REVIEW ARTICLE

Ferroptosis in viral infection: the unexplored possibility

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Virus-induced cell death has long been thought of as a double-edged sword in the inhibition or exacerbation of viral infections. The vital role of iron, an essential element for various enzymes in the maintenance of cellular physiology and efficient viral replication, places it at the crossroads and makes it a micronutrient of competition between the viruses and the host. Viruses can interrupt iron uptake and the antioxidant response system, while others can utilize iron transporter proteins as receptors. Interestingly, the unavailability of iron facilitates certain viral infections and causes cell death characterized by lipid peroxide accumulation and malfunction of the antioxidant system. In this review, we discuss how iron uptake, regulation and metabolism, including the redistribution of iron in the host defense system during viral infection, can induce ferroptosis. Fenton reactions, a central characteristic of ferroptosis, are caused by the increased iron content in the cell. Therefore, viral infections that increase cellular iron content or intestinal iron absorption are likely to cause ferroptosis. In addition, we discuss the hijacking of the iron regulatoy pathway and the antioxidant response, both of which are typical in viral infections. Understanding the potential signaling mechanisms of ferroptosis in viral infections will aid in the development of new therapeutic agents.

Keywords: viral infections; cell death; ferroptosis; iron; antioxidant response

INTRODUCTION

The incidences of emerging and re-emerging viral infections have surged despite the tremendous progress in preventing and controlling infectious diseases and the biomedical field for the past two decades. The occurrence of epidemics and pandemics, such as the Ebola virus [1], Influenza virus [2], middle east respiratory syndrome coronavirus (MERS-CoV) [3], severe acute respiratory syndrome coronavirus (SARS-CoV) [4], and SARS-CoV-2 [5] has posed a significant threat to humans. Several animal viruses, such as african swine fever virus [6], inflict significant economic loss. Virus infections have been shown to trigger cell death via various mechanisms, depending on the viral species, however elucidating the causes and effects can be difficult [7–9]. Cell death can be a double-edged sword during pathogenic infections [10, 11]. On the one hand, virus-associated cell death can help to prevent additional infection, while on the other hand, it contributes to the progression of many infections [10, 12–14]. On another facet, viral infection can lead to cell death due to viral activities within infected cells [15, 16], and the escape of viral progeny can cause cell death [15, 17]. It is noteworthy that some viruses encode proteins to inhibit cell death and facilitate their proliferation [7, 8].

Iron is an essential element for many enzymes in the cell. These enzymes include but are not limited to DNA primase, DNA helicases, ribonucleotide reductase, and ATPase [18], which are necessary for DNA expression. The unavailability of iron compromises multiple cellular functions, including genome replications [19]. The vital role of iron in cellular physiology maintenance and efficient viral genome replication places iron at the crossroads and makes it a competing chemical between the pathogen and the host [20, 21]. During infections, the immune response fortifies its defense in which iron is withheld from pathogens [22, 23]. However, various viral species have been found to interrupt iron uptake and the antioxidant response system [21], while others utilize iron transporter proteins as receptors (see Table 1). Interestingly, an increase in iron concentration facilitates ferroptosis.

Ferroptosis is a regulated cell death pathway that heavily depends on iron-mediated lipid free radical formation and accumulation [24, 25]. These actions can be inhibited by the enzyme glutathione peroxidase 4 (GPX4) and the antioxidant glutathione (GSH). Interruption of the cellular process that leads to ferroptosis can inhibit its occurrence [24–26]. Therefore, this interruption can serve as a therapeutic method to manipulate cells by either increasing their survivability or inducing death in infection conditions. Here, we review how iron uptake, regulations, and metabolism, including the redistribution of iron in the host defense system during viral infection, can induce ferroptosis. Described herein also is the inhibition of the antioxidant response during infections, emphasizing GSH and GPX4 as these are identified major inhibitors of ferroptosis.

FERROPTOSIS

Ferroptosis, as proposed by the Nomenclature Committee on Cell Death (NCCD), is a mechanism of cell death resulting from oxidative perturbations of the intracellular microenvironment, which is under

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Table 1. Effects of viruses on iron metabolism and the possible contribution to ferroptosis.

