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Smoking-induced Iron Dysregulation in the Lung

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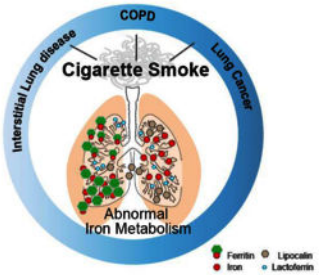
Abstract

Iron is one of the most abundant transition elements and is indispensable for almost all organisms. While the ability of iron to participate in redox chemistry is an essential requirement for participation in a range of vital enzymatic reactions, this same feature of iron also makes it dangerous in the generation of hydroxyl radicals and superoxide anions. Given the high local oxygen tensions in the lung, the regulation of iron acquisition, utilization, and storage therefore becomes vitally important, perhaps more so than in any other biological system. Iron plays a critical role in the biology of essentially every cell type in the lung, and in particular, changes in iron levels have important ramifications on immune function and the local lung microenvironment. There is substantial evidence that cigarette smoke causes iron dysregulation, with the implication that iron may be the link between smoking and smoking-related lung diseases. A better understanding of the connection between cigarette smoke, iron, and respiratory diseases will help to elucidate pathogenic mechanisms and aid in the identification of novel therapeutic targets.

Graphical abstract



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Keywords

Iron; Cigarette Smoke; Lung Disease

Introduction

Iron is an essential nutrient utilized in almost every aspect of normal cell function. Cellular systems require iron for proliferation, DNA biosynthesis, protein function and cell cycle progression. In the lung, the correct regulation of cellular iron metabolism is vital, as highlighted by accumulating evidence that the dysregulation of cellular iron metabolism is associated with a plethora of lung diseases, including but not limited to, chronic obstructive pulmonary disease (COPD), asthma, cystic fibrosis and lung cancer [1, 2]. In addition, regulation of iron acquisition by the lung is also critical to the metabolism and growth of most microbes and so the sequestration of iron is of great importance in lung defense. As a result, some of the most abundant proteins found in the alveolar extracellular space are those related to iron metabolism; including transferrin (one of the most abundant bronchoalveolar lavage (BAL) fluid proteins at 44.5%), ferritin, lactoferrin (a glycoprotein belonging to the transferrin family that sequesters iron), ceruloplasmin (a ferroxidase that oxidizes iron to the Fe^{3+} state), and lipocalin-2 (also known as neutrophil gelatinase-associated lipocalin or NGAL, a siderophore that sequesters iron), all of which are thought to be produced by secretory leukocytes, epithelial and/or endothelial cells of the lung [3–7]. Evidently, a complex extracellular and intracellular iron regulatory system operates within the lungs, which is subject to disruption [8].

The airways are constantly exposed to atmospheric iron sources, with additional occupational exposure to iron-containing environmental particulates and pollutants. Cigarette smoking is a particle related exposure, which consists of more than 5000 chemical constituents [9]. The particulate matter in cigarette smoke is thought to complex host iron and there is substantial evidence that cigarette smoking results in abnormal iron regulation in the lung [10–15]. Specifically, there are abnormally high levels of iron in both current and former smokers with increases in non-heme iron and ferritin levels in the BAL fluid and in alveolar macrophages of smokers when compared to non-smokers and redox-active iron levels in exhaled breath condensate (EBC) from smokers are increased when compared to non-smoking controls [16–25]. Such changes in intracellular and extracellular iron metabolism in the lung may contribute to an array of cellular perturbations including disrupted mitochondrial and lysosomal function, intracellular oxidative stress and cell death, as well as promoting the growth of bacteria, all of which are associated with smoking related diseases in the lung. This review aims to expand and elaborate on the role of cigarette smoking on lung iron metabolism and how this relates to the pathogenesis, susceptibility and progression of a number of chronic lung diseases.

Introduction to Iron Metabolism

The unique chemical properties of iron allow for flexible coordination chemistry involving the accepting or donating of electrons, which facilitates a plethora of diverse biological

reactions. As a result of its electropositivity, oxidized forms of iron (Fe^{3+}) display high affinity for oxygen-donor ligands [26]. However, such reactive properties can also promote harmful redox chemistry promoting the generation of reactive oxygen species (ROS), which in large doses can become detrimental in biological systems. As a result, cells have evolved sophisticated mechanisms to control the acquisition, usage, and detoxification of iron to ensure that iron metabolic needs are met, and the risk of iron toxicity is minimized [27].

