The "Iron"-y of Iron Overload and Iron Deficiency in Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease (COPD) is a debilitating inflammatory lung disease and the third leading cause of death worldwide (1). COPD is characterized by three major disease states: (*1*) chronic bronchitis or excess mucus production in the larger airways, (*2*) emphysema or peripheral lung destruction and loss of alveolar attachments, and (*3*) small airway disease characterized by inflammation and airway remodeling. In addition, several subphenotypes of COPD exist, including some with a more rapid deterioration of disease associated with frequent exacerbations (2). Systemic components also play a significant role, and comorbidities linked to COPD have a marked effect on an individual patient's quality of life and prognosis. Patients with COPD have a greater risk of cardiovascular disease, lung cancer, cachexia, infection, anemia, and polycythemia (3). The overwhelming risk factor for the development of COPD in the Western world is tobacco smoking. In the developing world, air pollution and the indoor burning of biomass fuels are also major risk factors (4). Although inhaled particulate exposure may act as a common disease driver in COPD, alternative mechanistic processes may be responsible for disease progression and for the incidence of comorbid conditions in COPD.

Genome-wide association studies (GWASs) of patients with COPD have highlighted the potential role of abnormal iron metabolism in COPD (5–9). A complex extracellular and intracellular iron-regulatory network operates within the lungs that is subject to disruption (10). Importantly, occupational exposure to iron-containing particulates and genetic susceptibility loci involving iron-associated genes are associated with manifestations of COPD (5). Moreover, because the airways are constantly exposed to atmospheric iron sources, with cigarette smoking further impacting these processes (10), there is a need for a regulatory network to sequester, detoxify, and excrete this prooxidant species and thereby maintain homeostasis. Abnormal iron regulation contributes to an array of cellular perturbations, including disrupted mitochondrial and lysosomal function (11–13), intracellular oxidative stress and cell death, and promotion of the growth of bacteria (14).

Disrupted iron homeostasis and cellular iron accumulation in COPD is not just a local phenomenon observed in the lungs; it is also present systemically. Anemia and nonanemic iron deficiency (NAID) often accompany COPD (15), with anemia being an independent predictor of mortality (16–18) and with iron deficiency being strongly associated with frequent exacerbations, in contrast to the presentation in control subjects (19). Biochemical, genetic, or molecular indicators of iron metabolism may therefore provide useful biomarkers of disease severity. The aim of this Pulmonary Perspective is to expand and elaborate on the role of iron in the pathogenesis, susceptibility, and progression of COPD, with a view toward emphasizing the prospective therapeutic interventions for treating both local and systemic iron misregulation in patients with COPD.

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Iron Handling in the Lung

Iron is an essential nutrient used in almost every aspect of normal cell function. All cells require iron to proliferate, iron being essential for DNA biosynthesis, protein function, and cell-cycle progression. 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 (14). Erythropoietic tissues require up to 20 mg of iron to maintain heme biosynthesis. The majority of total iron in the body is therefore bound by Hb in erythrocytes (approximately 50%) or is present in storage compartments of hepatocytes and macrophages (approximately 25%). Most of the iron that enters the extracellular fluid is recycled from senescent erythrocytes and is found in a chelated state (both ferrous [Fe^{2+}] and ferric [Fe^{3+}] forms of iron are highly reactive) to proteins or organic chelators (14). Globally, iron-regulatory responses are controlled via the action of the small peptide hormone hepcidin.

The human lung contains about 0.4–0.9 mg Fe/g dry weight (20, 21), which is comparable to the iron content of the liver (0.2–2 mg Fe/g dry weight) (22, 23) but considerably less than that of the heart (2–6 mg Fe/g dry weight) (24). The airways are exposed to exogenous inhaled iron sources on a continuous basis. Iron is the most abundant metal present in the atmosphere. In remote areas, iron levels in air range from 50 to 90 ng/m^3, and at urban sites, levels are about 1.3 μg/m^3. Concentrations up to 12 μg/m^3 have been reported in the vicinity of iron- and steel-producing plants (25), and iron is one of the most abundant metals in urban and rural particulate matter (10). Environmental pollutants complex iron and convert it into to a more soluble state that can be readily absorbed by the lung. The upper respiratory tract is exposed to about 10–25 μg of iron daily (25), approximately 1/1000th of that in the gastrointestinal tract.

