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Review

Allergy and ferroptosis

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Abstract: Allergic responses are defined by hypersensitive reactions against foreign antigens that activate immune cell interactions, leading B lymphocytes to produce IgE. This results in tissue mast cells and circulating basophil cells releasing leukotrienes and histamine, which causes an early inflammatory response; in the late phase, immune cells release chemokines and cytokines. Ferroptosis is an iron-dependently regulated cell death process in which excessive production of reactive oxygen species (ROS) causes massive lipid peroxidation–mediated membrane damage. Allergens, IgE regulation, inflammatory cytokines, and lipid metabolism from an allergic response can induce ferroptosis, which can then enhance the allergic response. This review summarizes the mechanism of ferroptosis and its key regulators. We particularly focus on the potential roles of allergen triggers, IgE regulation, inflammatory cytokines, and lipid metabolism in ferroptosis. We also describe recent research progress regarding ferroptosis in allergic asthma, allergic rhinitis, and allergic dermatitis. Further research on the process of ferroptosis in allergic responses and diseases can aid potential novel therapeutic tools.

Keywords: allergic response; ferroptosis; oxidation; IgE; lipid metabolism

1. Introduction

The term “allergy” was introduced by Dr. Clemens von Pirquet, an Austrian pediatrician, in a paper published in the Journal Münchener Medizinische Wochenschrift in 1906 [1]. It originally described a change in the reactivity of the organism regarding time, quality, and quantity. Today, the term *allergy* defines specific reactions of immunologic hypersensitivity against harmless foreign allergens. Common human allergens include house dust mites, nuts, pollens, and fungal spores, among others. The immune system of allergic individuals identifies these allergens as a threat and produces an allergic response. Such response is distinguished into two phases. The sensitization phase begins when antigen-presenting cells display allergen fragments to T lymphocytes. In a process that involves the secretion of cytokine IL-4 by T lymphocytes, B lymphocytes are activated and matured into plasma cells that produce allergen-specific IgE antibodies through immunoglobulin class switching recombination [2]. IgE antibodies then bind to receptors on tissue mast cells and circulating basophils, which activates enzyme cascades in the cell membrane involving protein kinase C, tyrosine kinase, phospholipase A2, phospholipase C, and an influx of calcium ions. This leads to the release of histamine, leukotrienes, and prostaglandins in the early-phase response. The late-phase allergic response is characterized by the migration of inflammatory cells from circulation. Recruitment effector cells are T_H2 lymphocytes, eosinophils, and basophils, which release inflammatory cytokines and chemokines. Allergic responses can result in relatively minor syndromes such as localized itching but can also be potentially fatal in more severe cases, such as anaphylaxis, a condition leading to upper respiratory obstruction and collapse [3].

Programmed cell death includes apoptosis, necroptosis, pyroptosis, and ferroptosis. It is controlled by a variety of extracellular and intracellular signals. The programmed cell death maintains tissue homeostasis and regulates the number of cells in multicellular organisms. Specific caspases mediate apoptosis, which is tightly regulated by several executioner and regulatory molecules, resulting in the condensation of chromatin, fragmentation of DNA, cell shrinkage, dynamic membrane blebbing, and loss of adhesion to extracellular matrices. Necroptosis is a form of regulated necrotic cell death mediated by the receptor-interacting protein kinase 1 (RIPK1) and receptor-interacting protein kinase 3 (RIPK3). Pyroptosis is a programmed cell necrosis mediated by the gasdermin protein family, in which the N terminals of proteins are cleaved and form pores on the cell membrane, causing cell death. Apoptosis, necroptosis, and pyroptosis have been reported to be involved with allergic diseases [4–6]; their mechanisms regarding allergic diseases have been reviewed extensively elsewhere.

Ferroptosis is another programmed cell death process, defined by an interaction between iron, oxygen, and oxidizable phospholipids. Ferroptosis is uniquely characterized by an accumulation of phospholipid peroxides [7]. Ferrous iron mediates the Fenton reaction and contributes to the generation of reactive oxygen species (ROS) [8]. Excessive oxygen radicals can further cause an accumulation of lipid peroxidation products, including PL-hydroperoxide (PLOOH), malonaldehyde (MDA), and 4-hydroxynonenal (4-HNE) [9]. Lipid peroxidation leads to the rupture of the plasma membrane, causing cell death. Recent research has shown that ferroptosis is involved in many diseases, from cancers to autoimmune diseases [10]. The relationship between ferroptosis and allergy has been less discussed. Allergic disorders, such as allergic asthma, allergic rhinitis, and allergic dermatitis, are mediated by oxidative stress. Excessive exposure to ROS is the hallmark of oxidative stress, leading to damage to proteins, lipids, and DNA. Oxidative stress occurs not only as a result of inflammation but also from