Iron acquisition is mediated through metal or metal-siderophore transporters that transport iron across the plasma membrane at the cell surface or across membranes of intracellular organelles. Iron can be acquired from a variety of forms: transferrin (TF)-bound iron (TBI), non-transferrin-bound iron (NTBI), hemoglobin, and heme. Depending on the cell type, plasma membrane transporters include the transferrin receptor 1 (TFRC1), DMT1 (SLC11A2, solute carrier family 11 member 2), heme-responsive gene-1 (HRG1), CD163 (scavenger receptor that transports hemoglobin-haptoglobin complex), ZRT/IRT-like protein-14 (ZIP14/SLC39A14), ZIP8 (SLC39A8) and natural resistance-associated macrophage protein 1 (NRAMP1, also known as SLC11A1) [28]. These proteins predominantly transport divalent iron and thus require enzymes (reductases) to reduce the abundant ferric iron (Fe^{3+}) to the more soluble ferrous iron (Fe^{2+}). Once iron is acquired it must be transported to sites of utilization such as the mitochondria (heme and Fe-S cluster synthesis), secretory pathways in the endoplasmic reticulum (in yeast), storage into the iron storage protein ferritin or into the vacuole/lysosome to protect cells against iron toxicity (Figure 1) [29]. In mammalian systems, while there are many systems to regulate iron acquisition, there is no regulated mechanism of iron loss and hence iron must be transferred from one tissue to another by cellular iron export into biological fluids (plasma). This process is mediated by the only identified plasma membrane iron exporter ferroportin1 (FPN1) [30].

Central to the regulation of cellular iron homeostasis are the Iron Regulatory Proteins (IRP1 and IRP2). These cytosolic proteins bind to iron-responsive elements (IREs) on untranslated regions of mRNAs that code for proteins that are involved with iron uptake (TFRC1 and DMT1); storage (ferritin); and export (FPN1), thereby regulating cellular iron availability [31]. They are key regulators of iron sensing (hypoxia inducible factor 2a), uptake (transferrin receptor1, DMT1, FPN1), heme synthesis (5-aminolevulinic acid synthase 2) and iron storage (ferritin) in all cells [32]. Another regulatory mechanism of cellular iron homeostasis is the existence of metallochaperone proteins including the poly C binding proteins (PCBP). PCBP1 is specific to mammals and was originally identified as an iron chaperone for ferritin that assists in the mineralization of ferritin [33]. PCBPs have also been shown to deliver iron to other client proteins regulating iron storage, iron incorporation into proteins and overall iron homeostasis, but do not appear to be required for iron delivery to mitochondria. The nuclear receptor coactivator 4 (NCOA4) protein has been described to assist in the release of iron from ferritin through an autophagy-mediated mechanism [34]. These mechanisms, both delivery of iron for storage and breakdown of ferritin during iron limitation allow for the tight regulation of cellular iron homeostasis (Figure 1).

In healthy organisms, iron is maintained at a stable concentration (0.1%) in the plasma (bound to the transport protein transferrin), to deliver iron largely to the erythropoietic bone

marrow, but also to every cell in the body [12]. Erythropoietic tissue in the bone marrow requires up to 20mg of iron to maintain heme biosynthesis [35]. The majority of total iron in the body is therefore bound by hemoglobin in erythrocytes (~50%) or is present in storage compartments of hepatocytes and macrophages (~25%). Most of the iron that enters the extracellular fluid is recycled from senescent erythrocytes and is found in a chelated-state (both Fe^{2+} and Fe^{3+} forms of iron are highly reactive) to proteins or organic chelators [12]. Globally, iron regulatory responses are controlled via the action of the small peptide hormone hepcidin [2].

Iron Handling in the Lung

The human lung contains a similar amount of iron per dry weight as the liver (~0.4–0.9mg Fe/g in lung versus 0.2–2mg Fe/g in the liver) and is continuously exposed to exogenous sources of inhaled iron [36–39]. Iron is the most abundant metal present in the atmosphere, and in remote areas, iron levels in air range from 50–90ng/m^3, to about 1.3μg/m^3 at urban sites. Concentrations of up to 12μg/m^3 have been reported in the vicinity of iron- and steel-producing plants and iron is one of the most abundant metals in urban and rural particulate matter [8, 40]. The upper respiratory tract is exposed to ~10–25μg iron daily, approximately 1/1000th of that seen by the gastrointestinal tract accounting for approximately 2–6% of the total amount of iron present in the lung per dry weight [40]. Therefore, in a similar manner to other organs in the body, the lung must obtain its iron from the pulmonary vasculature in the form of transferrin-bound iron, lactoferrin-bound iron, cell free hemoglobin/heme or non-transferrin bound iron (citrate or acetate bound iron). Both alveolar macrophages (AMs) and the bronchial and alveolar epithelia are able to sequester iron by various mechanisms including receptor-mediated uptake of ferric-iron, followed by safe storage within ferritin (ferritin is effective in limiting extra-cellular iron-catalyzed oxidative stress) [2]. In the lung intracellular iron import is chiefly undertaken by TFRC1, DMT1, and in macrophages and neutrophils by NRAMP [41, 42]. Lung cells also express other iron uptake molecules including ZIP-14 and the lactoferrin receptor, low-density lipoprotein receptor-related protein 1 (LRP1) [41, 43–45] (Figure 2). Iron is mostly localized inside lung tissues (55%) with remaining metal associated with bronchoalveolar lavage (BAL) protein as bound (22%) and unbound (5%) forms [46]. One of the most abundant genes in lung tissue is ferritin light chain (FTL) [47], which in addition to ferritin heavy chain (FTH), is localized to lung-resident leukocytes such as AMs and alveolar epithelial cells (AECs) and endothelial cells [43–45]. Lung epithelial, and endothelial cells, along with AMs transport iron out of the cell via FPN1, which also plays an important role in iron detoxification [48]. In macrophages and epithelial cells, FPN1 function is regulated by hepcidin (encoded by HAMP), a hormone chiefly produced in the liver, which regulates, and is in turn regulated by systemic iron levels [49]. Hepcidin expression and release is induced by increased serum iron, by bone morphogenic protein (BMP) signaling [50] and by a number of pro-inflammatory cytokines including IL-6 and IL-22 [51]. Up-regulation of hepcidin expression results in FPN1 endocytosis and proteolysis, preventing cellular iron export and reducing the influx of iron into the plasma from stores, as well as blocking further absorption of dietary iron [12]. Production of hepcidin by AMs has also been described, indicating a specific local role in the lung for this hormone [2, 52].

