Review

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Double-edged Sword Role of Iron-loaded Ferritin in Extracellular Vesicles

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Human epidemiological and animal studies have demonstrated that excess iron is a risk for cancer. The responsible mechanisms are: 1) increased intracellular iron catalyzes the Fenton reaction to generate hydroxyl radicals, leading to mutagenic oxidative DNA lesions; 2) iron is necessary for cellular proliferation as cofactors of many enzymes. Thus, iron-excess milieu promotes selecting cellular evolution to ferroptosis-resistance, a major basis for carcinogenesis. Ferritin is a 24-subunit nanocage protein required for iron storage under the regulation of the iron-regulatory protein (IRP)/iron-responsive element (IRE) system. Ferritin is a serum marker, representing total body iron storage. However, how ferritin is secreted extracellularly has been unelucidated. We recently discovered that an exosomal marker CD63 is regulated by the IRP/IRE system and that iron-loaded ferritin is secreted as extracellular vesicles under the guidance of nuclear receptor coactivator 4 (NCOA4). On the other hand, we found that macrophages under asbestos-induced ferroptosis emit ferroptosis-dependent extracellular vesicles (FedEVs), which are received by nearby mesothelial cells, resulting in significant mutagenic DNA damage. Therefore, cells, including macrophages, can share excess iron with other cells, via iron-loaded ferritin packaged in extracellular vesicles as safe non-catalytic iron. However, similar process, such as one involving FedEVs, may cause accumulation of excess iron in other specific cells, which may eventually promote carcinogenesis.

Key Words Ferritin, Extracellular vesicles, Iron, Ferroptosis, Asbestos

INTRODUCTION

The first life on earth was born under the ancient sea of abundant Fe(II) 3.8 Gya [1,2], and it is generally accepted that no independent life on earth can live without iron [3]. Iron is a major redox-active transition metal, which is used for various electron transfer reactions in the form of Fe(II), Fe-S cluster or heme [4]. During evolution, the life obtained the sulfhydryl systems [5], including glutathione, to counteract iron toxicity when present in excess, which might have been just insoluble FeS at first [6,7]. Finally, the life acquired the capacity to use molecular oxygen, which allows more flexible and versatile transfer of one to four electron(s) at a time and continuous electron flow inside the entire cells (Fig. 1) [8].

IRON AND OXYGEN FOR ELECTRON TRANSFER

During the O_2 metabolism, reactive oxygen species are inevitably produced. Superoxdie (O_2^-) and hydrogen peroxide (H_2O_2) are generated via enzymatic reactions whereas hydroxyl radical is produced via the chemical reaction called the Fenton reaction ($Fe[II] + H_2O_2 \rightarrow Fe[III] + \bullet OH + OH^-$) (Fig. 1) [9-11]. Catalytic Fe(II) is indeed dangerous for life when present unconfined. Now we can detect catalytic Fe(II) by use of turn-off or turn-on fluorescent probes in cellular experiments [12-14]. Fortunately, we have several distinct mechanisms to minimize this iron toxicity.

We fully utilize the advantageous characteristics of iron. Fe(III) is practically insoluble at neutral pH whereas Fe(II) is soluble [11]. Iron is transported by transferrin in higher organisms as Fe(III) [15]. Fe(III) has to be reduced to Fe(II) to be transported through the biomembranes with various transporters, such as divalent metal transporter 1 (DMT1) (solute carrier family 11 member 2 [SLC11A2]) [16] and ferroportin (solute carrier family 40 member 1 [SLC40A1]) [17]. Iron absorption through the duodenal mucosa is strictly regulated via iron storage status [18]. Excess iron in the cell is stored in

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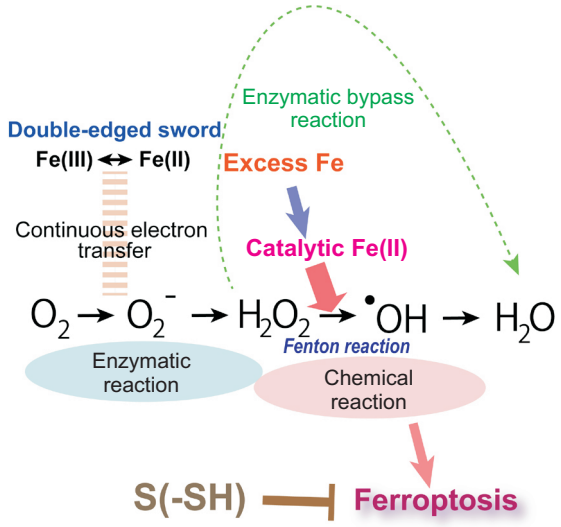