environmental exposure to air pollution and cigarette smoke [11]. In this review, we briefly introduce the molecular mechanisms of ferroptosis and some key regulators in the process. We focus on how the allergic response may lead to ferroptosis in cells, particularly for allergen triggers, IgE regulation, inflammatory cytokines, and lipid metabolism. We will then update the current research on ferroptosis in the contexts of allergic asthma, allergic rhinitis, and allergic dermatitis. Finally, we will briefly discuss future research on ferroptosis in allergic response and allergic diseases.

2. Mechanism of ferroptosis and key regulators

Landmark studies in the 1950's have established that cystines are required for the survival and proliferation of mammalian cells grown in culture conditions [12]. Afterward, it was found that the death of mammalian cells deprived of extracellular cystine coincided with the loss of intracellular glutathione (GSH) [10,13]. GSH peroxidase 4 (GPX4) can efficiently reduce lipid hydroperoxides to lipid alcohols in the lipid bilayer [14]. In 2012, the term "ferroptosis" was coined to describe a form of non-apoptotic cell death driven by iron-dependent lipid peroxidation [15]. Ferroptosis lacks the characteristic biochemical and genetic executioners of apoptosis but also plays a role in cellular development [16]. Ferroptosis has emerged as an important mechanism in many physiological and pathological processes in cells, leading to significant therapeutic advancements for many diseases.

Ferroptosis occurs through regulations in three key components. These include iron regulation, ROS generation, and lipid peroxidation [17]. This is an iron-dependent form of cell death with iron overload as the hallmark of cell death [18]. Iron participates in oxygen transport, ATP generation, and DNA biosynthesis to maintain cellular homeostasis [19]. Excessive ROS causes increased lipid peroxidation. When excessive ROS cannot be neutralized efficiently, it accumulates and disrupts plasma membrane integrity, and cells succumb to death [20]. The detailed mechanisms of ferroptosis have been discussed elsewhere [10,21], and many proteins and molecules have been reported to be able to regulate the three components above, promoting or inhibiting ferroptosis. Some key regulators are discussed below.

2.1. Iron regulation

Iron metabolism is regulated at both the systemic and cellular levels. The efflux of iron from duodenal enterocytes and macrophages is regulated by the liver peptide hormone hepcidin, which induces the degradation of the iron exporter ferroportin (FPN) [10]. Iron is a powerful immune system modulator. Excess iron causes a hyperactive immune system, which can attack undigested food peptides. Chemicals released during these intense allergic reactions can damage surrounding tissues [22].

If the capacity of transferrin to bind iron is exceeded, a potentially toxic form of iron will appear, namely non-transferrin-bound iron (NTBI). NTBI is taken up in an uncontrolled manner via NTBI importers such as ZIP14 and CD44. Iron uptake enlarges the iron pool. Through the generation of hydroxyl or hydroperoxyl by the Fenton reaction, free and redox-active iron can trigger lipid peroxidation to cause ferroptosis. Iron is imported by extracellular transferrin that binds to the transferrin receptor (TFR) on the cell membrane and is exported by ferroprotein [23]. The regulation of iron abundance through the action of the iron-storage protein ferritin (via ferritinophagy) dictates the sensitivity to ferroptosis [24,25]. Ferroptosis can be induced by TFR1 and nuclear receptor coactivator 4 (NCOA4), which is a selective cargo receptor that mediates the autophagic degradation

of ferritin, the cytosolic iron storage complex, in ferritinophagy [26]. Heme oxygenase 1 (HMOX1), also called heat shock protein 32, is ubiquitously expressed in human tissues. HMOX1 can metabolize heme into ferrous iron, carbon monoxide, and biliverdin/bilirubin [27]. Ferroptosis can be inhibited by FPN, a transmembrane protein that is the sole iron exporter in vertebrate species, responsible for exporting cellular iron to maintain iron homeostasis [28]. The process can also be inhibited by ferritin heavy chain 1 (FTH1) and ferritin light chain (FTL), both of which function by storing iron [29].