Cigarette Smoke and Iron

Just How Much Iron is in Cigarette Smoke?

An average cigarette contains 0.5mg of iron per gram of tobacco, but only 0.06% of this is transferred into mainstream cigarette smoke [53]. Therefore, one pack per day smoking (20 cigarettes) results in a daily inhalational iron exposure of about 6μg, which seems at first glance trivial but depending on the excretory capabilities of the lung can accumulate over years and decades. This increased iron load was again demonstrated in a recent study using modern cigarette brands such as Marlboro and Dunhill, analyzing both mainstream and side stream ("second-hand") smoke [54]. The amount of iron in aerosols derived from electronic cigarettes is significantly less than that of a conventional cigarette, but whether this route of delivery brings additional health hazards over time, especially from other aerosolized metals, remains to be evaluated [55]. Interestingly, the particulate matter in cigarette smoke (and wood smoke) is thought to complex host iron to generate a more severe oxidative and inflammatory response and aqueous extracts of cigarette smoke may react directly with amino acid residues in ferritin and induce the release of iron from ferritin, which can be enhanced under anaerobic conditions [10, 11, 56]. These findings suggest that while the amount of iron found in cigarette smoke is minimal, the ability of cigarette smoke to complex iron inside the lung has important ramifications for cellular iron metabolism and the oxidative stress response system.

Cigarette smoke, Iron and the Lung Epithelium

The epithelial barrier of the lung consists of airway epithelial cells (bronchial epithelial cell) and alveolar epithelial cells. Airway epithelial cells (AECs) line the respiratory tract and secrete numerous substances including mucins, lysozymes, defensins, siderophores and nitric oxide [57, 58]. Ciliated AECs drive the mucociliary escalator, a primary innate defense mechanism, in which motile ciliated epithelial cells eliminate particles and pathogens trapped in mucus from the airways [59]. Pulmonary alveoli, the basic units for gaseous exchange in the lung, are composed of alveolar type 1 (AT1) and alveolar type II (AT2) cells and regulate gaseous exchange and surfactant production, a surface-active lipoprotein complex which reduces the surface tension in the lungs respectively [60]. Iron uptake by AT1 and AT2 cells can occur via TFRC1, DMT1, or the ZIP8/14 transporters (Figure 2) [61]. Once inside, iron must be transported to sites of utilization such as the mitochondria (heme and Fe-S cluster synthesis), secretory pathways in the endoplasmic reticulum (in yeast) [29], storage into the iron storage protein ferritin or into the vacuole/lysosome to protect cells against iron toxicity. AEC with the high level of ferritin present in AECs indicative of the direct interaction between the lung and the external environment [8]. FPN1 is localized to the basolateral membrane of enterocytes, but can be found apically in AECs, where they not only take up but also release iron [48]. Iron can also present to AECs in the form of cell-free heme and hemoglobin, which has been shown to induce mitochondrial dysfunction and cell injury [62].

Cigarette smoke has a deleterious effect on the health and function of epithelial cells of the lung [63]. In general, exposure of rodent models to smoke increases the deposition of iron in lung epithelial cells [18, 31, 64]. Cigarette smoke extract (CSE), an *in vitro* model for smoke

exposure largely increases the concentration of iron inside lung epithelial cells, along with increased ferritin and DMT1 expression [18]. Similarly, exposure of lung epithelial cells to wood smoke results in increased total cell iron levels along with increased ferritin and DMT1 [11, 65]. In addition, ZIP8 mRNA and protein expression is increased in the lung of chronic smokers compared with nonsmokers [66, 67] (Table 1). Inappropriate levels of iron inside an epithelial cell can result in alterations in cellular homeostasis, which may have a profound effect on lung epithelial cell function and survival. Iron accumulation enhances the production of ROS and induces mitochondrial dysfunction [68, 69], both of which are extensively documented in smoke exposed model systems [18, 19, 23, 70–74]. Interestingly, the location of where this iron accumulates inside the cell may also be important. For example, cigarette smoking appears to increase the levels of mitochondrial iron in the lungs of a murine CS-exposure model [31]. Functionally, exposure of pulmonary epithelial cells to iron-containing particulates or CS results in apoptosis, proliferation and fibrosis [75, 76], increased release of cytokines [77] and impaired antimicrobial activity [78].