Little is known about the mechanisms by which the lung acquires iron independently to inhalation (only 0.025 mg). In a manner similar to that of other organs in the body, the lung most likely obtains its iron from the pulmonary vasculature in the form of transferrin-bound iron, lactoferrin-bound iron, cell-free Hb/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 Fe^{3+}, followed by safe storage within ferritin. (Ferritin is effective in limiting extracellular iron-catalyzed oxidative stress.) In the lung, intracellular iron import is undertaken chiefly by the transferrin receptor 1 and the divalent metal transporter 1 (also known as SLC11A2), and in macrophages and neutrophils by the natural resistance-associated macrophage protein 1 (also known as SLC11A1) (26, 27). 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 (26, 28–30) (Figure 1).

Iron is localized mostly inside lung tissues (55%), with remaining metal associated with bronchoalveolar lavage (BAL) protein as bound (22%) and unbound (5%) forms (31). One of the most abundant genes in lung tissue is ferritin light chain (32), which, in addition to ferritin heavy chain, is localized to lung-resident leukocytes such as AMs and alveolar epithelial cells, and endothelial cells (ECs) (28–30). Intracellular iron homeostasis is controlled chiefly by post-transcriptional feedback mechanisms involving the iron-regulatory proteins (IRPs). These cytosolic proteins (IRP-1 and IRP-2) bind to iron-responsive elements on untranslated regions of mRNAs that code for proteins that are involved with iron uptake (transferrin receptor 1 and divalent metal transporter 1), storage (ferritin light chain, ferritin heavy chain), and export (ferroportin), thereby regulating cellular iron availability (33).

Regulating extracellular free iron levels in the lung, numerous soluble iron-related proteins or carriers are found in BAL fluid, including transferrin (one of the most abundant BAL proteins [44.5%]) (34), ferritin (35), lactoferrin (a glycoprotein belonging to the transferrin family that sequesters iron) (36), ceruloplasmin (a ferroxidase that oxidizes iron to the Fe^{3+} state) (37), and lipocalin 2 (a siderophore that sequesters iron) (38), all of which are thought to be produced by secretory leukocytes, epithelial cells (EPIs), and/or ECs. Lung EPIs, AMs, and ECs transport iron out of the cell via the transmembrane iron transporter ferroportin (also known as SLC40A1) (39; Figure 1). Cellular iron efflux is also more subtly regulated by the plasma copper protein ceruloplasmin, the ferroxidase activity of which is required to stabilize ferroportin (37). Ferroportin-mediated iron release occurs at the apical membrane of ECs and plays an important role in iron detoxification (39).

In macrophages and EPIs, ferroportin function is regulated by hepcidin (encoded by *HAMP*), a hormone produced chiefly in the liver, which regulates, and is in turn regulated by, systemic iron levels (40) (Figure 2). Hepcidin expression and release are induced by increased serum iron, by bone morphogenetic protein signaling (41), and by a number of proinflammatory cytokines, including IL-6 and IL-22 (42). Upregulation of hepcidin expression results in ferroportin 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 (14). This may have profound consequences for the cell, particularly if iron-uptake stratagems remain operational, and may result in cellular iron accumulation and systemic hypoferremia or iron-deficiency (ID) anemia (40). Production of hepcidin by AMs has also been described (43), indicating a specific local role in the lung for this hormone.