Effect	Virus	Reference
Iron transport during viral infection		
Increases serum and cellular iron uptake and suppresses hepcidin expression	Hepatitis C virus (HCV)	[66, 67, 72, 150]
	Hepatitis B virus (HBV)	[72, 80, 150]
Potentially causes cellular iron overload and iron scavenging	Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)	[76, 151, 152]
Reduces serum iron, upregulates the expression of hepcidin	Human immunodeficiency virus (HIV)	[72, 153]
Increases cellular iron via hepcidin mediated degradation of ferroportin		[63]
Induces the expression NRAMP (DMT) and increases cellular iron uptake	Coxsackievirus B3 (CB3)	[81]
	West Nile virus (WNV)	[154]
Increases the expression of 12/15-LOX and mitochondrial iron content	Respiratory syncytial virus (RSV)	[155]
Iron metabolism and viral infection		
Viral genome amplification and viral replication is inhibited by iron	Influenza A virus (H1N1)	[156]
	Enterovirus 71 (EV-71)	[89, 157]
Increases serum ferritin concentration	Hepatitis C virus (HCV)	[158]
	Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2)	[76]
Various viruses on redox state and antioxidants		
Reduces the cellular concentration of GSH and/or affects GPX4 activity	Coronaviruses (CoVs)	[159]
	Dengue virus	[160]
	Human immunodeficiency virus (HIV)	[134, 161, 162]
	Herpes simplex virus (HSV)	[163, 164]
	Influenza virus	[165, 166]
	Japanese encephalitis virus (JEV)	[167, 168]
	Kaposi sarcoma-associated herpesvirus (KSHV)	[128]
	Zika virus	[169]
Produces lipid peroxide free radicals (L-ROS)	Japanese encephalitis virus (JEV)	[170]
Upregulates the expression of system xc⁻	Human immunodeficiency virus (HIV)	[161]
	Japanese encephalitis virus (JEV)	[127]
Interrupts system xc⁻ function	Kaposi sarcoma-associated herpesvirus (KSHV)	[128]
Lysosomal disruption		
Causes lysosomal damage using viral protein	Avian Influenza A virus (H5N1)	[45]
	Severe acute respiratory syndrome-coronavirus (SARS-CoV)	[171]
Receptors mediating viral entry		
Uses TfR1 as a cellular receptor	Hepatitis C virus (HCV)	[172]
	New world hemorrhagic fever viruses (NWHFVs)	[91, 173]
	New world arenaviruses (NWAVs), e.g., Machupo and Junin	[174–178]
	Gastroenteritis virus (GEV)	[179]
	Mouse mammary tumor virus (MMTV)	[180]
Uses NRAMP as a cellular receptor	Sindbis virus	[181]

constitutive regulation by GPX4 [25], which is heavily marked by iron driven lipid peroxidation (Fig. 1) and lipotoxicity accumulation due to Fenton reactions and failure of the antioxidant defense to inhibit or terminate the pathway. Dixon et al. [24] observed that ferroptosis is distinct from other forms of cell death in many facets. Morphologically, it is marked by small mitochondria with a higher membrane density, reduced or absent mitochondrial crista, and raptured out membranes [24, 27]. These changes may be controlled by the BH3-interacting domain death antagonist (BID) and BCL2-binding component 3 (PUMA) [28, 29]. Reportedly, the cell nucleus during ferroptosis does not change in size [30] but can be electron-lucent [31]. The integrity of the nuclear membrane is jeopardized, causing the release of High Mobility Group-Box 1 (HMGB1). Suggestively, the nucleus membrane damage may be caused by

lipid peroxides, and the damage may extend as far as the inner membrane [31]. Biochemically, ferroptosis is marked by the depletion of GSH and reduced GPX4 activity and lipotoxicity [27]. Genetical changes that may alter iron homeostasis and facilitate lipid peroxidation, the two main features of ferroptosis, are also involved. However, it is worth noting that the process is regulated by multiple genes associated with iron uptake, lipotoxicity, and antioxidation responses. (Further reading on genes that regulate ferroptosis [24, 32–37]).

IRON UPTAKE
Stable iron ion homeostasis is vital for cell function and survival. Iron in the body can be acquired by absorption in the intestine or
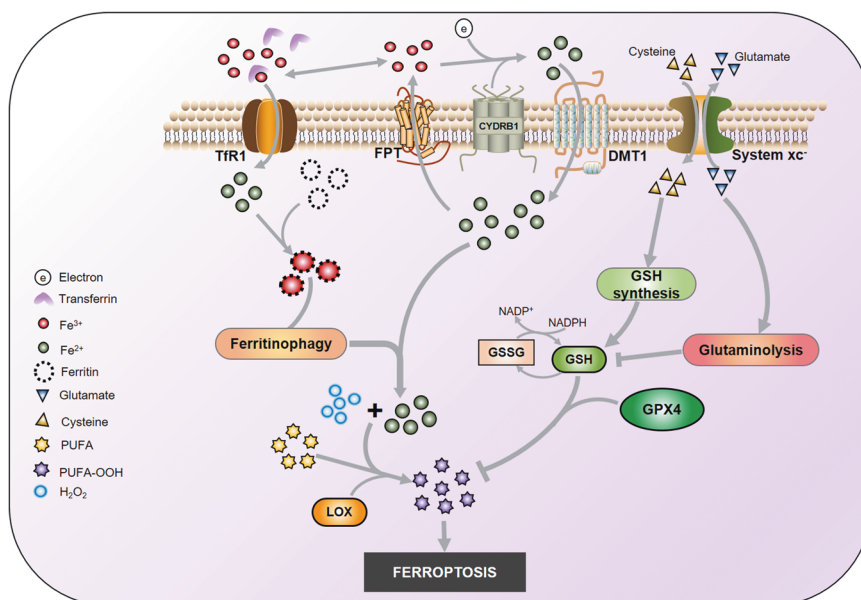
Fig. 1 Ferroptosis inducing pathways. Iron enters the cell via TfR1 or DMT1 and is exported by FPT. DMT1 uptakes Fe^{2+} and requires CYDRB1 to reduce Fe^{3+}. When inside the cell, iron binds to ferritin, which can be degraded by a lysosomal activity known as ferritinophagy. Non-ferritin iron can then react with O_2 molecule, e.g., H_2O_2 the by-products of this reaction then reacts with PUFAs forming lipid peroxides. System-xc⁻ imports cysteine and exports glutamate. Cysteine is used in the synthesis of GSH, which, together with GPX4, reduces lipotoxicity. Glutamate participates in glutaminolysis. GSH can be inhibited by downstream metabolites of glutaminolysis. An increase of iron or inhibition of GSH/GPX4 results in ferroptosis. TfR1 Transferrin receptor protein 1, DMT1 divalent metal transporter, FPT ferroportin, CYDRB1 Cytochrome B Reductase 1, PUFAs short for polyunsaturated fats, GSH Glutathione, GSSG Glutathione disulfide, GPX4 Glutathione Peroxidase 4, LOX Lysyl Oxidase.

