significantly increased in VILI group [31]. Mairead Hayes and co-authors observed that human mesenchymal stem cells (hMSCs) improved lung compliance, reducing alveolar edema, and restoring lung architecture. hMSCs attenuated lung inflammation, decreasing alveolar cellular infiltration, and decreasing cytokine-induced neutrophil chemoattractant-1 and interleukin-6 while increasing keratinocyte growth factor concentrations, as result level of ROS and mtROS [10].

The outcome of progressing of chronic inflammation of lung tissue, excessive number of mesenchymal cells near inflammatory area, dysfunction of cells will lead to excessive accumulation of macromolecules in extracellular matrix, thereby cause the scar and loss of elasticity in lungs. Both fibroblasts and myofibroblasts are the principal effectors cells of the lung for the generation of extracellular matrix [33]. M. Bueno and co-authors (2015) have highlighted the importance of mitochondrial function and mitophagy in the pathogenesis of lung fibrosis. It has been shown that damaged or dysfunctional mitochondria accumulate in alveolar epithelial cells of patients with idiopathic pulmonary fibrosis [5]. However, it is not clear whether mitochondrial dysfunction and mitophagy impairment occur in (myo) fibroblasts during pulmonary fibrosis. Also further studies are required to determine how mitochondrial dysfunction in lung epithelial cells interacts with (myo)fibroblasts, leading to fibrogenesis [34]. It has been shown that once released mtDNA recruits peripheral blood mononuclear cells and stimulates epithelial cells to generate TGF-β1 [16]. Targeting mtDNA by DNase I protects against paraquat-induced pulmonary fibrosis [16]. Interestingly, TGF-β1 increases the number of mitochondria, mitochondria-specific proteins, voltage-dependent anion channels, adenine nucleotide transporter and mtDNA content, whereas mitochondrial oxidative phosphorylation and mitophagy are impaired during fibroblast differentiation [21, 27, 34]. Authors proposed that mitochondrial biogenesis is needed for fibroblast differentiation that this effect is further promoted by mitophagy impairment and damaged mitochondria during fibrogenesis. However, it is not clear how TGF-β1 alters mitochondrial homeostasis, inducing the accumulation of damaged mitochondria and subsequent fibrogenesis [34]. M. Bueno et al. (2015) and M. L. Susulski et al. (2015) admitted in relation aging in developing lung fibrosis. They has shown that it participate in the pathogenesis of lung fibrosis as both mitochondria respiration and mitophagy are compromised in aging, whereas the levels of the mitochondrial biogenesis marker PGC1α, mitochondrial transcription factor A TFAM and mitochondrial gene cytochrome c are comparable between young and old mouse lungs [5, 27, 34].

Reducing the effects of increased production of oxidative stress components that enhance the development of pulmonary fibrosis remains it is actuality. The treatment of Phyllanthus emblica leaves (PELE) to CC14 exposed rat demonstrated strong repairing ability as manifested by the elevation in activity level of catalase, superoxide dismutase, glutathione peroxidase and GSH in the pulmonary samples of rat. PELE was also able to ameliorate the oxidative injuries induced with CC14 and decreased the elevated level of TBARS, H2O2 and nitric oxide in lung samples of rat. The repairing abilities of PELE on the histopathology of...
lungs showed normal alveoli with explicit alveolar spaces and bronchioles having slight cell degeneration, intraalveolar septa thickening were observed in most lung regions [29].

In the modeling experimental condition that will cause the development of pulmonary fibrosis mainly associated with bleomycin. It was found that Nrf2 and its downstream antioxidant factors are involved in the pathogenesis of IPF [18, 26]. Nrf2 agonist attenuated pulmonary fibrosis induced by bleomycin (BLM) via the oxide level in lung tissue [15]. Y. Liu and co-authors (2017) demonstrated that Bach1 knockout inhibited the progression of BLM-induced pulmonary fibrosis by regulating the expressions of Nrf2 and its downstream anti-oxidant factors [17]. The changes in lung tissue induced by bleomycin characterized by alveolar edema, a significant increase in septum width and increased inflammatory cells infiltration on 14 days and the alveolus collapsed or disappeared, the structure was markedly damaged, and a large number of inflammatory cells and fibroblasts were infiltrated on 42 days respectively. Administration of pirfenidone (PED) for 4 weeks ameliorated the inflammatory infiltration, the damaged structure in lung tissue and fibrosis as compared to that of the BLM group [18]. Other study demonstrated that celestrol also reduces inflammation in BLM-induced rats as evidenced by decrease in the expressions of mast cells, Tumor necrosis factor-alpha (TNF-α) and matrix metalloproteinases (MMPs) 2 and 9 [7]. O. Khazri and co-authors (2016) admitted the role of grape seed and skin extract properties that could find potential application in the protection against bleomycin-induced lung fibrosis [14].