2.2. ROS generation

Iron can directly generate excessive ROS through the Fenton reaction, thereby increasing oxidative damage. ROS are free radicals generated by redox reactions during the regulation of cell survival. Small synthetic molecules can induce ROS levels. Erastin is a small synthetic molecule that induces ferroptosis [15] through a variety of molecules, including the cystine-glutamate transport receptor, the voltage-dependent anion channel (VDAC), and p53 [30]. Ras-selective lethal small molecule (RSL3) inhibits the antioxidant system as it increases intracellular iron accumulation. RSL3 inhibits the activity of GPX4, thus inducing ferroptosis [31]. Ferroptosis suppressor protein 1 (FSP1) is a glutathione-independent molecule that exerts a ferroptosis inhibition role parallel to the glutathione-dependent lipid GPX4 [32]. Dihydroorotate dehydrogenase (DHODH) is an enzyme localized on the outer face of the mitochondrial inner membrane that can inhibit mitochondrial ferroptosis [33]. Ferrostatin-1 (Fer-1) has been proven to inhibit erastin-induced ferroptosis [34].

The antioxidant defense is a key system in cells to inhibit ferroptosis. The key players are the cystine transporter solute carrier family 7 member 11 (SLC7A11) and GPX4. SLC7A11 is an antiporter and biomarker that regulates tumor cell metabolism in the tumor microenvironment (TME). Drugs blocking the SLC7A11 pathway can induce ferroptosis. Most cancer cells mainly rely on SLC7A11 to import extracellular cystine; once imported into the cytosol, cystine is reduced to cysteine, which is subsequently used to synthesize GSH for antioxidant defense [35]. GPX4 has been identified as the second mammalian glutathione peroxidase [14] and the key upstream regulator of ferroptosis [36,37]. GPX4 has the unique function of reducing complex hydroperoxides, including phospholipid hydroperoxides and cholesterol hydroperoxides, to their corresponding counterparts, thereby interrupting the lipid peroxidation chain reaction [38]. GPX4 catalyzes GSH, oxidizes GSH to glutathione disulfide (GSSG), and removes cellular lipid peroxides. Other antioxidant elements include ferroptosis suppressor protein-1 (FSP1) [39], coenzyme Q10 (coQ10) [40], GTP cyclohydrolase I (GCH1) [41], and tetrahydrobiopterin (BH4) [42].

2.3. Lipid peroxidation

The generation of reactive oxygen species and subsequent hydroxyl radical (OH)-mediated lipid peroxidation in the plasma membrane causes damage and is the core event leading to ferroptosis. These processes are inhibited by integrated antioxidant or membrane repair systems. Acyl-CoA synthetase long-chain family member 4 (ACSL4) is an essential agent for ferroptosis execution [43]. Lysophosphatidylcholine acyltransferase 3 (LPCAT3) is primarily responsible for esterifying arachidonic acid (AA) into lysoPLs [44]. Lipoxygenases (LOXs) are not essential for the execution of ferroptosis but may play a role in its initiation by contributing to the cellular pool of lipid hydroperoxides that promote lipid autoxidation [45]. 5-LOX selectively catalyzes PE-AA oxidation

and executes ferroptotic cell death. Polyunsaturated fatty acids (PUFAs) are the substrate of LOX [46]. Steroyl-CoA desaturase 1 (SCD1) is a fatty enzyme that converts saturated fatty acids into monounsaturated fatty acids, being a critical modulator of the fatty acid metabolic pathway and ferroptosis [47]. Its role in mitochondrial dysfunction through mitochondrial membrane potential or mtROS accumulation still needs to be investigated [33]. On the other hand, elevated levels of SCD1 protect cancer cells against ferroptosis [48].

The activation of acyl-CoA synthetase long-chain family member 3 (ACSL3) converts monounsaturated fatty acids (MUFAs) to acyl coenzyme A esters that bind to membrane phospholipids, providing protection against ferroptosis [49]. Liproxstatin-1 not only inhibits mitochondrial lipid peroxidation but also restores the expression of GSH, GPX4, and ferroptosis suppressor protein 1 [50].

The major regulators of iron regulation, ROS generation, and lipid peroxidation in ferroptosis are listed in Table 1.

3. Allergic reaction and ferroptosis

3.1. Allergenic triggers in allergy and ferroptosis

Allergens not only cause allergic response but may also induce cell ferroptosis. The most studied allergens are house dust mites (HDMs) and pollen.