Box 1 The emerging role of organelles and signaling pathways in ferroptosis

Lack or depletion of functional mitochondria disrupts cellular sensitivity to cysteine depletion or deprivation [56]. The hyperpolarization of the mitochondrial outer membrane potential can cause the depletion of GSH via deprivation of cysteine [56], which can facilitate cysteine deprivation-dependent ferroptosis while inhibiting cellular cysteine uptake. The mitochondrial promotes the exhaustion of GSH, thereby attenuating the antioxidant mechanism [182]. Disruption of mitochondrial processes, TCA cycle, electron transport chain and glutaminolysis, has been reported to inhibit ferroptosis [56, 118, 182]. On top of this, mitochondrial lipids serve as a source for lipid peroxides [56].

Lysosomes are no bystanders in ferroptosis. Lysosomal activity influences iron availability in the cell by disrupting transferrin transport and degradation of ferritin [183, 184]. In addition, the lysosomal activity also produces ROS, inclusive of lipid peroxides. Autophagic activities mediated by the lysosome are likely to participate in ferroptosis, as shown by studies [43, 185]. Cysteine deprivation significantly reduces following the knockdown of autophagic genes ATG3 and ATG13 [43]. Autophagy is also likely to cause ROS accumulation and induction of ferroptosis [36]. Lysosomal cathepsin B has also been known to induce GSH depletion. STAT3 is an activator of cathepsin B and can therefore participate in ferroptosis [36, 43].

The endoplasmic reticulum may also play a role in ferroptosis as inducers of ferroptosis cause ER stress [118]. Erastin-induced ER stress activates the ATF4 signaling pathway, and the downstream of the pathway promotes degradation of GSH [186]. The role of ER and ER stress remains highly uninvestigated. However, ER stress promotes autophagy [187], and autophagy can degrade ferritin, causing ferroptosis.

Signaling pathways that may inhibit system xc- or increase cellular iron availability are also likely to cause ferroptosis. The heme oxygenase 1 (HO-1) [188], HSPB1 [48], and FANCD2 [189] pathways influence iron availability and have been linked to ferroptosis. FANCD2 targets genes involved in iron metabolism and GPX4, leading to iron increase while reducing the antioxidant effect. p53 [190] and its activator G3BP1-interacting lncRNA [191] facilitate ferroptosis by targeting the SLC7A11 component of the system xc- thereby attenuating its function.

ZRT/IRT-like proteins have also been identified as transporters of Fe^{2+} that are not bound to transferrin [38, 39]. While inside the cell, Fe^{3+} is encapsulated in the acidic endosome, where it is reduced back to Fe^{2+} by the six-transmembrane epithelial antigen of the prostate 3 (STEAP3), which also facilitates TfR1 dependent iron uptake [40] or stored in ferritin [41]. From here, the iron is then released into the cytoplasm with the help of divalent metal transporter 1 (DMT1) (DMT1 is also present on the plasma and organelle membranes) for usage or balancing iron deficiency. Iron is exported out of the cell via ferroportin (FPT), an iron efflux pump that can oxidize Fe^{2+} to Fe^{3+} [42].

The inhibition of iron export and/or the increase in uptake promotes ferroptosis. Processes that increase free iron content in the cell, such as ferritinophagy, which is the degradation of ferritin leading to the release of iron into the cytosolic labile iron pool, promote iron accumulation and is reported to induce ferroptosis [43] (Fig. 1). Ras mutation also causes ferroptosis by increasing the expression of TfR1 while reducing the expression of ferritin [44]. The degradation of organelles that have high deposits of iron, such as lysosome [45] and mitochondria [46], can also cause cytosolic iron increase and thereby leading to ferroptosis (Box 1). The accumulated iron can react with lipids forming lipid reactive species while inhibition of iron accumulation in the cell attenuates ferroptosis [24, 47, 48].

