EDITORIAL

Regulated iron in chronic inflammation disease

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ABSTRACT

Heart Chronic Obstructive Pulmonary Disease (COPD) is characterised by a lack of airflow and persistent respiratory symptoms. The pathogenesis of COPD, on the other hand, is unknown. It is currently understood to include the reduction of alveolar surface area (emphysema) and airway inflammation (bronchitis), both of which are predominantly caused by Cigarette Smoke inhalation (CS). Pneumoemphysema is caused by the loss of epithelial cells caused by CS. CS also causes a buildup of iron in the mitochondria and cytoplasm, which leads to programmed cell death. Despite the fact that apoptosis has long been thought to be the only form of programmed cell death in COPD, mounting evidence suggests that a regulated form of necrosis called necroptosis, as well as a unique iron-dependent form of non-apoptotic cell death called ferroptosis, are involved in the disease's pathogenesis.

Key Words: *Chronic obstructive pulmonary disease; Iron, reactive oxygen species*

INTRODUCTION

As one of the top three causes of death worldwide, chronic obstructive pulmonary disease (COPD) is a sign-ficant economicand social burden. Chronic airflow restriction is caused by a combination of small airway disorders and pulmonary emphysema, which is typically brought on by continuous exposure to unpleasant particles or gases [1]. The most frequent risk factor for COPD is cigarette smoke (CS), with smokers having a higher COPD death rate than non-smokers. More than 4000 components have been found in CS, which leads to an increase in oxidative stress. The particular molecular pathways behind the CS-induced progressive decline of lung function, however, are still unknown.Eukaryotic cells are distinguished by their mitochondria. They're most recognised for their involvement in oxidative phosphorylation, which allows them to produce energy (OXPHOS) [2].

Mitochondria are hotspots of Reactive Oxygen Species (ROS) production and are vital for controlling critical physiological processes such as cell death and inflammation. OXPHOS is made up of an Electron Transport Chain (ETC) that produces ATP by electron transfer and a proton gradient. Mitochondrial reactive oxygen species (mtROS) are produced during OXPHOS and serve as second messengers in physiological situations [3]. Premature leaking of electrons from complexes I, II, and III, resulting in a one-electron reduction of oxygen to superoxide, is the most common mechanism by which ETC produces mtROS.

In apoptosis and necroptosis, outer mitochondrial membrane permeabilization and mitochondrial permeability transition are involved. Previously, apoptosis was thought to be the only type of programmed cell death, while necrosis was thought to be uncontrolled cell death produced by physical or chemical stress. Recent data, however, has revealed the existence of a controlled kind of necrosis known as necroptosis [4]. Necroptosis is defined as necrotic cell death that is mediated by the receptor-interacting protein kinase 3 (RIPK3).

In this review, we look at the growing body of evidence that suggests CS-induced ROS generation and programmed cell death play a role in COPD pathogenesis. Mitochondria are no longer considered basic energy producers. Instead, they're thought to serve as key organelles that control cell death and inflammation. Understanding the influence of these systems on disease development could lead to the discovery of new COPD treatment targets [5]. Several investigations have found that smokers and COPD patients have higher oxidant burdens and, as a result, higher expression of oxidative stress markers in their airspaces, exhaled breath, blood, and urine. The key risk factor for COPD, CS, increases the oxidative burden in the lungs considerably. CS also activates immunological cells (such as macrophages and neutrophils), which produce Reactive Oxygen Species (ROS) and cause systemic inflammation, accelerating the onset and progression of Concomitant Cardiovascular Diseases (CVD). An excess of 1 1015 oxidant molecules is expected to be present in a single puff of CS. Gas-phase smoke makes up 92 percent

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of mainstream CS, while particulate matter (or tar) makes up the remaining 8% [3].

Inhalation of cigarette smoke and the production of reactive oxygen species (ROS) in the lungs

In the pulmonary macrophages of elderly smokers and COPD patients, Nrf2 expression is diminished. Nrf2 deficiency increases susceptibility to CS-induced emphysema. Heme oxygenase-1 (HO-1) is an inducible isoform of heme oxygenase and one of the NRF2-inducible antioxidant enzyme genes that protects the lungs from oxidative and inflammatory attacks.In bronchial epithelial cells, CS increases HO-1 expression by activating Nrf2 [7]. There has also been evidence of increased HO-1 expression in macrophages in smokers' alveolar spaces. Interestingly, HO-1 si RNA increased ROS generation in bronchial epithelial cells produced by CS.