Iron and Infection in the Lung

Given that iron acquisition is critical to the metabolism and growth of most microbes, limiting iron availability through the safe transport and sequestration of iron is of great importance in lung defense. Virtually all successful pathogens have evolved to acquire iron locally from their host, most by releasing siderophores, which scavenge iron from the host. During infection, the host chelates serum iron to transferrin, lactoferrin, and ceruloplasmin and to reticuloendothelial macrophages, and it also decreases the release of iron into the circulation by increasing hepcidin and ferritin expression. Lung infection results in increased iron-storage pathways inside cells and host production of lipocalin 2, (also known as neutrophil gelatinase-associated lipocalin), which is secreted by neutrophils, AMs, and EPIs to capture bacterial siderophores and sequester iron away from the pathogen (44–46). Infiltrating or

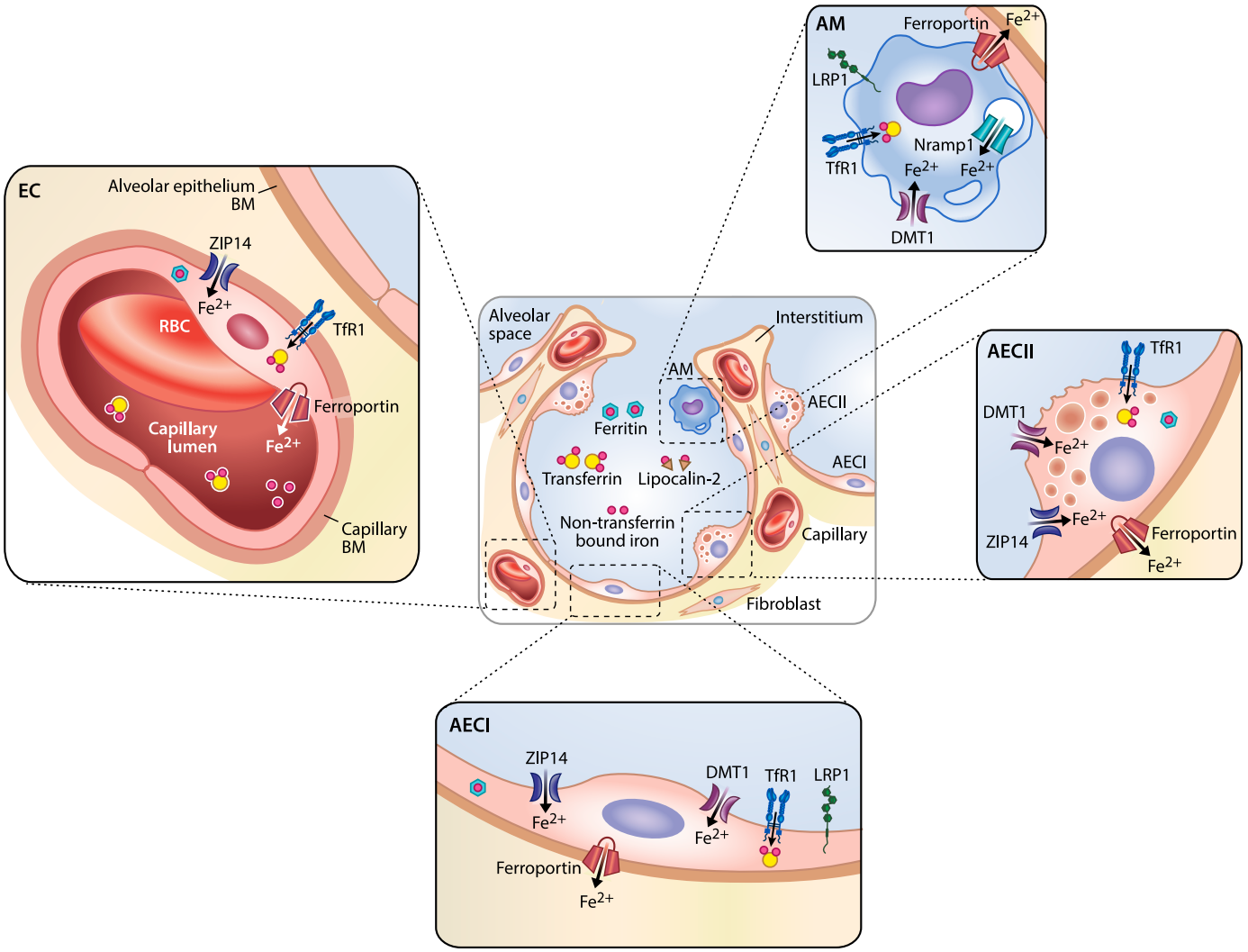

Figure 1. Iron import and export in the lung. Both alveolar macrophages and the bronchial and alveolar epithelial cells are able to sequester iron through transferrin receptor 1, divalent metal transporter 1 (DMT1, also known as SLC11A2), and in macrophages and neutrophils by natural resistance-associated 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). AECI = alveolar epithelial cell type I; AECII = alveolar epithelial cell type II; AM = alveolar macrophage; BM = basement membrane; EC = endothelial cell; RBC = red blood cell; TfR1 = transferrin receptor 1; ZIP14 = zinc transporter ZIP14.

resident leukocytes also produce or recycle iron, releasing it into the alveolar space.