Figure 1. Molecular oxygen as versatile electron acceptors, and its association with ferroptosis. Superoxide and hydrogen peroxide are generated through various enzymatic reactions whereas hydroxyl radicals are produced via chemical reactions. Enzymatic bypass reactions indicate direct decomposition of hydrogen peroxide to water by a variety of enzymes, such as catalase and glutathione peroxidase. Hydroxyl radicals are closely associated with ferroptosis, which is counteracted by sulfhydryls (-SH).

cytosol as ferritin in the form of Fe(III). Furthermore, recently identified iron chaperones play roles in the safe transport of Fe(II) in the cytosol. These chaperones are poly *rC* binding protein 1 (PCBP1) and PCBP2, which were first reported as nuclear proteins responsible for transcriptional regulation [19,20]. Both PCBPs accept 3 molecules of Fe(II) and the resulting complexes are redox-inactive. Whereas PCBP2 can accept Fe(II) from DMT1 [21] and heme oxygenase 1 [22] and can transfer Fe(II) to ferroportin [23], PCBP1 can load Fe(II) to ferritin (Fig. 2) [24]. PCBP1 and PCBP2 antagonize to each other, where PCBP1 works as a tumor suppressor [25,26] and PCBP2 as an oncogene in general [27,28]. Ferritinophagy, a form of autophagy, is used to retrieve Fe(III) from ferritin cores, which is reduced in lysosome to Fe(II) via six-transmembrane epithelial antigen of prostate 3 (STEAP3) [29].

IRON-DEPENDENT EXCRETION OF FERRITIN AS EXTRACELLULAR VESICLES

Ferritin is a 24-subunit nanocage protein, consisting of light chain (FTL) and heavy chain (FHL), for safe iron storage under the regulation of the iron-regulatory protein (IRP)/iron-responsive element (IRE) posttranscriptional system. Ferritin is also a serum marker representing body iron storage [30]. However, how ferritin is secreted extracellularly has been completely unknown in the absence of secretory signal peptides [31]. We recently discovered for the first time that an

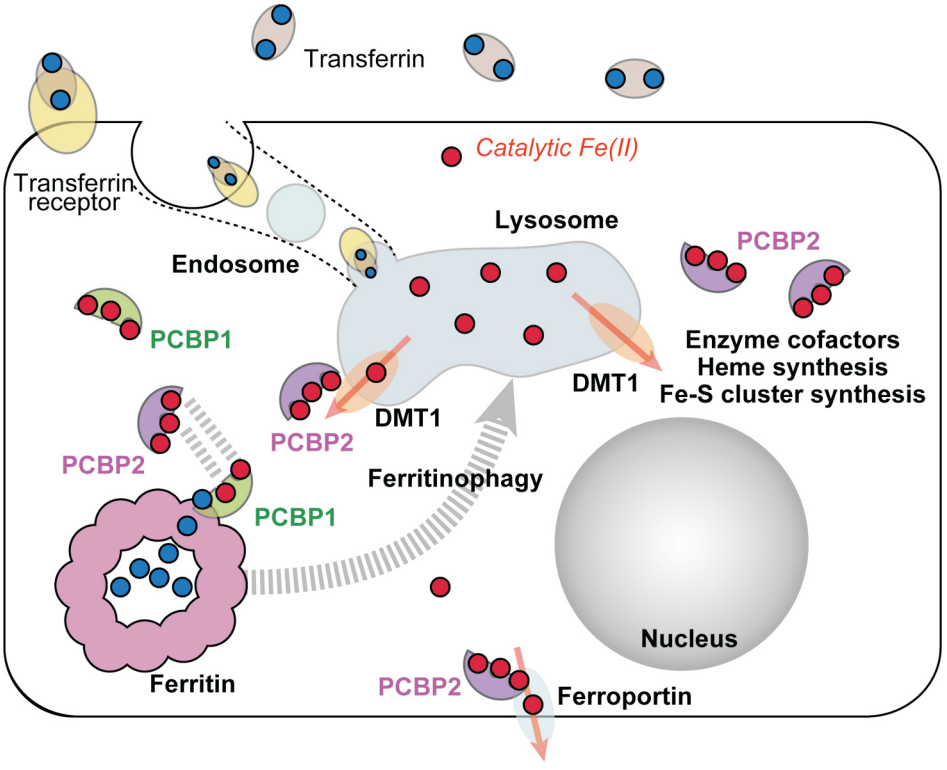

Figure 2. Cytosolic iron chaperon systems. Iron is incorporated by binding of transferrin to transferrin receptor into the cellular cytosol through late endosome/lysosome. Iron retrieved and reduced by STEAP3 (six-transmembrane epithelial antigen of the prostate 3) to Fe(II) in late endosome/lysosome goes through divalent metal transporter 1 (DMT1) (solute carrier family 11 member 2 [SLC11A2]) to cytosol, where Fe(II) is immediately chaperoned by poly *rC* binding protein 2 (PCBP2). PCBP1 is another Fe(II) chaperone, competing each other. PCBP1 can load iron to ferritin, where Fe(II) is oxidized to Fe(III) via ferritin heavy chain (FTH). PCBP2 appears to play wider roles in transporting Fe(II) in the cytosol. If Fe(II) is not chaperoned by PCBP1/2 due to pathologic causes, unchaperoned Fe(II) is catalytic. Red filled circle, Fe(II); blue filled circle, Fe(III). Note that Fe(III) is insoluble at neutral pH.