LIPID PEROXIDATION

Iron-mediated lipid peroxidation occurs mainly using the polyunsaturated fatty acids (PUFA), which are susceptible to peroxidation due to their acyl tail. PUFA phospholipids can be generated by the enzymes Acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT). LPCAT is also responsible for PUFA activation and remodeling into transmembrane lipid [49, 50]. Aside from this, PUFAs can also be obtained from dietary sources or synthesized by the enzyme acetyl CoA carboxylase. These phospholipids require esterification
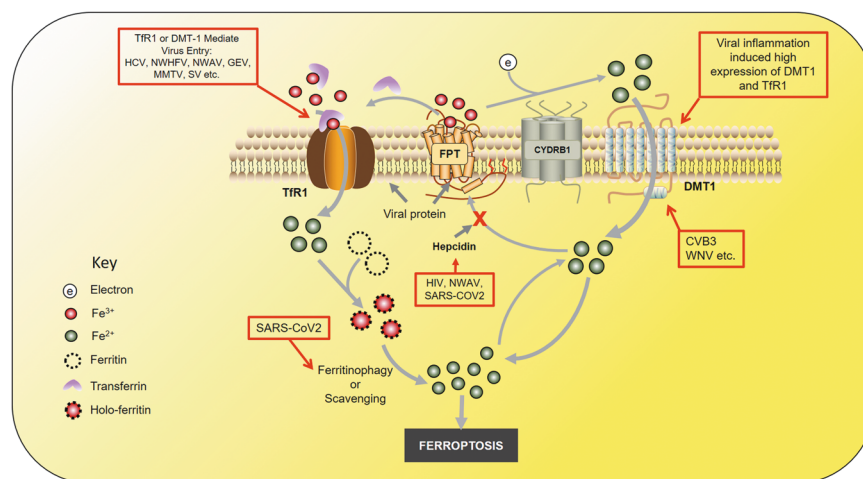
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from the degradation of erythrocytes. Intestinal iron uptake involves haem iron transporter HEPH, DMT1, FPN1, and TfR1. Intestines are a major source of iron. Iron uptake in the intestine is heavily influenced by the microbiota and is absorbed in Fe^{2+}. Ferrous is transported into the cell via the TfR1 receptor protein.

Fig. 2 Viruses, iron, and iron receptors. Iron transport proteins such as TfR1 and DMT1 serve as receptors of many viruses. TfR1 and DMT1 are upregulated by a viral infection, causing increased iron uptake. Iron-bound in ferritin is scavenged by viruses via viral-induced ferritin degradation or disruption. Viral activity causes hepcidin expression, which inhibits iron export and leads to excessive cellular iron. These eventually cause cell death via ferroptosis. TfR1 Transferrin receptor protein 1, DMT1 divalent metal transporter, FPT ferroportin, CYDRB1 Cytochrome B Reductase 1.

and oxidation to function as a synthetic signal transduction medium [51]. Reportedly the oxygenation attack occurs on the acyl-arachidonoyl (AA) and the adrenoyl acid (AdA) phosphatidy-lethanolamine (PE) end of the lipid chain [52]. This oxygenation can be directly achieved by 12/15-lipoxygenases (12/15-LOX), cytochrome P450 oxidoreductase, as well as other iron-containing sources of oxidation such as AKR1C1-3 [27, 53–55]. The oxygenated PE then functions as death signals and causes the depletion of PE and other PUFAs [53]. When iron in the cytoplasm reacts with H_2O_2 (Fenton reaction), producing OH•, which attacks PUFAs (Fig. 1), a chain reaction that produces lipid peroxides starts [24]. Aside from this, iron is a cofactor of enzymes that catalyze lipid peroxidation [51, 55]. Lipid peroxidation can also occur in the lysosome [43] as well as the mitochondrial [56] (Box 1).

ANTIOXIDANTS
The suppression of GPX4 activity leaves lipid peroxidation unchecked and facilitates ferroptosis, achieved by RSL3/5, ML162, ML210 DPIs, and FIN02, etc., which can interfere with the GPX4 [26, 27, 47]. GPX4 activity can also be inhibited by buthionine sulphoximine (BSO), which terminates the synthesis of GSH [27], and FIN56, which causes a short supply of selenocysteine tRNA by inhibiting the melanovate pathways, attenuats GPX4 synthesis [57, 58]. FIN56, together with acetyl-CoA carboxylase, can also degrade GPX4 [52]. The melanovate pathway is likely to play a role in the inhibition of ferroptosis due to its production of ferrostatin and liproxstatin, which reduces lipotoxicity [26, 47]. The downregulation of GPX4 has been shown to increase cell sensitivity to ferroptosis [44]. Other molecules known to induce ferroptosis via direct or indirect induction are artesunate, lanperisone, and acetaminophen [59, 60]. The voltage-dependent ion channel proteins 1 and 3 (VDAC1/3) of the outer membrane of the mitochondria can cause the exhaustion of cysteine and, therefore, may likely cause cysteine deprivation [30]. Gao et al. reported the mitochondria as an antagonist of antioxidants in ferroptosis [56].

VIRUSES, IRON METABOLISM AND FERROPTOSIS
Iron regulation and viral infection
Hepcidin, a key protein to regulate systematic iron homeostasis, binds to the iron transporting protein ferroportin causing its internalization and degradation (Fig. 2), resulting in an increase in the cytoplasmic iron and a negative regulatory effect on iron uptake [61, 62]. Degradation of ferroportin can facilitate viral genome transcription as observed in HIV-1 [63]. The expression of hepcidin is modulated by the increase in iron availability due to intestinal absorption or the release from macrophages iron recycling, a cellular increase of iron stores, inflammation, or infection. Many viral infections have shown an inverse relationship between the increase in cellular iron endosomes and hepcidin upregulation [64]. An increase of hepcidin is accompanied by high ferritin, thereby storing iron in an inactive state. The cell is deprived of iron and is protected from further infection and the production of free radicals [65].