Cigarette Smoke, Iron and Immune Cell Regulation

Cigarette smoke exposure has been shown to cause immune cell dysfunction, affecting both innate (AMs, dendritic cells, NK cells, and neutrophils) and adaptive immunity (antibody production and T lymphocytes) [79–82]. While there is little research that connects cigarette smoke, iron, and immune cell regulation all together, smoking is associated with iron loading in AMs, and there is growing evidence that cellular iron status affects macrophage activation and function (Table 1) [19, 22, 23]. AMs exposed to cigarette smoke have been shown to ineffectively clear respiratory pathogens such as *S. pneumoniae* and *P. aeruginosa*, as well as damaged epithelial cells [83–85]. Furthermore, macrophages exposed to smoke have defective response to activating stimuli, and in turn ineffectively produce the necessary cytokines for immune activation, especially during infection [86, 87].

Cigarette smoke also seems to affect macrophage polarization, with transcriptional profiling studies showing suppression of M1-related inflammatory genes and induction of M2-related genes in AMs obtained via lavage fluid from smokers [88]. Classically-activated (M1) macrophages are typically considered pro-inflammatory while alternatively-activated (M2) macrophages are considered anti-inflammatory, but even more relevant is the fact that these different macrophages have opposing expression profiles in the genes involved in iron homeostasis. Genes involved in iron uptake and retention, such as TF, HAMP, and FTH1 are more highly expressed in M1 macrophages, and genes involved in iron release such as FPN1 are more highly expressed in M2 macrophages [89, 90]. This divergence in iron handling likely evolved as a defense stratagem: because of the critical dependence on iron by essentially all microbes, in the event of an infection the host must rigorously sequester iron from its invaders, a key task for its pro-inflammatory immune cells (such as M1 macrophages) [12, 91]. Conversely, M2 macrophages are scavengers that clean up the inflammatory response, and subsequently release iron to surrounding cells for the repair process. Indeed, *in vitro* studies have demonstrated that supplementing mice with excessive iron biases macrophage polarization toward an M2 phenotype, and dampens the M1 inflammatory response from activating stimuli such as LPS [92]. Whether iron loading is the mechanism behind smoke-dependent macrophage reprogramming remains to be seen.

These immunologic defects have important correlations, as AMs are recognized to be dysfunctional in smoking-related lung diseases such as COPD [93]. These resident cells are the main sentinels of the airway, and even small decreases in function can have profound effects on the microbiologic makeup of their environment, as the lung is constantly exposed to external threats. Infections are by far the most common cause of exacerbations in COPD, and even without overt infection, alveolar macrophage dysfunction, possibly involving iron is likely a factor in causing the changes in lung microbiome seen in COPD [94–96].

Cigarette Smoke, Iron and the Microbial Environment of the Lung

Smoking is a strong risk factor for respiratory infections such as community-acquired pneumonia and tuberculosis, and also modulates diseases of immunity as diverse as from HIV to inflammatory bowel disease [97–101]. Nevertheless, while it is unsurprising that smoke-induced immune cell dysfunction results in increased infection risk, it is clear that lung iron bioavailability also plays a significant role in changing microbial environment in the lung. Virtually all successful pathogens have evolved to acquire iron locally from their host, most by releasing iron scavenging molecules known as siderophores. During infection, the host chelates serum iron to transferrin, lactoferrin, and ceruloplasmin, and relocates iron to reticuloendothelial macrophages while also decreasing the release of iron into the circulation by increasing HAMP and ferritin expression [102–104]. Lung infection similarly results in increased iron storage pathways inside cells and host production of lipocalin-2, which is secreted by neutrophils, AMs and epithelial cells to capture bacterial siderophores and sequester iron away from the pathogen [105–107].

There is substantial evidence behind the importance of iron control in infection. Lipocalin-2 has been shown to be critical in host defense against both extracellular and intracellular pulmonary pathogens [108, 109]. Similarly, exogenous lactoferrin is able reduce the severity of *Pseudomonas* and *M. pneumoniae* infections in infectious disease models [110, 111]. Iron itself changes pathogen biology, and was found in one study to be essential to bacterial biofilm formation but not planktonic growth [112]. Many bacteria species have limited capabilities to obtain iron, but can cause fulminant and often lethal infections in iron overloaded hosts [113]. Interestingly, lipocalin-2 is also upregulated in many non-infectious pulmonary diseases, such as COPD, lung cancer, and cystic fibrosis, suggesting that it may have additional roles in the pathogenesis of respiratory diseases [7, 114–120]. Taken together, it seems that by altering iron homeostasis in the lung, cigarette smoke impacts the lung microbial environment directly, in addition to the effect it has on immune cells.