exosomal marker CD63 is regulated by the IRP/IRE system and that iron-loaded ferritin is secreted as extracellular vesicles (EVs) with the guidance of nuclear receptor coactivator 4 (NCOA4) [32]. This is an efficient sustainable mechanism to share excess iron with nearby or distant cells in a safe manner (Fig. 3).

EXCESS IRON AND CARCINOGENESIS

It is well known that iron metabolism is a semi closed system for an individual in higher animals. Namely, the daily fraction of incomings and outgoings is extremely small in comparison to the total amount (~0.025%). In humans, adult males retain ~4 g of iron in total whereas premenopausal females have ~2.5 g of iron [33]. There is no active pathway to excrete iron to the outside of the body. The only exceptions are hemorrhage or phlebotomy to lose red blood cells, and the use of redox-inactive iron chelating agents, such as desferal, deferasirox and deferiprone [34]. Accordingly, iron would be present in excess during aging by the decrease in metabolic rate, causing ferroptosis time-dependently in a fraction of cells in various organs of rats [35].

Excess iron has also been associated with carcinogenesis, according to the human epidemiological study of the general population or specific diseases, including genetic hemochromatosis and ovarian endometriosis [36-38] as well as various animal studies [4,8,39]. The responsible mechanisms are: 1) increased intracellular iron catalyzes Fenton reaction to generate hydroxyl radicals, leading to mutagenic oxidative DNA lesions [40-42]; 2) iron is necessary for cellular proliferation as cofactors of many enzymes [4,8,10,33,43,44].

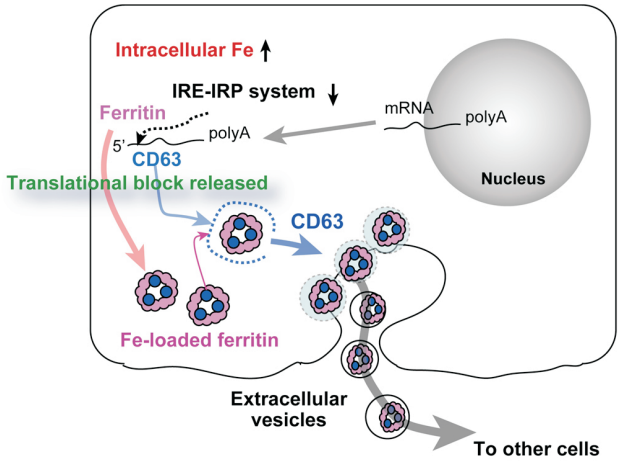

Figure 3. Iron-loaded ferritin is secreted through extracellular vesicles under the regulation of IRP/IRE in CD63. CD63 is one of the exosomal markers. In iron excess conditions, not only an iron storage protein, ferritin, but also CD63 is induced. CD63 recruits nuclear receptor coactivator 4 (NCOA4) to pack iron-loaded ferritin to release as extracellular vesicles. Of note, *CD63* gene was discovered to possess the IRE consensus sequence at the 5' untranslated region of mRNA, similar to that of *ferritin* gene, which blocks the translation of CD63 in the presence of ample amount of iron under the IRE/IRP system. IRE, iron-responsive element; IRP, iron-regulatory protein. Refer to text and the reference [32] for details.

EXCRETION OF FERRITIN AS BY-PRODUCT OF ASBESTOS-INDUCED FERROPTOSIS

Asbestos, a natural nanofibrous mineral, is still used worldwide, especially in some Asian countries, Russia, and South America due to the economic merits, in spite of the designation by World Health Organization as a definite human carcinogen (Group 1 by International Agency for Research on Cancer [IARC]) [45]. Asbestos is resistant to heat, acid and friction, and is also flexible for various industrial use. The association of asbestos exposure and mesothelioma is well established [45,46]. Asbestos is inhaled through the airway to the pulmonary parenchyma. However, the major target cells for carcinogenesis are parietal mesothelial cells in the pleural cavity, which has been a long mystery to be solved [47,48].