Contrary to this, research in chronic hepatitis C viral (CHCV) infection reports differently as hepcidin is downregulated instead of upregulated [66]. This dysregulation causes the systematic increase of ferritin in the blood and transferrin saturation, which has been attributed as a major contributing factor to the accumulation of iron in hepatic cells during CHCV infection, the progression of the infection as well as its resistance to treatment [66–68]. Iron released into circulation via ferroportin during recycling can cause serum iron overload [69, 70]. The host response to viral infection by redistributing iron makes it prone to co-infection by other pathogens. Joann and the team reported the subsequent association between HIV-induced iron redistribution and tuberculosis [71]. High cellular iron concentration can induce hepcidin expression. Possibly, virally infected cells experience increased iron uptake before the hepcidin expression is elevated, and viruses have been known to produce proteins that target regulatory proteins of iron metabolism, such as TfR1 (Fig. 2), which has been reported in HIV infections but is not investigated in other viral infections [72–74]. Certain viruses have also been found to hijack cells that are actively taking in iron [21]. Ameglio and the team reported the downregulation of ferritin two days post-infection due to viral replication in HeLa-derived cells RD, C8166, and HeLa-T4-6c [75]. The team also suggested that this possibly causes iron toxicity.

On the contrary, in a surveying study on COVID-19 patients, it was observed that there was a high concentration of serum ferritin in patients who had pronounced inflammatory responses [76]. However, ferritin may serve as a source of iron, while some viral protein may scavenge iron or interfere with hepcidin activity [77] (Fig. 2). Iron scavenging and toxicity have been elucidated in
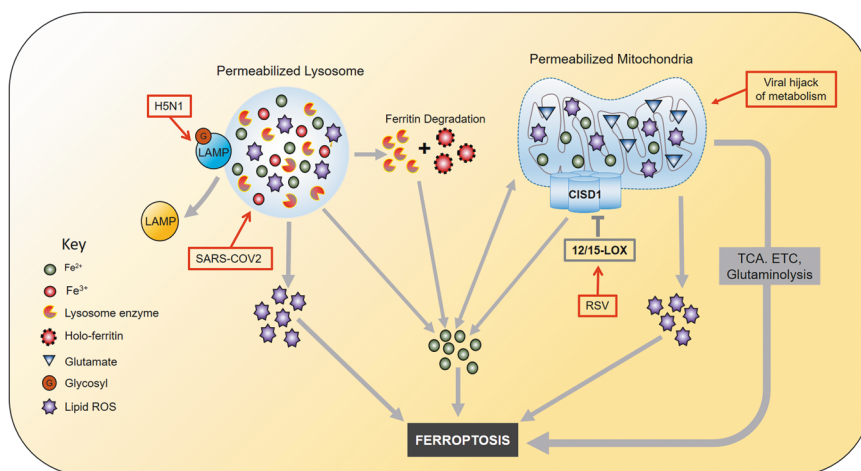
Fig. 3 Iron-rich organelles in viral infection. The iron in lysosomes and mitochondria with permeabilized membranes is released into the cytosol, causing cytosolic iron accumulation. Lysosomes and mitochondria can also be a source of lipid ROS. 12/15 LOX inhibits CISD1, which increases mitochondrial iron uptake consequently. 12/15 LOX is upregulated during RSV infection. Viruses hijack cell metabolism and increase the TCA cycle, ETC activity, and glutaminolysis which facilitates ferroptosis. H5N1 can deglycosylate LAMP, thereby disrupting or permeabilizing the lysosome and causes lysosomal content leakage. Lysosomal enzymes degrade ferritin causing further accumulation of iron. The iron can then participates in lipid peroxidation, or the lysosome/mitochondria lipid ROS causes ferroptosis. ROS Reactive oxygen species, CISD1 CDGSH Iron Sulfur Domain 1, LOX Lysyl Oxidase, LAMP Lysosomal Associated Membrane Protein, TCA cycle tricarboxylic acid cycle, ETC Electron Transport Chain, RSV Respiratory Syncytial Virus.

bacterial infections but are not highly investigated in viral infection [77–79], further suggesting the need to investigate iron uptake and ferritin in various viral infections prior to and post increased hepcidin expression. The accumulation of cellular iron due to viral infection can cause Fenton reactions and finally ferroptosis. (Further reading on Viruses and Iron [22, 80–87]).

Inhibition of viral infection depending on iron
In mammals, blood hosts an abundant supply of iron. This iron is either free or binds to haeme. Iron can regulate the replication of numerous viral infections in different organisms. In humans, iron inhibits the replication of the hepatitis C virus by suppressing viral RNA and protein expression via inhibiting the nonstructural protein 5B (NS5B) polymerase [88]. Ferric-containing salts such as ferric ammonium citrate (FAC) have also been shown to inhibit other viruses, including Influenza A virus, Zika virus, EV-71, HIV [89]. However, this inhibition depends not just on the iron contained in the salt but also on the citrate. Organisms that acquire nutrition from other organisms via blood meals obtain most of their iron from these blood meals. Mosquitoes are one kind of such an organism, and Zhu and coworkers found that the prevalence of dengue virus in the mosquito was regulated by the host serum iron [90]. The host serum iron was utilized by the iron metabolism pathway of the mosquitoes to inhibit viral ROS generation, thereby reducing viral infectivity. (Further reading on viruses and iron metabolism proteins [77, 91–95]).