Macrophages play a key role in host-driven inflammatory and immune responses to infection and injury, and they also have other homeostatic functions, including facilitating body iron turnover and storage (14). AMs act as key regulators of iron in the lower respiratory tract. Macrophages can be differentially phenotyped, dependent on environmental and biological signals, to a variety of phenotypes, including the classic M1 or M2 macrophages. In broad terms, M1 cells exhibit a proinflammatory/bactericidal phenotype, whereas M2 cells display antiinflammatory, scavenging, and tissue repair properties (47). Iron-regulatory responses differ between these phenotypes: M1 cells accumulate iron as part of a bacteriostatic stratagem linked to the anemia of chronic inflammation, whereas the opposite is the case for M2 cells, where iron release is favored (48).

Cigarette Smoking Alters Iron Homeostasis in the Lung

Regular cigarette smoking greatly increases lung exposure to iron. Tobacco smoke contains 440–1,150 μg/g of iron (49); however, only 0.06% of this is transferred into mainstream cigarette smoke (CS). This equates to approximately 5.2–13.8 μg of iron daily in a subject smoking 20 cigarettes daily (50). Both current and former smokers have abnormally high levels of iron as a result of iron having a high affinity for oxygen donor ligands found in CS particles, leading to a higher rate of deposition in the lung (51). Furthermore, total nonheme iron and ferritin levels are increased in BAL fluid and in AMs of smokers compared with nonsmokers (49, 51–58), and redox-active iron levels in