Dust mite allergy is an IgE-mediated type 1 hypersensitivity reaction to dust mite allergens, commonly found in household dust [51]. Inhalation of HDMs can increase ROS and decrease GSH levels in mouse lungs [52]. HDM inhalation induces dysmorphic small mitochondria with decreased crista, as well as condensed, ruptured outer membranes. The activities of GPX4 and SLC7A11 are significantly decreased, and protein expression levels of ACSL4 and LOX1 are upregulated, compared with mice in the control group. These results indicate that HDMs can induce airway hyperresponsiveness (AHR) through airway inflammation and ferroptosis through lipid peroxidation and ROS levels [52].

Pollen allergies affect more than 10% of the global population; up to one-third of the affected individuals having hay fever symptoms will later develop allergic asthma [53]. Normally, pollen cannot enter the thoracic regions of the respiratory tract due to its large size but can affect the nasopharyngeal mucous membrane [54]. Birch pollen can be ruptured and released as an aerosol from 30 nm to 4 μm. It primarily contains Bet v1 allergen, a prominent elicitor of allergic sensitization and asthma [55]. Bet v1 was found to increase ROS levels and enhance inflammation independently of pollen-derived intrinsic nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity. It can induce ferroptosis underlaid T_H2 and T_H17 hybrid asthma [56].

Other environmental factors could be allergic triggers and cause ferroptosis as well. Postnatal arsenic exposure increases the risk of childhood allergic rhinitis [57]. Arsenic exposure can also decrease ferritin level and decrease GPX4 to induce ferroptosis [58,59]. Asbestosis is an interstitial lung disease caused by the inhalation of asbestos fiber [60], which can cause weak allergic disease [61]; ferroptosis-dependent extracellular vesicles act as a key mutagenic mediator by transporting iron, which contributes to asbestos-induced mesothelial carcinogenesis [62]. Long-term exposure to particulate matter 2.5 (PM2.5) can cause allergic diseases [63] and induce ferroptosis in human endothelial cells through iron overload and redox imbalance [64].

Table 1. Key regulators in ferroptosis.

Regulator	Name	Function	References
Iron metabolism			
Promotion			
TFR1	Transferrin receptor protein 1	Transporting Fe^{3+} to intracellular domain	[23]
NCOA4	Nuclear receptor coactivator 4	Maintaining intracellular iron homeostasis	[26]
HMOX1	Heme oxygenes1	Releasing free iron from heme	[27]
Inhibition			
FPN	Ferroportin	Transporting Fe^{2+} to extracellular domain	[28]
TFL/FTH1	Ferritin light chain/ferritin heavy chain 1	Storing iron ion	[29]
Oxidation			
Promotion			
Erastin	Erastin	Regulating cystine-glutamate transport receptor	[15]
RSL3	RAS-selective lethal small molecule 3	Promoting xCT lysosomal degradation through ROS/AMPK/mTOR	[31]
Inhibition			
SLC7A11	Solute carrier family 7 member 11	Transporting cystine into cells	[35]
GPX4	Glutathione peroxidase 4	Key antioxidant enzyme in cells	[14]
GSH	Glutathione	Co-factor of GPX4	[13]
Fer-1	Ferrostatin-1	Inhibiting RSL3 or erastin	[34]
Lipid peroxidation			
Promotion			
ACSL4	Acyl-CoA synthetase long chain family member 4	Catalyzing the activation of long-chain fatty acids	[43]
LPCAT3	Lysophosphatidylcholine	Catalyzing FuFA-CoA to produce PE-AA and PE-AD acyltransferase 3	[44]
LOXs	Lipoxygenases	Catalyzing PE-AA oxidation and ferroptotic execution	[46]
SCD1	Stearoyl-CoA desaturase-1	Inducing ferroptosis through lipid metabolism or inhibiting ferroptosis through mTOR pathway	[47,48]
Inhibition			
ACSL3	Acyl-CoA synthetase long-chain family member 3	Key to MUFA-induced ferroptosis resistance	[49]
Lp-1	Liproxstatin-1	Preventing lipid ROS build-up	[50]
FSP1	Ferroptosis suppressor protein-1	Working through coenzyme 10	[32]
DHODH	Dihydroorotate dehydrogenase	Inhibiting mitochondrial ferroptosis	[33]

3.2. IgE regulation in allergy and ferroptosis

IgE is the central molecule in the allergic response, traditionally associated with atopic disease and systemic anaphylaxis [65]. In our previous experiments examining the factors that regulate immunoglobulin class switching in B lymphocytes and the generation of IgE, we identified the circadian oscillation gene *BHLHE40* as central to antibody class switching during stimulation [2]. *BHLHE40* can regulate ferroptosis in dual ways: It may inhibit ferroptosis through SREBF1 [66] or it can promote macrophage pro-inflammatory gene expression and function of genes including *PTGS2* and *SERPINB2* [67]. The two associated proteins have been found to promote ferroptosis in cells.