Iron receptors and transport proteins usage by viruses
Iron receptors on cells of different organisms have also been known to serve as entry points of viruses (Table 1, Fig. 2). The natural resistance-associated macrophage protein (NRAMP), a common iron receptor in *Drosophila* and *A. aegypti* was found to be the serve receptor of Sindbis virus, and its downregulation due to iron supplements resulted in the inhibition of the viral replication in a research study by Hitoshi and the team [96]. TfR1 in mammals has also been identified as receptors of several viral species, including but not limited to New World hemorrhagic fever viruses, Machupo virus, Junin virus, Canine Parvovirus, Mouse mammary tumor virus [91, 97]. Some viruses like the coxsackievirus B3 tend to facilitate the expression of proteins

involved in cellular iron uptake, such as metallothionein 1/3 and DMT1 upon early days of infections [81].

VIRUSES, IRON RICH ORGANELLE, AND FERROPTOSIS
Viral activities such as viral gene expression, host-virus triggered signaling, virus-physiological stress, among others, can destroy organelles of the host. The destruction of cellular organelles that abundant house iron-containing or iron-requiring proteins such as lysosome and mitochondria results in releasing the iron into the cytosol. The organelle contents are likely to participate in ferroptosis or infection progression (Fig. 3).

The mitochondria
The mitochondria possess a high iron content, as is required in the ATP synthesis during the electron transporting process. Exogenous factors, including viral infections, have been known to induce loss of mitochondrial membrane potential (MMP) [98, 99]. MMP can cause leakage of many mitochondrial contents, which may disrupt many cellular processes. Although there is no research showing the link between viral infection and the release of mitochondrial iron, recent findings suggest that this is likely to occur when the mitochondria membrane integrity is jeopardized [100, 101]. Investigations in this area may provide new therapeutic targets and further understand why viral infections are worsened in older people. Iron uptake by the mitochondria increases with age, and this may cause iron overload [46]. Reportedly iron overload causes leakage of mitochondrial oxidants and ROS [102]. Mitochondrial ROS has been known to inhibit hepcidin transcription, leading to iron accumulation [100, 103]. Iron can then participate in lipid peroxidation and eventually cause ferroptosis cell death. Notably, in some viral infections, mitochondrial damage seems to be inhibited [100]. Alternatively, with the depletion of GSH and the inactivity of GPX4, 12/15-lipoxygenase (12/15-LOX) can be activated in the mitochondria to oxidize PUFAs [55, 104, 105]. Activated 12/15-LOX has been reported to oxidize mitochondria membrane lipids in neuronal cells [105], which causes the accumulation of lipid peroxides in the mitochondrial membrane. 12/15-LOX activation has also been known to increase mitochondrial iron content via its inhibition of the CDGSH iron-sulfur domain 1 (CISD1) [105, 106]. CISD1 plays a key
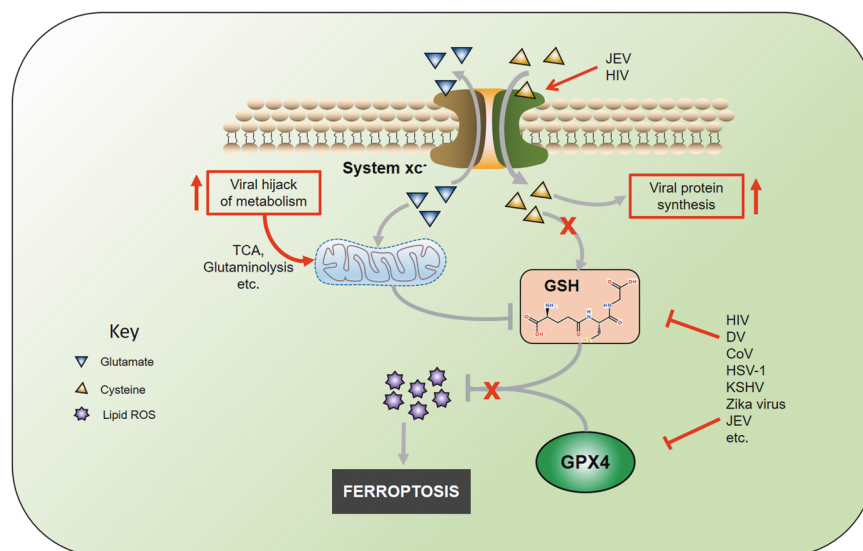
Fig. 4 Antioxidants of ferroptosis during viral infection. System-xc⁻ influxes cysteine and effluxes glutamate. Cysteine is used in viral protein synthesis, causing reduced GSH synthesis. Viruses inhibit GPX4 and GSH by either attenuating synthesis or degrading the protein and molecule. Virally hijacked metabolism produces metabolites that inhibit or degrade GSH. Lack of antioxidant activity leads to the accumulation of lipid ROS and eventually causes ferroptosis. GSH Glutathione, GPX4 Glutathione Peroxidase 4, ROS Reactive oxygen species, TCA tricarboxylic acid.

role in the modulation of iron uptake by the mitochondria, and its loss of function increases iron content [107, 108]. This iron can cause Fenton reactions in the mitochondria or can be released in an event where the mitochondria membrane integrity is jeopardized. Yuan et al. reported that the inhibition of CISD1 contributes to mitochondrial lipid peroxidation and eventually ferroptosis [109]. Certain viruses hijack the mitochondria to evade the mitochondrial antiviral signaling and replication [110], and this may cause hyperpolarization, which can impair the antioxidant mechanism [56].