Nicotine is primarily found in the particulate (tar) phase of CS and is used to aid in the cessation of smoking. Nicotine reaches peak levels in the bloodstream quickly after smoking tobacco, stimulating both sympathetic and parasympathetic ganglionic cells. While nicotine addiction is thought to begin with high-affinity nicotine binding to nicotinic acetylcholine receptors (nAChRs) in the brain, nAChR expression in the human airway has been linked to lung function. Through ROS-mediated autophagy impairment, nicotine caused apoptosis and senescence in bronchial epithelial cells. Nicotine did, in fact, cause the human alveolar epithelial cell line A549 to produce mtROS. Nicotine did, in fact, cause the human alveolar epithelial cell line A549 to produce mtROS. In human bronchial epithelial cells, however, discovered that nicotine reduced mitochondrial permeability transition pore opening and eliminated cytochrome c release, indicating that nicotine has a pro-survival effect through inhibiting mitochondria-driven apoptosis. As a result, nicotine may have a direct effect on bronchial epithelial cells; nevertheless, the specific involvement of nicotine in emphysema pathogenesis is unknown. Iron metabolism has recently gotten a lot of press as a possible relationship between CS and mtROS generation. Tobacco contains 440–1150 mg iron per gramme, and only about 0.1 percent of this iron makes its way into mainstream smoke. Some CS ingredients release iron from ferritin, causing oxidative stress in lung cells to be amplified. Furthermore, iron builds up in the lungs of cigarette smokers. In inflated lung sections and whole-lung homogenates, CS-exposed mice had more non-heme iron than mice exposed to room air [6]. The iron-responsive element-binding protein 2 (IRP2) gene has been identified as a key COPD susceptibility gene, and IRP2 protein levels are higher in COPD patients' lungs. The levels of mitochondrial ROS in cells can be dramatically increased by a relatively high dose of iron. In addition to mtROS, CS has been linked to lipid peroxidation [8]. Smokers had higher amounts of F-2-isoprostanes, which are circulating products of lipid peroxidation. Signal transmission that triggers the inflammatory response in the lungs is aided by lipid peroxidation. There is growing evidence that aldehydes, which are produced endogenously during lipid peroxidation, are implicated in a variety of oxidative stress-related pathophysiological processes in cells and tissues. In this regard, lipid peroxidation has recently been shown to have an important role in the pathophysiology of COPD. Furthermore, iron promotes CS-induced lipid peroxidation in pulmonary epithelial cells, which leads to pulmonary epithelial cell death via ferroptosis, a non-apoptotic cell death that is iron-dependent [9]. CS causes ferrous iron (Fe^{2+}) to accumulate in the mitochondria and cytoplasm. In pulmonary epithelial cells, ferrous iron overload causes mitochondrial malfunction and mitochondrial ROS generation, which results in necroptosis activation. RIP3 phosphorylates MLKL in the necrosome, and translocation of phosphorylated MLKL to the cell membrane results in direct pore formation and DAMP release. In the cytosol, ferrous iron reacts with hydrogen peroxide (H2O2) to produce hydroxyl radicals (OH, Fenton reaction). The hydroxyl radicals produced by the Fenton reaction oxidise the phospholipids (PL-H) and form phospholipid hydroperoxides in "lipid peroxidation" (PL-OOH). Peroxidation-induced lipid damage can be repaired by glutathione peroxidase 4 (GPX4).

Ferroptosis is a type of cell death caused by the loss of GPX4 and FSP1 activity, which leads to an accumulation of lipid-based ROS, especially ferrous iron-associated PL-OOH.

COPD and programmed cell death

A COPD is characterised by chronic respiratory difficulties and restricted airflow. COPD is characterised by chronic airflow limitation due to emphysema and bronchitis, as well as mucus blockage of the airways, which is frequently induced by CS. Because pulmonary emphysema is characterised by the loss of alveolar walls as a result of CS-induced epithelial cell death, apoptosis is widely recognised as a key biological mechanism in the development of emphysema. However, despite the fact that COPD is marked by lung inflammation that remains long after smoking cessation, apoptosis occurs in the absence of inflammation due to the limited or non-release of DAMPs. As a result, alternative ways to bridge the gap between apoptosis and airway inflammation have been proposed. Necrosis was previously characterised as uncontrolled cell death caused by physical or chemical stress. However, mounting evidence suggests that necroptosis, a genetically designed and regulated form of necrosis, exists. Unlike apoptosis, necroptosis causes inflammation directly by causing a large release of DAMPs from dead cells. CS-induced mitochondrial damage regulates necroptosis, which contributes to the pathophysiology of COPD, according to a recent study. In pulmonary epithelial cells, CS extract (CSE) dramatically increases mtROS generation and mitochondrial depolarization. Treatment with necrox-5, an antioxidant necrosis inhibitor, and ciclosporin A, which protects against the loss of mitochondrial membrane potential, substantially reduced CSE-induced pulmonary epithelial cell death. Inhibition of ceramide-generating acid sphingomyelinase reduced CS-induced necroptosis in pulmonary epithelial cells, demonstrating that C16-Cer buildup contributes to CS-induced necroptosis. In mice, DAMPs released in response to CS-induced necroptosis cause airway inflammation. These data suggest that mitochondrial integrity and necroptosis could be potential COPD treatment targets. Ferroptosis is a new type of non-apoptotic cell death that is characterised by lipid peroxidation and is iron-dependent. In the cytosol, ferrous iron (Fe2+) accumulates and interacts with hydrogen peroxide (H2O2) to produce hydroxyl radicals (OH). The Fenton reaction is the name for this. In a process known as lipid peroxidation, the produced hydroxyl radicals oxidise phospholipids (PL-H) and produce phospholipid hydroperoxide (PL-OOH). Ferroptosis develops to cell death if lipid damage continues. Glutathione Peroxidase 4 (GPX4) is a glutathione-dependent lipid hydroperoxidase that prevents ferroptosis by converting PL-OOH into non-toxic lipid alcohols and phospholipid hydroxides (PL-OH). Have recently published papers on this topic.