PTGS2 is a gene encoding the cyclooxygenase-2 (COX-2), markedly increased in cells treated with ferroptosis inducers [68]. COX-2 is a key enzyme in prostaglandin biosynthesis. Increased expression of PTGS2 is associated with ferroptosis [69]. PTGS2 was found to be augmented in bronchial smooth muscle tissues of experimental asthma [70]. Mutations of *PTGS2* genes are associated with diisocyanate-induced asthma [71].

Serpin family B member 2 (SERPINB2) is a member of the serine protease inhibitor family and the main product of monocyte/macrophage activation after infection or inflammation. SERPINB2 has been identified through protein–protein interactions in asthma [72]. SERPINB2's regulatory effects on inflammation seem to play a double role: It is associated with T_H2 response and also acts as an anti-inflammatory gene [73,74]. It also promotes the progression of inflammation [75,76]. A genome-wide association study identified the *SERPINB* gene cluster as a susceptibility locus for food allergies [77]. Increased SERPINB2 potentiates 15LO1 expression via STAT6 signaling in epithelial cells in eosinophilic chronic rhinosinusitis with nasal polyps [78].

3.3. Inflammatory cytokines in allergy and ferroptosis

Ferroptosis originates and propagates from several organelles, including mitochondria, endoplasmic reticulum (ER), Golgi, and lysosomes. Recent data revealed that immune cells can both induce and undergo ferroptosis [16]. Disordered redox biology and increased lipid peroxidation can activate multiple inflammatory cells and pathways; also, such inflammatory cells can aggravate intracellular oxidate stress and excessive lipid peroxidation [79]. Inflammatory cytokines, including IL-1β, IL-6, TNF-α, and IFN-γ, can regulate the synthesis of ferritin to influence iron storage in cells and tissues [80]. Multiple inflammation signaling pathways, including JAK-STAT, NF-Kb, and MAPK, are closely related to ferroptosis; also, ferroptosis can affect such signaling pathways [81]. IL-13 is a cytokine that is associated with allergies [82] that can also induce ferroptosis. The MDA serum level, an index of lipid peroxidation, has been found to positively correlate with IL-13 levels and negatively correlate with the predicted forced expiratory volume in 1 s (FEV1%) in asthmatics. IL-13 facilitates ferroptosis by upregulating the suppressor of cytokine signaling 1 (SOCS1) [83]. In human osteoblast-like MG63 and umbilical vein endothelial cells (HUVEC), TNF-α signaling promoted cystine uptake and GSH biosynthesis, providing protection against a low-dose of ferroptosis-inducer erastin. TNF-α facilitates ferroptosis in the presence of high-dose erastin through ROS accumulation. TNF-α regulates ferroptosis-induced osteogenic and angiogenic dysfunctions [84]. Interferon-γ produced by tumor-infiltrating T cells can kill cancer cells through the induction of ferroptosis [85]. These cytokines are central to an allergic response and ferroptosis.

3.4. Lipid metabolism in allergy and ferroptosis

One of the key elements in ferroptosis is abnormal lipid metabolism. In recent years, the *ORMDL3* gene on chromosome 17 has been linked to allergic asthma [86]. ORMDL3 is an important transmembrane protein anchored in the ER [87]. The ER is the cytoplasmic membrane system responsible for the storage of calcium, protein folding, and lipid synthesis. ORMDL3 facilitates the unfolded protein response to cellular stress by influencing ER calcium ATPase and ER-mediated Ca^{2+} flux [88]. It interacts with the serine palmitoyltransferase (SPT) enzyme complex in sphingolipid synthesis, especially for ceramide and sphingosine-1-phosphate (S1P) levels [89]. ORMDL3 works in multiple pathways, regulating airway inflammation in epithelial cells [90]. It can promote eosinophil trafficking and activation. The overexpression of *ORMDL3* in eosinophils causes increased rolling, distinct cytoskeletal rearrangement, extracellular signal-regulated kinase phosphorylation, and nuclear translocation of NF-kb [91]. ORMDL3 upregulates airway smooth muscle proliferation, contraction, and Ca^{2+} oscillations in asthma airway smooth muscle cells [92]. These biological functions have been intensively reviewed [90,93]. ORMDL3 influences almost all organelles in the cell with specific roles in ferroptosis [94].