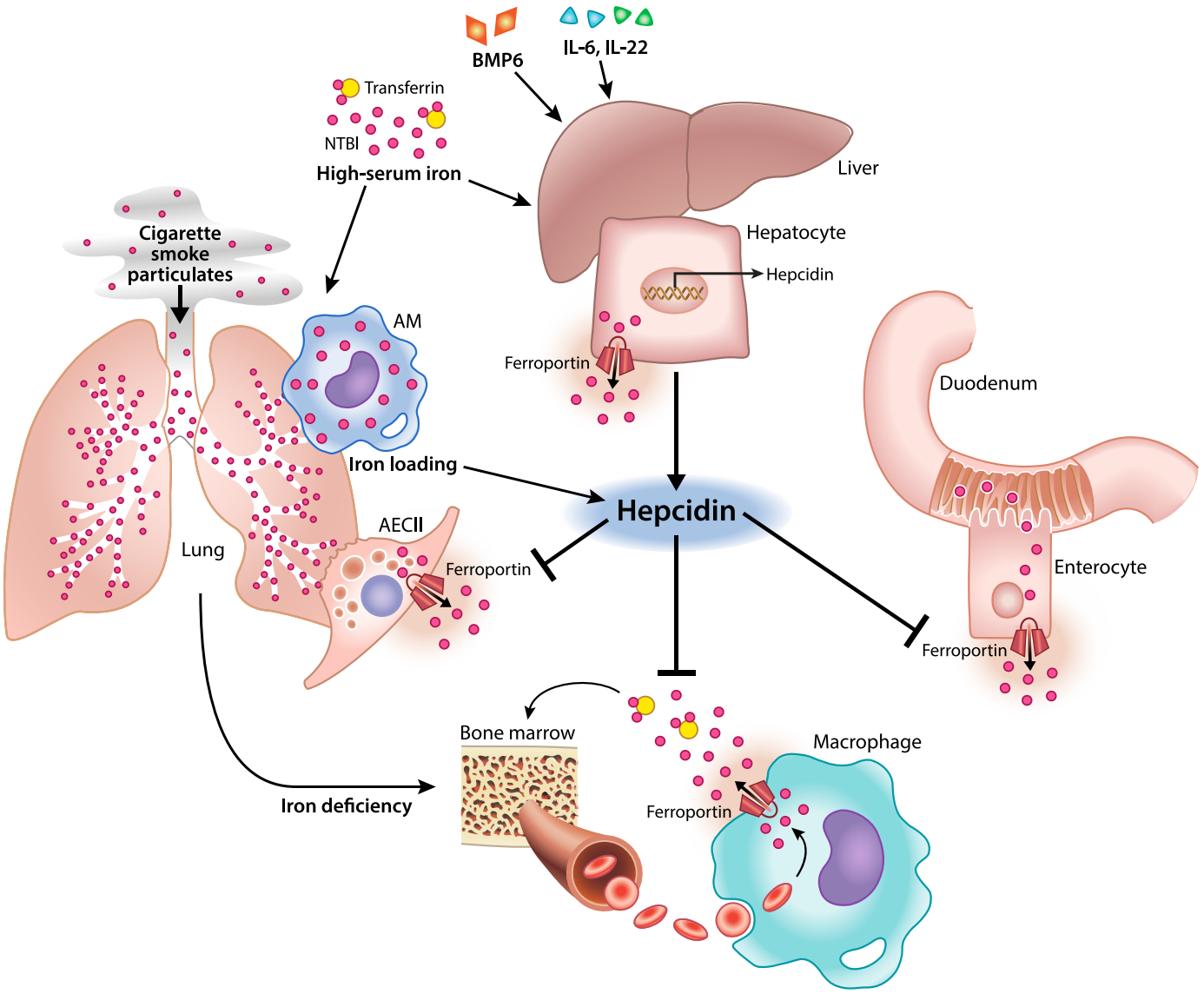

Figure 2. Hepcidin and systemic iron homeostasis in chronic obstructive pulmonary disease (COPD). Hepcidin (encoded by *HAMP*) is a hormone produced chiefly in the liver, which regulates, and is in turn regulated by, systemic iron levels. Hepcidin expression and release is induced by increased serum iron; by bone morphogenetic protein 6 (BMP6) signaling; and by a number of proinflammatory cytokines, including IL-6 and IL-22. Up-regulation of hepcidin expression results in ferroportin 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. This may have profound consequences for the cell, particularly if iron-uptake stratagems remain operational, and may result in cellular iron accumulation and systemic hypoferremia or iron-deficiency anemia. Consistent with increased iron loading into cells, tissues, and iron-chelating proteins, serum hepcidin is increased in patients with COPD. Increased hepcidin may result in less iron delivery to extracellular fluid, in macrophages failing to release recycled iron, and in a rapid drop in systemic iron levels, leading to iron deficiency. AECII = alveolar epithelial cell type II; AM = alveolar macrophage; NTBI = non-transferrin bound iron.

exhaled breath condensate from smokers are increased compared with those of nonsmoking control subjects (59).

Systemically, serum ferritin levels are increased in former or current smokers (51, 60), a phenomenon thought to associate with spirometric resistance to CS (61), with higher serum iron being beneficial to lung health (62). Cigarette smoking increases blood Hb levels (63, 64), suggesting protection from anemia; however, CS may affect the incidence as well as the diagnosis of anemia by negatively affecting hematopoiesis and inducing polycythemia (65). Smoking may increase the risk of anemia during pregnancy, may worsen iron accumulation, and may exacerbate preexisting iron-related conditions such as sickle cell disease (60, 66, 67). Smokers also have lower serum ceruloplasmin levels than nonsmokers, suggesting impaired protection from reactive Fe^{2+} (68).