Smoking-Related Respiratory Diseases and Iron

Chronic Obstructive Pulmonary Disease (COPD)

COPD is a progressive debilitating respiratory illness and is among the top four leading causes for mortality worldwide [121]. It can present as chronic cough, sputum production, or dyspnea in an at-risk patient, but can only be diagnosed with a post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio of less than 0.7, which is indicative of persistent airflow obstruction [122]. COPD pathobiology likely begins in the small airways of the lung, and with gradual airway loss and remodeling, ends in

irreversible parenchymal destruction, i.e. emphysema [123, 124]. The pathogenesis of COPD remains poorly understood but involves aberrant inflammatory responses of the lung to noxious particles or gas, most commonly cigarette smoke. While smoking is the leading risk factor for developing COPD, its underlying pathobiology is complex, with likely multiple overlapping genetic and environment factors contributing to disease phenotype.

Multiple genetic-association studies have indicated a role for iron in the genetic susceptibility to COPD, with the most compelling evidence for iron regulatory protein 2 (*IREB2*) [125–127]. In particular, several single nucleotide polymorphisms (SNPs) such as rs2568494 and rs13180 have appeared in geographically and ethnically diverse populations and from independent analyses [125, 127–129]. IREB2 is co-localized with several components of the nicotinic acetylcholine receptor on chromosome 15q25, and while several additional loci on 15q25 are associated with heavy smoking behavior, the association *IREB2* and COPD has also been shown to be smoking independent [130–132]. In experimental COPD models, iron accumulates in the lungs of rodents exposed to smoke and IRP2 deficient mice are protected from the effects of cigarette smoke, likely via mitochondrial iron regulation [18, 31].

Clinically, iron content and iron-binding molecules such as ferritin and lipocalin-2 (NGAL) are increased in the lung tissue, sputum, BAL fluid and alveolar macrophages of smokers, and increased further in those of COPD patients [7, 17, 18, 21]. These iron parameters correlate with clinical measures of disease severity such as the degree of airflow obstruction on pulmonary function tests and the extent of radiographic emphysema, but it is still unknown whether iron overload can be predictive of disease progression or mortality [18, 21]. AMs are known have defective activation and phagocytic ability in COPD, persisting even after smoking cessation, but this has not been linked directly to iron loading [85, 133]. Notably, while some studies indicate a role for systemic iron markers such as serum ferritin in COPD, this has not been demonstrated in other biomarker studies using large, well-characterized cohorts [134–136].

Interstitial Lung Diseases

Interstitial lung diseases (ILDs) consist of a wide spectrum of heterogeneous disorders of known or unknown cause, generally characterized by dyspnea, diffuse parenchymal lung infiltrates, restrictive pulmonary dysfunction, and impaired gaseous exchange [137]. Suggested risk factors for the initiation and progression of ILDs include genetic and epigenetic abnormalities as well as infection or environmental exposures (such as cigarette smoking or silica exposure). Cigarette smoking is a risk factor for the development of several ILDs including desquamative interstitial pneumonia (DIP), respiratory bronchiolitis-associated interstitial lung disease (RBILD), pulmonary Langerhans' cell histiocytosis (PLCH), and idiopathic pulmonary fibrosis (IPF) [137]. IPF is the most frequent, severe and most studied form of ILDs, where lung function decline is gradual and the overall prognosis of patients with IPF is unpredictable and poor with a median survival after diagnosis of approximately 3.8 years [138]. IPF is characterized by the aberrant deposition of extracellular matrix, as a result of repetitive injury to the alveolar epithelium. Such repetitive injury may be associated with smoking and other environmental factors, such as exposure to

dust, silica and infection. As a result, epithelial cells release mediators that activate fibroblast proliferation leading to the presence of abundant foci of highly activated fibroblasts and myofibroblasts that are resistant to apoptosis and lead to extensive lung remodeling. IPF also displays elements of a pathologic adaptive immune response, including dysregulated T-and B-cell responses [139].

Recent studies have shown that total iron levels, the generation of iron-associated oxygen radicals and iron-laden macrophages are elevated in the lungs of IPF patients compared to controls [140–142]. In particular, alveolar macrophage iron accumulation has been described in association with increased capillary density, pulmonary vascular lesions and pulmonary arterial hypertension in IPF [140, 143–145]. Exposure to synthetic fibers, an elevated risk factor for the development of ILD has also been associated with increased deposition of ferruginous bodies in the lung and iron increases the pro-fibrogenic effect of dust suggesting an *in vivo* accumulation of iron [146, 147]. Rodent models of fibrosis including the bleomycin-induced lung fibrosis model and the silica-induced lung injury model are associated with an accumulation of iron [148–151]. Interestingly, bleomycin directly complexes redox-active iron resulting in DNA degradation and iron deficiency or chelation is associated with a reduction in the severity of bleomycin-induced pulmonary fibrosis. Similarly, an iron-depleted diet diminishes fibrotic injury after dust instillation, whereas loss of DMT1 increases bleomycin-induced lung injury [150–154]. Another recent study showed that a FPN1 mutation resulted in iron accumulation in AMs and lung epithelial cells with subsequent development of restrictive lung disease [155]. Changes in iron metabolism therefore clearly play a role in both human IPF and murine models of this disease where such increases in iron may drive macrophage generation of ROS and promote a heightened pro-inflammatory state [92, 142]. Whether or not smoking plays an important role in these observations remains to be determined. Iron accumulation in the lungs of patients with IPF appears to be smoking-independent, however systemically, iron levels are increased in patients with active IPF and falls in patients with inactive disease, which appeared to be dependent on smoking status, with more serum iron detected in smokers [140–142, 156]. Further studies are required to deduce the role of iron dysregulation in IPF and smoking status.