Lysosomes
Lysosomes have been long known to contain a relatively large amount of redox-active iron due to their role in iron metabolism [111, 112]. Lysosomal damage can occur in viral infections, resulting in the release of lysosomal content, including redox-active iron. Xiangwu and the team found that the neuraminidase (NA) of the H5N1 influenza virus can degrade and deglycosylate the lysosomal associated membrane protein (LAMP) (see Fig. 1) [45]. Lysosomal enzymes are often glycosylated to prevent the hydrolysis of lysosomal environment content [113, 114]. The deglycosylation effect of NA on LAMP, which makes up at least 50% of the lysosome membrane content, can cause digestion and rapture of the lysosome membrane (see Table 1) [45]. Reportedly this can cause the release of lysosomal content inclusive of hydrolytic enzymes and the high content of iron which is often present in the lysosomal, thereby leading to an increase in the cytosolic iron labile pool [45, 115]. The accumulated iron can then mediate Fenton lipid peroxidation. Iron catalyzed lipid peroxidation in the absence of reductants and causes lipid peroxide accumulation, leading to cell death.

Furthermore, the released lysosome enzymes can degrade the ferritin via proteolytic methods. Ferritin is degraded by the lysosome to supplement cellular iron deficiency or in an autophagic manner by the process of ferritinophagy using lysosome enzymes [116]. The autophagy degradation of ferritin has been reported to cause ferroptosis [36]. Suggestively, permeabilization of the lysosome is likely to cause the release of enzymes involved in ferritin degradation and the degradation of proteins involved in iron regulation into the cytosol, which can increase the cytosolic iron ion

content leading to the dysregulation of iron metabolism. Lysosomal permeabilization can induce or participate in multiple cell death mechanisms, including but not limited to lysosomal dependent cell death, necrosis, necroptosis, and apoptosis [117]. Other viruses have been known to induce lysosome permeabilization, although the mechanism remains unclear [115].

VIRUSES, ANTIOXIDANTS, AND FERROPTOSIS
System-xc⁻ antiport and cysteine
The cysteine can be prevented from entering the cell by blocking or inhibiting the cysteine/glutamate antiporter system-xc⁻ or preventing the participation of cysteine in GSH formation. Inducers of ferroptosis include but are not limited to glutamate, erastin sulfasalazine, and sorafenib. These molecules can directly interfere with the activity of system xc⁻ thereby interrupting the supply of cysteine and consequently damages the endoplasmic reticulum [24, 118, 119]. The supply of cysteine is essential in the synthesis of GSH [120]. Jiang L and Sato have reported P53's ability to repress cysteine absorption via the downregulation of SLC7A11, a key active component of the system-xc⁻ [121, 122]. This process is, however, dependent on the presence of ROS-induced stress [123]. System-xc⁻ functions involve the influx of cysteine in the cytosol and the efflux of glutamate into the extracellular space [124]. The released glutamate represents the principal source of extracellular glutamate in brain regions and causes excitotoxicity implicated in several neuronal diseases [125, 126]. Certain viruses such as the Japanese encephalitis virus have been known to enhance the system-xc⁻ activity and therefore facilitate neuronal damage, but this also has been found to reduce oxidative stress in the cells [127]. Research by Dai and coworkers reported reducing intracellular GSH and inducing viral lytic gene expression following the inhibition of system-xc⁻ in PEL cells infected with the Kaposi's sarcoma-associated herpesvirus (KSHV) [128]. In the same research, it was suggested that the inhibitors of system-xc⁻ can prevent PEL tumor progression. The inhibition of the antiporter results in the reduction of GSH synthesis, GPX activity and weakens the antioxidant defense. There is limited knowledge on the role and state of system-xc⁻ antiport in viral infection. However, current data suggest that inhibiting the antiport can facilitate ferroptosis. Suggestively as most viruses incorporate

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Box 2 GPX4 in antiviral innate immunity