Although CS-induced iron accumulation in the mitochondria resulted in the generation of mtROS, a recent study found that CS also raises intracellular free iron levels and causes lipid peroxidation, leading to ferroptosis. High levels of lipid peroxidation, non-apoptotic cell death, DAMP release, and exacerbated COPD phenotypes of airspace enlargement and narrow airway thickness were seen in CS-exposed GPx4+/ mice (compared to wild type mice), all of which are decreased in GPx4 overexpressing mice. These findings, coupled with those of our earlier research, suggest that iron metabolism controls CS-induced necroptosis and ferroptosis, both of which have been linked to COPD pathogenesis. During COPD development, oxidative stress regulates the novel kinds of cell death, necroptosis and ferroptosis, according to current research. Iron

metabolism is implicated in both necroptosis and ferroptosis, which is interesting. The relative roles of necroptosis, ferroptosis, and apoptosis in the pathophysiology of COPD are fascinating to consider. To create meaningful therapeutic approaches, careful evaluation and further kinetic investigations of necroptosis, ferroptosis, and apoptosis are required to understand the time sequence of molecular and cellular events utilising tissues recovered from a CS exposure model. Current evidence demonstrates that oxidative stress regulates the new forms of cell death, namely necroptosis and ferroptosis, during COPD pathogenesis. Interestingly, iron metabolism is involved in both necroptosis and ferroptosis. The relative contributions of necroptosis, ferroptosis, and apoptosis to the pathogenesis of COPD are interesting aspects to consider. Careful considerations and further kinetic analyses of necroptosis, ferroptosis, and apoptosis to determine the temporal sequence of the molecular and cellular events using tissues recovered from a CS exposure model are required to develop valid therapeutic interventions.

REFERENCES

1. Halpin DM, Celli BR, Criner GJ, et al. The gold summit on chronic obstructive pulmonary disease in low- and middle-income countries. Int J Tuberc Lung Dis. 2019;23:1131-1141.

2. Kohansal R, Martinez-Camblor P, Agustí A et al. The natural history of chronic airflow obstruction revisited: an analysis of the framingham offspring cohort. Am J Respir Crit Care Med. 2009;180:3-10.

3. Pryor WA. Cigarette smoke radicals and the role of free radicals in chemical carcinogenicity. Environ. Health Perspect. 1997:105.

4. Tait SW, Green DR. mitochondria and cell death: outer membrane permeabilization and beyond. Nat Rev Mol Cell Biol. 2010;11:621–632.

5. Schumacker PT, Gillespie MN, Nakahira K. et al. Mitochondria in lung biology and pathology: more than just a powerhouse. Am J Physiol Lung Cell Mol Physiol. 2014;306:962–974.

6. Zhao RZ, Jiang S, Zhang Yu. Mitochondrial electron transport chain, ros generation and uncoupling (Review). Int J Mol. Med. 2019;44:3–15.

7. Murphy, M.P. How mitochondria produce reactive oxygen species. Biochem J. 2009;417:1–13.

8. Loewen AHS, Tye R, Fraser KL, et al. Pneumothorax in chronically ventilated neuromuscular and chest wall restricted patients– A case series. J Pulmonol. 2017;1(1) 12-16.

9. Diego RS, Bejarano J, Castro EJ, et al. Benefits of the physical exercise in the obstructive apnea syndrome of the sleep (Sahos) and its comorbilities, recommendations in cardiopulmonary rehabilitation. J Pulmonol. 2017;1(1):6-8.