Lung Cancer

An estimated 1.8 million new cases of lung cancer were diagnosed in 2012, accounting for 13% of all cancer diagnoses [157]. Despite being one of the most preventable cancers, lung cancer is the leading cause of cancer deaths in both men and women, especially in developed nations [157]. 85% of patients with lung cancer have non-small cell lung cancer (NSCLC), of which the common subtypes are adenocarcinoma and squamous cell cancer, and the remaining 15% mostly have small cell lung cancer (SCLC) [158]. All lung cancers are associated with cigarette smoking, but the strongest relationships are with squamous cell cancer and SCLC, whereas adenocarcinoma is the most common histology amongst nonsmokers, especially in East Asian women [159].

Abnormal iron metabolism appears to have a role in lung cancer biology. IRP2 has been shown to drive the growth of lung cancer cell lines, an effect exacerbated with iron loading

and blunted when IRP2 expression is turned down [160, 161]. Likewise, the proliferative phase of a SCLC cell line was found to be coordinated with increased transferrin expression, and blockage of iron uptake in this setting markedly inhibited growth [162]. NSCLC tumors have been shown to stain strongly for transferrin, with the degree of staining associated with survival in one study, especially in larger tumors (T2 or T3 by TNM staging) [163, 164]. Both serum and BALF ferritin have been found to be useful biomarkers in lung cancer, with serum ferritin in one study correlating with sensitivity to chemotherapy [4, 165]. Lipocalin-2 was found to be associated with radiation sensitivity in a lung cancer line, and with a fivefold increase in hazard ratio for overall survival if strongly stained in lung tumor tissue in another analysis [166, 167]. Unsurprisingly given the poor prognosis of lung cancer, this abundance of preclinical data has encouraged investigators to consider iron pathways as potential therapeutic targets, with already several formulations of iron chelators being studied [168–170]. Further understanding in lung iron biology will likely enhance the development of novel antitumor agents.

Therapeutic Interventions

Cigarette smoke increases the exposure to iron by the respiratory system, but also likely changes the underlying biology of lung cells such that there is both increased iron uptake and decreased iron release [53, 171]. Although not directly etiologically linked, both cigarette smoke and iron status affect epithelial and immune cells in the lung, change the underlying microbial environment, and are associated with a variety of respiratory diseases. Iron chelators may therefore be potentially novel therapeutic agents for these diseases, and while further studies are needed to assess for any accompanying side effects, if these agents can be delivered directly into the airway (perhaps via nebulized therapy), unwanted systemic effects can be minimized [31, 172]. There are a number of iron chelators to choose from and selecting the correct type will be crucial in eliciting the correct therapeutic effect. Factors to consider include: size, as large chelators will unlikely be able to passive diffuse into a cell; selectivity and specificity for iron while not removing other biologically important cations such as copper or zinc; and efficacy in enclosing iron ions and minimizing the formation of reactive oxygen species [173]. Intracellular iron chelators such as deferiprone, which can ferry excess iron between organelles and even between cells, may be more efficacious than deferoxamine, which is larger and may not enter cells as readily [174]. Alternatively, targeting hepcidin may be another approach to treating iron overload, as hepcidin agonists will induce ferroportin expression, leading to the export of excess iron and unloading the cell. This can be achieved either by agents that mimic hepcidin activity such as minihepcidins, or by using agents to stimulate endogenous hepcidin production [49].

There is evidence that suggests it is iron deficiency, rather than iron overload, that is characteristic of COPD, with high serum iron levels and high iron diet both shown to be protective against the development of COPD in smokers [175–177]. In one study, an intravenous iron intervention not only improved hematologic markers in COPD patients hospitalized with exacerbations, but alleviated their sensation of dyspnea [178]. However, there is also evidence to suggest that serum ferritin reduction improves peripheral arterial disease in smokers and that phlebotomies may improve exercise tolerance in COPD patients (with high hematocrit) with PAH and severe secondary polycythemia, provided patients do

not enter an iron deficient state [179–181]. The reader is referred to a more comprehensive review on the role of systemic iron mishandling and COPD [2]. Systemic iron deficiency is clearly under recognized in COPD, but it is possible that the blood compartment may not be representative of the local lung environment, especially given the airway's proximal exposure to cigarette smoke. It therefore follows that nebulized or inhaled therapy may serve to correct a key disease pathway in the lung without excessive systemic adverse effects, much as inhaled corticosteroids have done already in COPD and other airway diseases.

Conclusions

Cigarette smoke drives pathogenic changes in the vast majority of cells in the lung, and underlies or at least contributes to a number of important respiratory diseases. Many of these diseases, despite being leading causes of mortality, still lack effective, etiology-driven treatments [121]. That cigarette smoke additionally results in the dysregulation of iron homeostasis in these same cells strongly suggests a common pathogenic mechanism. While much remains to be learned about iron, cigarette smoke and disease pathogenesis in the lung, evidence for dysregulated iron metabolism is marked in a range of lung diseases, confirming the importance of iron regulatory process in human health and disease. Additional research is desperately needed to further explore the relationship between smoke, iron, and lung disease; the fruit of this labor may not be merely a deeper understanding of mechanism, but also the development of novel therapeutic agents, ones that target iron-related pathways and can possibly change standards of care.