The most direct evidence of ORMDL3 being involved in ferroptosis is that it regulates HOMX1. *ORMDL3* knockdown epithelial cells have lower HMOX1 expression [90]. HMOX1 could metabolize heme into ferrous iron, carbon monoxide, and biliverdin/bilirubin [95]. HMOX1 expression is highly inducible in response to various stimuli, including heavy metals, oxidative stress, inflammation, and UV radiation. Different cis-acting elements on the promoter of *HMOX1* facilitate the binding of different transcriptional factors to the promoter and activate HMOX1 expression. HMOX1 is not only a rate-limiting enzyme in heme metabolism but an important regulator in allergic response through the regulation of various immune cells, such as dendritic cells, mast cells, basophils, T cells, and macrophages [96]. In monolayer retinal pigment epithelium (RPE) cells, a modulated expression of HMOX1 could elicit ferroptosis [97]. Lipoxygenases (LOXs) are enzymes that catalyze the peroxidation of polyunsaturated fatty acids (arachidonic acid and linoleic acid) [98]. The LOX pathway is involved in allergic tracheal contraction [99], and LOXs have been implicated as central players in ferroptosis [45].

The factors for both ferroptosis and allergic reactions are listed in Table 2; the potential mechanisms for allergic response and ferroptosis are shown in Figure 1.

Table 2. Factors influencing both allergy reaction and ferroptosis.

Factors	Role in allergic response	Role in ferroptosis	References
Allergen triggers			
HDM	Inducing IgE mediated Type 1 hyperresponsive reaction	Decreasing GPX4 and SLC7A11 and upregulated ACSL4 and LOX1	[51,52]
Pollen	Inducing IgE	Increasing reactive oxygen species (ROS)	[56]
Arsenic	Inducing allergic rhinitis	Increasing ferritin and decreasing GPX4	[57,58]
Asbestosis	Causing weak allergic reactions	Mediator by transporting iron	[60,61]

Continued on next page

Factors	Role in allergic response	Role in ferroptosis	References
PM2.5	Allergic causes	Through iron overload and redox imbalance	[63,64]
IgE regulation			
BHLHE40	Regulating IgE	Regulating PTGS2 in ferroptosis	[2,67]
PTGS2	Regulating prostaglandin E2	Lipid peroxidation	[70,71]
SERPINB2	Food allergy	Involving ferroptosis	[77]
Cytokines			
IL13	Allergic cytokines	Upregulating SCO_3 in ferroptosis	[83]
TNFα	Allergic cytokines	Osteogenic and angiogenic dysfunctions in ferroptosis	[84]
IFNγ	Allergic cytokines	Infiltrating T cells in ferroptosis	[85]
Lipid metabolism			
ORMDL3	Cell stress, sphingolipids HRV infections	Regulating HOMX1 in ferroptosis	[90,93]
HMOX1	ORMDL3 regulated	Releasing free ion from heme	[27]
LOXs	Regulating allergy	Inducing peroxidation	[99,46]