Iron and COPD

Genetic and Epidemiological Evidence

Researchers in multiple gene expression and genetic association studies have examined

the onset, progression, and severity of disease in COPD (69). Some of these differentially expressed genes indicate a role for iron in the genetic susceptibility to COPD. The most compelling evidence is for *IRP2* or iron-responsive element-binding protein 2 (*IREB2*). *IRP2* is associated with COPD susceptibility (5–9) and with pulmonary artery enlargement in COPD (70). This association may be sex specific (8, 71) and independent of smoking (72, 73), and it may also associate with severe alpha-1 antitrypsin (AAT) deficiency (71) and lung cancer (74, 75). *IRP2* is located within a cluster of genes on chromosome 15q25, which includes several components of the nicotinic acetylcholine receptor. The 15q25 locus has also been associated with lung cancer, peripheral arterial disease, and nicotine addiction (70, 75–78).

Further evidence for the role of iron in genetic susceptibility to COPD includes observations that single-nucleotide polymorphism variants in the IL-6 gene (*IL6* −174G/C) associate with a rapid decline in FEV_1 (1) and susceptibility to COPD in smokers (79). IL-6 is important in the pathogenesis of COPD and is known to regulate iron homeostasis through induction of hepcidin expression (42). Genetic mutations in the Z allele at the AAT gene serpin family A member 1 (*SERPINA1*) have also been linked to altered systemic iron homeostasis (80, 81). Interestingly, some hemochromatosis (*HFE*) mutations are also strongly associated with AAT deficiency (82). Other potential genetic associations related to iron metabolism include porphyria, which results in disrupted mitochondrial iron/heme metabolism and has been linked to greater susceptibly to COPD (83). Epidemiological evidence derived from ferrous metallurgy workers demonstrated an increased risk of developing COPD, along with other respiratory symptoms, including persistent airway inflammation and compromised lung function, compared with nonindustry control subjects (84–87).

Increased Iron Loading in COPD

As is true of smokers, iron content and iron-binding molecules, including ferritin, lipocalin 2, and lactoferrin, are all increased in the lung tissue, sputum, BAL fluid, and AMs of patients with COPD (20, 35, 38, 51, 53, 55). Iron levels increase with disease severity and with reductions in lung function. IRP-2 protein and mRNA levels increase in COPD lung tissue (5), and there is a consequent reduction in the amount of free iron observed in exhaled breath condensate (59). Table E1 in the online supplement details these biomarkers together with their normal functional roles.

Despite iron loading occurring in the lungs of patients with COPD, this is not consistently reflected in systemic markers of iron metabolism. Serum iron is higher during exacerbations of COPD, and serum ferritin and lipocalin 2 levels are increased in COPD (18, 51, 60). Overall, higher serum iron may be beneficial and predictive of better spirometric values in older patients (61), and it is associated with a reduced the risk of developing COPD (88). Nevertheless, some studies have shown no difference in serum iron levels between patients with COPD and control subjects (Table E1).

Consistent with increased iron loading into cells, tissues, and iron-chelating proteins, serum hepcidin is increased in patients with COPD (18, 89). Increased hepcidin may result in less iron delivery to extracellular fluid, in macrophages failing to release recycled iron, and in a rapid drop in systemic iron levels, leading to ID (Figure 2) (90). Over time, elevations in hepcidin resulting from chronic inflammation may not respond appropriately to declining iron stores and may induce a functional ID. Interestingly, patients with COPD may have an inappropriate suppression of hepcidin in response to ID (18, 91) and may have less hepcidin expression in severe end-stage disease (91).

Prevalence of Anemia and ID in COPD

NAID is characterized as the decrease of total body iron content defined by serum ferritin concentrations less than 100 μg/L. In general, NAID can be characterized as absolute ID (in which iron stores are low) or functional ID (in which iron supply is inadequate to meet the demand for erythropoiesis and other cellular functions despite normal or abundant body iron stores). Functional ID frequently arises from a chronic inflammatory state associated with increased hepcidin and increased ferritin, and it is therefore hard to define in the face of chronic inflammation.

NAID is observed in 40 to 50% of patients with COPD (18, 92). However, existing strategies to define ID in patients with COPD may be confounded by pseudo increases in inflammation-associated ferritin (93), signifying that ID may be underdiagnosed in COPD. In addition, ID could be particularly deleterious in patients with COPD with extrapulmonary manifestations such as pulmonary hypertension (PH). PH is one of the strongest predictors of decreased survival in COPD, and there is some evidence to suggest that ID augments PH in COPD (18, 93). In COPD, NAID is also associated with hypoxemia (independently of airflow limitation) (18), and ID also disturbs normal responses to hypoxia, as evidenced by exaggerated hypoxic PH that is reversed by subsequent iron administration (94).