Molecular mechanisms underlying asbestos-induced mesothelioma have been intensively studies for these two decades. The important point is that the biopersistent nanofibers go through pulmonary parenchyma, by penetrating visceral pleura, into the pleural cavity after collecting hemoglobin originating from red blood cells on the surface and hence iron, depending on the negative pressure of the cavity, and then injures the parietal pleural mesothelial cells [48,49]. Amazingly, this process requires a few decades.

The ability of mesothelial cells to phagocytose asbestos fibers provides a high risk for DNA double strand breaks and the resultant mutations because asbestos fibers present a high affinity for histones as well [50,51]. The tumor suppressor $p16^{INK4a}$ is activated in response to DNA damage as well as oxidative stress. Therefore, it is no wonder that homozygous deletion of $p16^{INK4a}$ is the major mutation observed in human and rat mesothelioma [52,53], representing direct DNA double-strand breaks by asbestos fiber in mesothelial cells and the following erroneous end-joining of DNA strands [47,48]. Of note, homozygous deletion of $p16^{INK4a}$ is the major target mutation also in the Fenton reaction-induced renal cell carcinoma in rats [42]. However, the role of macrophages in mesothelial carcinogenesis has not been clear other than what is called “frustrated phagocytosis [54].”

According to our 2020 report, macrophages generate mutagenic milieu for the surface mesothelial cells via ferroptosis, catalytic Fe(II)-dependent regulated necrosis accompanied by lipid peroxidation, upon taking up asbestos fibers as foreign material [55]. We have further sublimated this concept into a more concrete one in 2021 that macrophages under asbestos-induced ferroptosis emit ferroptosis-dependent extracellular vesicles (FedEVs) [56] which are received by mesothelial cells, resulting in significant mutagenic DNA lesions (Fig. 4).

Therefore, various cells, including macrophages, can share

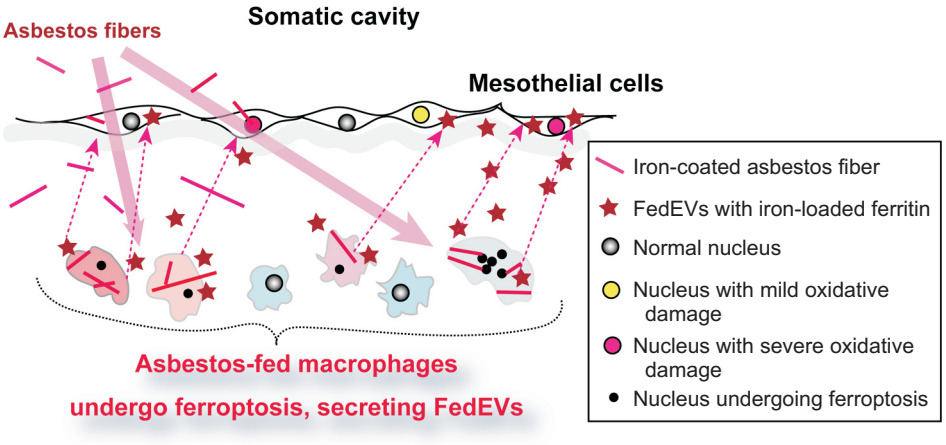

Figure 4. Asbestos-induced ferroptosis in macrophages emits ferroptosis-dependent extracellular vesicles (FedEVs; filled stars), which is received by surface mesothelial cells resulting in oxidative DNA damage. Note that there are direct and indirect damage by asbestos fibers to surface mesothelial cells in the somatic cavities. Macrophages with pyknotic nucleus are undergoing ferroptosis while the other macrophages are alive. Mesothelial cells with yellow/red filled nucleus present mild/severe oxidative damage in the genomic DNA, predisposing to carcinogenesis.

excess iron with the other cells of different types via ferritin in extracellular vesicles as safe non-catalytic Fe(III). However, a similar process, one involving FedEVs, may cause accumulation of excess iron in other specific cells, which may eventually contribute to carcinogenesis.

CONCLUSION

The major causes of human mortality in most countries are cancer and atherosclerosis (myocardial infarction and cerebral infarction/hemorrhage) except for emerging infectious diseases, such as COVID-19. We believe that these conditions, especially cancer, are associated with the long-term use of iron and oxygen [4]. Thus, modifying iron metabolism would be important as a practical way to prevent carcinogenesis. The present finding on the role of EVs in the transport of iron-loaded ferritin is important to consider future strategy for cancer prevention. We have been using plastics thus far so much in our daily life for convenience, which currently causes microplastics and nanoplastics pollution in the sea [57]. Surprisingly, the microplastics and nanoplastics are coming back to us as part of seafood diet [58], which is an emergent issue in current ecotoxicology to be further explored from the viewpoint of iron and foreign body.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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