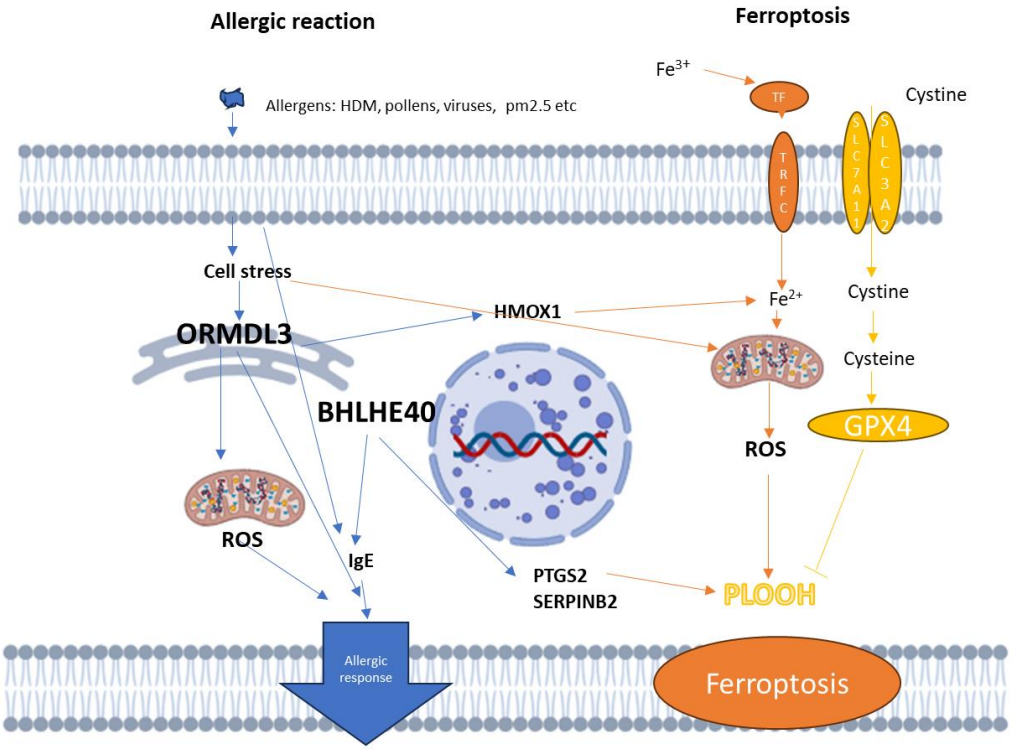

Figure 1. The potential mechanism of ferroptosis in allergic response. Allergens can influence cell stress, inducing the generation of IgE and cytokines release. BHLHE40 regulates IgE production and induces PTGS2 and SERPINB2 to regulate ferroptosis. The allergic gene *ORMDL3* regulates HMOX1, which regulates iron metabolism. ORMDL3 also regulates cell stress and lipid synthesis involved in ferroptosis.

4. Ferroptosis and allergic diseases

Currently, only a few papers have discussed the relationship between ferroptosis and allergic diseases. Several conclusions can be drawn by studying iron metabolism, oxidation, and lipid peroxidation in allergic diseases.

4.1. Allergic asthma

Allergic asthma is the most common type of asthma. In the United States, approximately 25 million people have asthma, and among them approximately 60% have allergies [100]. Allergens such as HDMs can induce allergic asthma through generations of allergic-specific IgE triggering an allergic response. In a study of HDM-induced mouse asthma, HDM exposure significantly increased airway hyperresponsiveness (AHR), inflammatory cell infiltration, and mucus secretion around the airways [52]. The mice had elevated IgE levels, and IL-5 and IL-13 levels in the bronchoalveolar fluid (BALF) and lung eosinophilia in BALF were also observed. Interestingly, inhalation of HDM increased ROS production and decreased the levels of GSH in the mouse lungs. HDM inhalation induced dysmorphic small mitochondria with decreased crista, as well as condensed, ruptured outer membranes—signs of ferroptosis. The research also demonstrated that the activities of GPX4 and SLC7A11 were significantly decreased and protein expression levels of acyl-CoA synthetase long-chain family member 4 and 15 lipoxygenase 1 were upregulated. Results suggested that HDM inhalation can induce ferroptosis in the lungs in allergic asthma patients [52].

Interleukin-17A (IL-17A) levels are elevated in patients with allergic asthma. IL-17A was significantly upregulated within serum in allergic asthma cases [101]. In a report with human bronchial epithelial cells (BEAS-2B) and ovalbumin (OVA)-induced allergic asthmatic mice, IL-17A was found to significantly increase ferroptosis. It regulated and activated lipid peroxidation to induce ferroptosis, whereas *IL-17A* knockdown effectively inhibited ferroptosis *in vivo* by protecting airway epithelial cells via the xCT-GSH-GPX4 antioxidant system, also reducing airway inflammation. Mouse mRNA sequencing results indicated that the TNF pathway was significantly altered in the *IL-17A* knockout OVA group. N-acetylcysteine inhibits the TNF signaling pathway, which was found to protect BEAS-2B cells from IL-17A-induced lipid peroxidation and ferroptosis damage [102].

4.2. Allergic rhinitis (AR)

AR relates to an inflammation (redness and swelling) of the inner human nose caused by an allergen. Symptoms of allergic rhinitis include sneezing, itchiness, and blocked or runny nose. Some people only get seasonal allergic rhinitis due to being allergic to tree or grass pollen. Other people suffer from allergic rhinitis all year round. Ferroptosis can occur in epithelial cells in AR [103], suggesting that novel tools for AR prevention could be explored in the near future.