ID anemia occurs when ID is sufficiently severe to reduce erythropoiesis. Only a small percentage of patients with COPD with ID present with concurrent anemia, suggesting that these two entities should be considered separately (95). *See* Table E2 for studies related to ID and anemia in COPD.

Anemia is defined as a reduction in one or more of the major red blood cell (RBC) measurements: Hb concentration, hematocrit, or RBC count. Anemia is a frequent comorbidity found in 5 to 30% of patients with COPD and predicts a worse outcome (90), both in terms of hospitalization with an acute exacerbation (16) and in the long term (17). Low Hb levels observed in anemic patients with COPD may result in lower exercise capacity and anaerobic threshold. In patients with NAID and COPD, exercise limitation might be a result of diminished oxygen use in the muscle cells caused by impaired function of iron-containing enzymes (96).

Cellular Repercussions of Abnormal Iron Homeostasis in COPD

Inappropriate levels of tissue iron (accumulation or deficit) can result in alterations in cellular homeostasis. In general, iron accumulates inside cells and tissues of *in vitro* and *in vivo* COPD models (49, 51, 57). Increased cellular iron may be both a pathogenic (33) and a protective (55) stratagem in COPD. Either way, cellular iron retention beyond normal limits has profound consequences for lung cell function and survival. Iron accumulation enhances the production of reactive oxygen species and induces mitochondrial dysfunction (97, 98), both of which are extensively documented in patients with COPD and model systems (49, 51, 57, 99–103). Functionally, exposure of

pulmonary EPIs or AMs to iron-containing particulates or CS results in apoptosis, proliferation, and fibrosis (104); increased release of cytokines (105); and impaired antimicrobial activity (106). All of these have potential implications for COPD.

Mitochondria are the main cellular consumers of iron, and a number of vital cellular processes rely on precise mitochondrial iron regulation. Failure to correctly regulate mitochondrial iron leads to mitochondrial dysfunction, which is observed in response to wood smoke (loss of mitochondrial iron [107]) and CS (increased mitochondrial iron [33]). In mice, *IRP2* deficiency protects against CS-induced COPD and CS-induced mitochondrial iron loading. Importantly, mitochondrial iron chelation or the use of iron-restricted diets ameliorated such responses, again highlighting the important role of disrupted iron homeostasis at the cellular/subcellular level in COPD (33).

Removal of damaged mitochondria by autophagy (mitophagy) may counterbalance abnormal cellular iron homeostasis (108). However, iron accumulation resulting from mitophagy and from the breakdown of iron-saturated ferritin, localized as hemosiderin, coupled with an acidic environment, maintains a prooxidant (Fe^{2+}) iron pool within the lysosome (11). Lysosomal membranes are vulnerable to iron-catalyzed peroxidation and rupture under such circumstances, releasing more reactive iron into the cytosol (109). CS induces mitophagy *in vitro* (12, 13), and loss of mitophagy is protective in murine models of COPD (110), suggesting that increased mitophagy, though it is a protective strategy, may ultimately be detrimental in the context of COPD.

Therapeutic Opportunities

Exposure of the respiratory system to particles (smoke, pollution) increases the uptake of iron into lung cells and BAL fluid of the lung. Increased inflammation in response to such exposures also results in the marked sequestration of iron into serum iron, iron storage proteins, and AMs, as well as decreased release of iron into the circulation by increasing hepcidin and ferritin. Increased iron deposition in the lungs of smokers and patients with COPD is therefore a key pathophysiological feature of COPD (20, 35, 38, 51, 53, 55). Genetic factors may enhance or exacerbate this pathophysiological component of COPD (5–9). Increased iron deposition in the lung renders the lung more susceptible to respiratory infections such as pneumonia while altering the normal physiological functions of AMs, alveolar epithelial cells, and other lung cells (14).