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Highlights:

- Cigarette smoke induces significant dysregulation of iron homeostasis in the lung
- Iron dysregulation is observed in a number of smoking-related lung diseases
- Iron is an intriguing target for novel therapies in smoking-related lung diseases

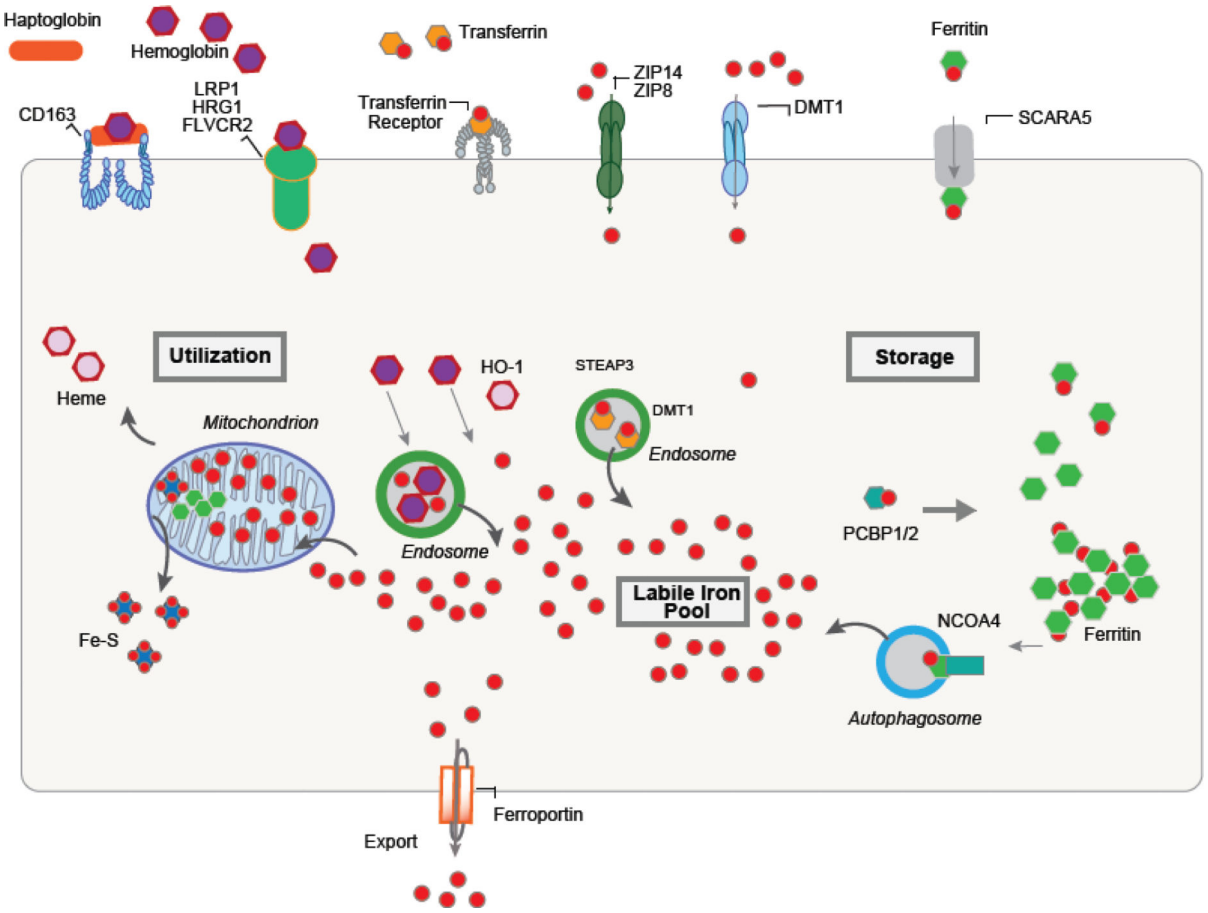

Figure 1.

In eukaryotes, iron acquisition is mediated through metal or metal-siderophore transporters transferrin receptor, Solute Carrier Family 39 Member 8 (SLC39A8 or ZIP8), Solute Carrier Family 39 Member 14 (SLC39A14 or ZIP14), Solute Carrier Family 11 Member 2 (SLC11A2 or DMT1), the heme receptors/transporters LDL receptor-related protein 1 (LRP1), Solute Carrier Family 48 Member 1 (SLC48A1 or HRG1) and Feline Leukemia Virus Subgroup C Cellular Receptor Family (FLVCR2). Once inside the cell, iron must be transported to sites of utilization such as the mitochondria (heme and Fe-S cluster synthesis), storage into the iron storage protein ferritin or into the lysosome to protect cells against iron toxicity. Poly C binding proteins (PCBP) act as iron chaperones that assists in the mineralization of ferritin. Nuclear receptor coactivator 4 (NCOA4) protein assists in the release of iron from ferritin through an autophagy-mediated mechanism. Iron is exported from the cell by ferroportin1 (FPN1).