Lecithin-bound iodin (LBI) has been used to treat the disease symptoms. In an OVA-induced allergic rhinitis mouse model, LBI has been found to suppress OVA-specific IgE production by attenuating germinal center (GC) reaction in the draining lymph nodes. The antiallergic effect of LBI is most likely attributed to increased serum iodine levels. An *in vitro* treatment of activated B cells with potassium iodide could induce ferroptosis by increasing intracellular ROS and ferrous iron in a concentration-dependent manner. LBI diets increased ROS levels in GC B cells of the draining lymph

nodes. This suggests that iodine directly promotes ferroptosis in activated B cells and attenuates GC reactions, leading to the alleviation of allergic symptoms [104].

In AR, the epithelial barrier composed of nasal epithelial cells is the first line of defense, which is crucial to protect the host immune system from harmful stimuli. Moreover, irreversible structural changes in nasal epithelial cells can occur in response to different allergens. Ferroptosis and allergic responses in nasal epithelial cells can be regulated by many genes, interacting with multiple signaling pathways.

4.3. Allergic dermatitis

Allergic contact dermatitis (ACD) is a prevalent inflammatory skin disease that occurs due to an immune response induced by skin exposure to various allergens. The prevalence of ACD is increasing, currently afflicting approximately 20% of the world's population [105].

In a report of 2,4-dinitrochlorbenzene (DNCB)-induced ACD mice, ferroptosis activation was found to be more remarkable in the dermis rather than the epidermis. *Gpx4*-knockout mice showed similar severity of skin dermatitis as control mice, but ferroptosis inhibitor Fer-1 alleviated skin inflammation in mice and reduced ferroptosis in neutrophils and $CD8^+$ T cells presenting ACD [106].

The skin system provides an indispensable barrier for the human anatomy, shielding it from external influences. Dermatological disorders result from a complex interplay of inflammation, oxidative stress, and other elements caused by genetic, immunological, infectious, and environmental factors. Currently, there has been a surge in interest in the exploration of ferroptosis in inflammation, recognized as a critical factor in the pathogenesis of skin diseases. Ferroptosis can incite the release of damage-associated molecular patterns (DAMPs), which can further elicit immune cells' activation and stimulate the expression of inflammatory cytokines, therefore facilitating an inflammatory response [105,107].

5. The future works of ferroptosis and allergic disease

Regulating ferroptosis can potentially be explored as a therapeutic strategy for reversing cancer therapy resistance [108]. Inhibition of ferroptosis could be applied to therapeutic treatments for neurodegenerative diseases and strokes [109]. For allergic diseases, targeting ferroptosis should consider inflammatory cytokines and IgE regulation. Inducing ferroptosis can lead to the release of cytokines, enhancing the allergic response. On the other hand, inducing ferroptosis in antibody-producing B lymphocytes could result in less IgE production, therefore reducing the allergic response. Recent investigations on dietary iodine found that it can attenuate allergic rhinitis by inducing ferroptosis in activated B cells [104]. Targeting the ROS system, inflammatory cytokines, and lipid metabolism pathways in ferroptosis may bring new therapeutic treatments for allergic disease, as could the research on the mechanisms and pathways of ORMDL3 and BHLHE40 in allergic diseases and ferroptosis [93].

Many questions about allergy and ferroptosis remain. What is the threshold of damage from the allergic response to induce ferroptosis? How does the allergic reaction cause iron overload and oxidative damage? What is the balance between ferroptosis and T_H2 inflammatory response in an allergic response? How can ferroptosis physiologically regulate macrophage subset development, function, and survival in allergy responses?

6. Conclusions

Allergic responses to allergens trigger an inflammatory response that can cause ferroptosis through iron accumulation, oxidative stress, and lipid metabolism. Ferroptosis regulates allergy response in two different ways: It can control cell death due to iron overload and enhance allergic response through major signal pathways and T_H2 cytokines. The challenge of researching ferroptosis in allergy is the lack of good animal models and cellular models available. Specific translational strategies, such as developing GPX4 agonists or iron chelators, may provide additional tools to treat allergies. Further investigations regarding the ferroptosis pathways in allergic response could bring new insights into potential therapeutic targets to intervene in allergic diseases in the future.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

All authors contributed to write the manuscript. Y.Z finalized the draft.

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