Another experimental model that initiate fibrosis close linked to lipopolysaccharide (LPS). Toshio Suzuki and co-authors (2017) presented hypothesis in which that stated that LPS exposure leads to pulmonary fibrosis via endothelial-to-mesenchymal transition (EndMT). Given that one of the main initial targets of endotoxins is vascular endothelial cells especially in case of acute respiratory distress syndrome from extra-pulmonary origin [6, 22, 28]. EndMT could thus be closely involved in the pathogenesis of pulmonary fibrosis after systemic endotoxic injury [28]. Morphological examination following LPS induction revealed that several histopathological alterations, including cell structure destruction, neutrophil infiltration, alveolar wall thickening and lung edema, had occurred in the lung tissue [35]. The development of morphological changes may be diminished if antioxidants are used. G.F. Zhu and co-authors (2015) provided in vitro regular LPS induction, a significant increase was observed in the myeloperoxidase (MPO) activity and the number of neutrophils in the lung tissues, compared with the phosphate buffered saline-treated (PBS) healthy control group [35]. Toshio Suzuki and co-authors (2017) in vitro showed that in model of pulmonary fibrosis after systemic endotoxic injury, CD26/dipeptidyl peptidase 4 (DPP-4) expressions is upregulated in pulmonary vascular endothelial cells (PVECs) in both the presence and absence of immune cells. Vildagliptin treatment attenuated the accumulation of DPP-4 in PVECs, and was associated with an inhibition of fibrotic change and reduced EndMT-cells in lungs. It can be result of direct action of DPP-4 inhibitors on ROS production in PVECs and attenuating EndMT [30]. Also increase in MPO activity and neutrophils was eliminated by the eriodictol pretreatment, as compared with the LPS-induced ALI [35].

In other study Naif O. Al-Harbi and co-authors (2015) discovered the role of riboflavin in comparing to dexamethasone as a method of attenuation lipopolysaccharide-induced lung injury. Cellular LPS-induced changes including interstitial edema, hemorrhage, infiltration of PMNs, etc., which were reversed by riboflavin (100 mg/kg, p.o.) administration, which showed similar protective effects as dexamethasone (1 mg/kg, p.o.) [2].

C. Luo and co-authors (2015) evaluated the role of intestinal ischemia-reperfusion (IIR) that can resulted in severe damage to the lungs, with collapse of the alveoli, interstitial edema, haemorrhage in the alveoli and mesenchyme, neutrophil infiltration and atelectasis. But they discovered that pretreatment with sevoflurane SEV and apocynin (AP) significantly prevented the lung damage induced by IIR in the way of: protecting type II alveolar epithelial cells from the injury induced by IIR and mast cell degranulation, inhibiting inflammatory responses and decreasing the level of ROS [19].

Conclusions and prospects for future development

1. Overall we can state the widespread prevalence of pulmonary tissue diseases and their possible complications caused by oxidative stress and inflammation most studies in vitro approved the role of antioxidants in the decreasing of the degree of morphological changes: inflammatory cells infiltration and alveolar edema, permeability and inflammation. In vivo the role of antioxidants, compared to anti-inflammatory medicines have the same results and can be prescribe to the patients to ameliorate the pathogonomic signs or prevent them. Therefore importance of including in treatment of these diseases antioxidants remains an important recommendation.

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КЛІНИКО-МОРФОЛОГІЧНЕ ДОСЛІДЖЕННЯ ЛЕГЕНЕВИХ ЗАБОЛЕВАНЬ НАКРИВИСТАНЬ ТА БЕЗ НИХ
Король Т.М., Агафонов К.М.

Анотація. Мета роботи - аналіз сучасних поглядів на морфологічні зміни легеневої тканини при запальних захворюваннях у клінічних та експериментальних умовах і результати їх корекції за допомогою антиоксидантів. Королюється на основі зарубіжних статей за 2014-2019 роки з використанням наукометричних баз даних PubMed, Web of Science та Google Scholar. Відповідно до останніх даних ВОЗ та WORLD HEALTH RANKINGS 5-річна смертність від такої хвороби як хронічний обструктивний астматичний бронхіт, залежить від ступеня тяжкості захворювання, тоді як 2-річний рівень смертності для людей із важкою формою ХОЗЛ становить близько 50%. Відомо, що майже 90% смертей від ХОЗЛ припадає на країни з низьким та середнім рівнем доходу, до яких відносять і Україну. Рівень смертності від запальних захворювань легеневої тканини в Україні становить 11,11%. Це захворювання часто супроводжаються запальними і окислово-нітратними стисками. Останні може спричинити дисфункцію мітохондрій, динамічні зміни та порушення мітофаґії, що призводить до збільшення кількості супероксидних аніонів, перекису водню, залежно від запального реакцій та клітинного старіння. Все вони відіграють важливу роль у патогенезі хронічних захворювань легеневих органів, таких як ХОЗЛ, легеневий фіброз та бронхолегенева дисплазія. Багато досліджень in vitro підтвердило роль антиоксидантів у запобіганні запальним шляхам і патогенезі інфільтрації запального клітинними класами та нейтрофілами. Розвиток хвороби в i vivo в основному пов'язаний з більшістю станих, залежно від їх тяжкості та можливого поєднання з іншими захворюваннями. У лікуванні таких захворювань застосовують, наприклад, екстракт листя різних трав, який містить антиоксидантні речовини, такі як ериодциклоксин, екстракт листя бамбука та інші. Макроскопічна, клініко-трофологічна та іноді історична картина захворювання містить інформацію про тривалий період інтенсивності заболування, що може впливати на ефективність лікувальної тактики.

Ключові слова: реактивні види кисню, антиоксиданти, острі та термінові огляди, запалення локалізоване, окислово-нітратний стрес.

КЛІНИКО-МОРФОЛОГІЧНЕ ІССЛЕДУВАННЯ ЛЕГЕНЬ ЛЕГЕНЬ НАКРИВИСТА НИХ АНТИОКСИДАНТІВ РІЗНОГО ПОХОЖЕННЯ ТА БЕЗ НИХ
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