Inhaled iron chelators may therefore offer potential therapeutic relief for patients with acute exacerbations of COPD (33, 111). However, further studies are required to assess the effects of using inhaled iron chelators on systemic iron metabolism. In addition, selecting the type of iron chelator will be crucial in eliciting the correct therapeutic effect. Intracellular iron chelators such as deferiprone, which specifically target intracellular iron deposits and relocate them outside the cell to prevent cellular iron loading (112, 113), may have more therapeutic efficacy than regular cell-impermeable iron chelators such as deferoxamine (114).

During acute COPD exacerbations, repeated bursts of inflammation may lead to further dysfunction of iron homeostasis, with increased levels of inflammatory cytokines and alterations in the synthesis, release, and activity of hepcidin playing a significant role. As described above, elevated hepcidin levels result in a functional ID, with or without anemia (17). These individuals are not classically iron deficient; rather, their iron is unavailable for other physiological processes (18). Several strategies to antagonize hepcidin are currently under development and include decreasing endogenous hepcidin production (antagonists of hepcidin-stimulatory pathways such as bone morphogenetic protein or IL-6 signaling), neutralizing hepcidin peptides (antihepcidin antibodies or engineered protein or nucleic acid–based binders such as anticalins and Spiegelmers), and interfering with hepcidin binding to ferroportin using antiferroportin antibodies or small molecules such as fursultiamine (40). These have proved successful in animal models, and several agents are being evaluated in clinical trials for treatment of anemia of cancer and chronic kidney disease (40). However, whereas hepcidin is increased in stable COPD and during acute exacerbations (18, 91), patients with severe COPD may have lower hepcidin levels. Further studies are therefore required to more extensively define the role of hepcidin in the development and progression of COPD.

Several studies have assessed the therapeutic benefit of blood transfusions and iron supplementation to treat anemic patients with COPD (115, 116). RBC transfusion reduces mean minute ventilation and work of breathing in anemic patients with COPD, as well as improves unloading of the respiratory muscles in ventilated patients with COPD with anemia (115, 116). Erythropoiesis-stimulating agents in combination with intravenous iron improves anemia and possibly improves dyspnea in anemic patients with COPD (92). The relationship between iron, hypoxia, inflammation, and erythropoietin is complex (117–120), and patients with hypoxia may benefit from ensuring adequate iron status (121). Intravenous iron therapy may also have beneficial effects for ID patients with COPD independently of Hb or respiratory outcomes, especially those patients with extrapulmonary conditions such as PH. Intravenous iron therapy has been shown to improve the symptoms and quality of life of patients with chronic heart failure and ID, with or without anemia (122).

Although iron supplementation therapy may prove beneficial, the risks must be weighed against the potential benefits for each patient. Iron supplementation is known to cause oxidative stress in the body (123), and intravenous iron provided in excess may lead to increased morbidity and mortality (124). In addition, there is some evidence to suggest that serum ferritin reduction improves peripheral arterial disease in smokers (125) and that phlebotomy may improve exercise tolerance in patients with COPD (with high hematocrit) with PH and severe secondary polycythemia, provided these patients do not enter an iron-deficient state (126, 127).

Conclusions

Cellular iron accumulation is a common manifestation observed in patients with COPD. Although anemia of inflammation is a systemic response, the consequences for the lungs and airways may be more profound, not least because these organs are continually exposed to exogenous iron sources, including particulate matter and, for some, continuing CS exposure. In addition, functional ID in COPD may be

underdiagnosed and may represent an entirely separate entity from ID with anemia, especially in relation to extrapulmonary manifestations such as PH. Strategies to define ID in patients with COPD may be confounded by pseudo increases in inflammation-associated ferritin and the presence of ID before a loss of Hb or mean corpuscular volume. The use of a more accurate definition of ID (ferritin between 100 and 300 μg/L and transferrin saturation <20%) and the complementary measurement of soluble transferrin receptor or hepcidin may offer a more sensitive assessment of iron status and response to therapy in patients with COPD.

Additional studies are required not only to accurately define ID in COPD but also to investigate the balance between alleviating iron overload in the lung with systemic ID. Therapeutic approaches must consider both sides of the coin. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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