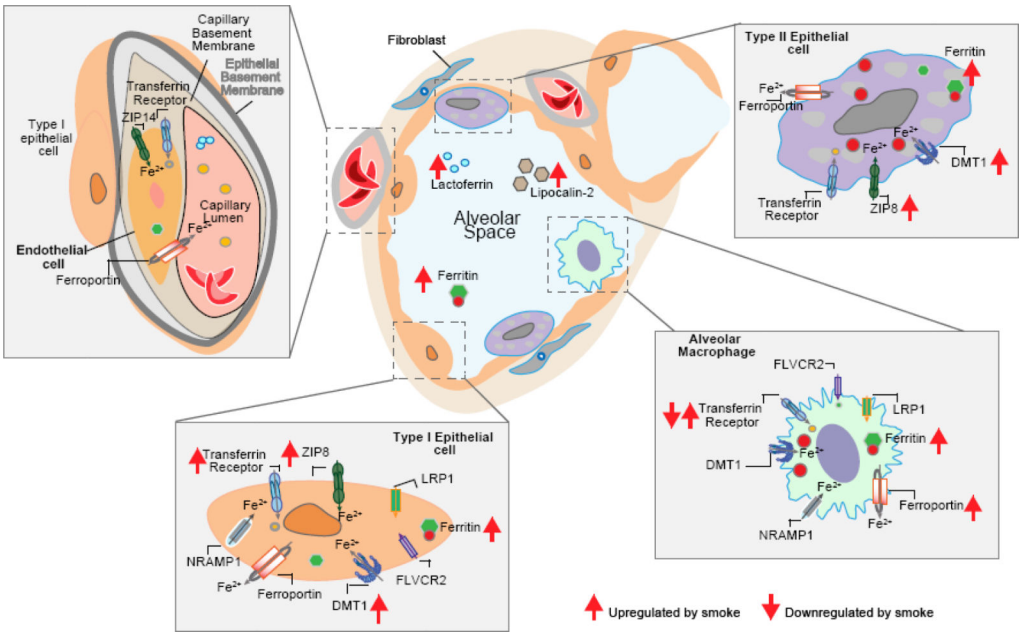

Figure 2. Iron import and export in the lung and disruption upon smoke exposure.

The lung obtains its iron from the microenvironment along with the pulmonary vasculature. Both alveolar macrophages and the bronchial and alveolar epithelia are able to sequester iron through transferrin receptor 1 (TFRC1), divalent metal transporter 1 (DMT1, also known as SLC11A2), and in macrophages and neutrophils by natural resistance-associated macrophage protein 1 (NRAMP1, also known as SLC11A1). Lung cells also express other iron uptake molecules including ZIP-14 (also known as SLC39A14), and the lactoferrin receptor, low-density lipoprotein receptor-related protein 1 (LRP1). Lung epithelial cells, alveolar macrophages and endothelial cells transport iron out of the cell via the transmembrane iron transporter ferroportin (also known as SLC40A1). Cigarette smoking alters many molecules involved in iron metabolism on lung epithelial cells, alveolar macrophages and possibly endothelial cells.

Table 1.

Alterations of Iron metabolism Proteins upon Cigarette smoke Exposure

Iron Parameter	Cell type(s)	Regulated	Disease Relevance	Reference
Intracellular Iron Regulation				
Ferritin	Alveolar epithelial cells (AECs)	Increased by cigarette smoke (CS), wood smoke	COPD	[11, 18]
Ferritin	Whole lung, AMs	Increased mRNA in COPD, increased sequestration in AMs increased staining in AMs in IPF	COPD (increased disease severity), IPF (increased pulmonary artery pressure)	[16, 17, 19-23]
IREB2/IRP2	Whole lung, AMs	Increased mRNA in whole lung, decreased in AMs in COPD patients	COPD	[21]
Mitochondrial Iron	Whole lung	Increased by CS	COPD	[30]
Iron Transporters				
Divalent metal transporter 1 (DMT1)	AECs	Increased by cigarette smoke (CS), wood smoke	COPD	[18]
Transferrin Receptor (TfR)	Whole	Increased mRNA in whole lung	COPD	[21]
Ferroportin	Whole lung, AMs	Increased mRNA in whole lung, altered in AMs in COPD patients	COPD	[21]
ZIP8	Whole lung	Increased in smokers	Not clear	[64, 65]
Extracellular Iron Transporters/Siderophores/Regulators				
Transferrin (Tf)	Whole lung, AMs	Increased mRNA in whole lung, decreased in AMs in COPD patients	COPD	[21]
Lipocalin-2	AMs, AECs	Increased secretion	COPD, lung cancer, cystic fibrosis	[7, 109–115]
Hepcidin	Cellular source?	Pro- form increased in serum of COPD patients; mutation resulting in restrictive disease	COPD, restrictive lung disease	[25, 150]