While GPX4 function has been mainly attributed to reducing oxidized molecules, it is noteworthy that GPX4 also plays a role in the innate immune system. Research by Matsushita and the team reported that the absence of GPX4 in antigen-specific T cells (CD8$^+$ and CD4$^+$) altered the physiological response of the T cells [192]. This alternation was manifested in the form of the failure to expand and protect from acute lymphocytic choriomeningitis virus (LCMV). GPX4 was therefore found to be crucial in the expansion of the T cell and the protection of viral and parasitic infections. Notably, GPX4 is required for T cell survival under noninflammatory conditions [192]. However, the requirement for survivability may differ among the subsets of T cells. GPX4 deficient T cells died via ferroptosis, and this prevented immunity to infection by LCMV. Returning normal functionality and increased survivability were observed in cells under lipid peroxyl stress after treatment with Vitamin E [192]. Vitamin E is known to be an inhibitor of ferroptosis due to its antioxidant GPX4 activity and has been shown to improve cell survival in GPX4 deficient cells [192, 193]. GPX4 also indirectly activates the stimulator-of-interferon genes (STING), which is important in sensing foreign nucleic acid material in the cytoplasm. This activation is achieved by maintaining the redox state of the cell. Jia et al. reported the carbonylation of STING in HSV, which was facilitated by GPX4 deficiency and is inhibited by GPX4 [194]. In the same experiment, the inhibition of STING by GPX4 reduced HSV infection. The role that GPX4 plays in the immune system is not well elaborated and may require further investigation. There is supporting evidence that low levels of GPX4 can exacerbate infections by enhancing cell death and altering the function of the T cells. (Further reading on GPX4 in the immune system [194–197]).

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cysteine in their protein, it is likely to occur that the antiport can maintain its function during viral infection, yet the antioxidant response is jeopardized.

Glutathione and GPX4

Glutathione (GSH), a molecule that plays a key role in the cellular response to ROS and their elimination. It is formed by glutamate-cysteine synthetase by covalently combining cysteine and glutamate. In this process, cysteine is the rate-limiting reactant, and its absence reduces the cells' capability to respond to ROS effects [120, 129] (Fig. 4). Cysteine enters the cell via the system xc⁻. GSH often detoxifies hydrogen peroxide (H_2O_2), which is often involved in many reactions that produce ROS, including Fenton reactions. Enzymes of the GPX family then use GSH as a substrate to reduce H_2O_2 into water producing a hydroxyl (OH^-) molecule, which oxidizes GSH and forms GSSG. GSSG is not an antioxidant and requires to be reduced to GSH to function as an antioxidant, achieved by using NADPH as a cofactor, and the enzymes glutathione reductase (GSR) catalyzes the reaction, which yields GSH and NAD$^+$ [120, 129, 130]. Unfortunately, the oxidation and reduction of GSH can produce excess free radicals that damage molecules (via oxidation) that play critical roles in cellular homeostasis [131].

ROS in a cell can have beneficial functions as signal molecules in immune response [132]. Different viruses may have various ways by which they can induce ROS and lead to its accumulation. These ROS targeting antioxidant defense proteins are often inclusive of the GPX family of enzymes [133]. Morris et al. reported low cellular GSH in macrophages with an increased concentration of GSSG in HIV infection [134] (see Table 1), and a higher concentration of free radicals, pro-inflammatory cytokines were observed. Aside from the ROS oxidation of GSH to form GSSG, the production of pro-inflammatory cytokines such as IL-1 can cause the depletion of cysteine concentration in the cell [135]. Cysteine depletion can also be attributed to the excessive and rapid incorporation of cysteine in the viral genome RNA proteins, which have several cysteine amino acids containing domains, which occurs mainly during viral replication and contributes to a decrease in GSH [136, 137]. In response to the inflammation and depletion of cysteine, key enzymes in the synthesis of GSH are downregulated [138–140], which impairs the antioxidant function of GSH and its availability, leading to cellular loss of GPX4 function. As established earlier, GPX4 is identified as a key enzyme in response to lipid peroxidation and an inhibitor of ferroptosis. The lack of GSH will cause GPX4 inactivity, and this, therefore, can promote

cell death by ferroptosis due to the accumulation of lipid-free radicals or lipid peroxides. Some studies found that GPX4 expression, together with other selenoproteins, was reduced due to HIV infection [141], which may require further investigation into other viruses. On top of this, ROS molecules produced during viral-induced inflammation may facilitate ferroptosis. Interestingly, some viruses can encode GPX4 in their genome, as observed in the human dermatotropic poxvirus [142]. GPX4 is not only essential in the antioxidant mechanism but also the immune system (Box 2).

CONCLUSION AND PERSPECTIVES

Viruses are no strangers to hijacking and disrupting multi-cellular processes to favor their proliferation, which can have unfavorable consequences on host cells and lead to cell death. Various mechanisms of cell death have been observed in many viral infections. A recently described mechanism of cell death, ferroptosis, is likely to be among the forms of cell death during viral infections. Common features of ferroptosis, such as reduced cysteine and consequently reduced GSH, reduced GPX4 activity, and increased cellular iron availability, among others, have been found to occur in viral infections, suggesting the possible occurrence of ferroptosis, especially when occurring together with dysregulated cell metabolism. However, it is noteworthy that the induction and process may differ from one virus to another, and some viruses may not cause ferroptosis. Iron is essential for viral replication, which may be the reason for the viral usage of iron transporters as receptors, while the underlying mechanism that viruses interrupt iron metabolism remains elusive.

Gut which serves as a major site for dietary iron uptake and a site for iron regulation by hepcidin, and the role of microbiota in iron uptake during viral infections may also provide new insights. Certain viruses target intestinal enterocytes as primary cells of infection. Advances in understanding the mechanism of ferroptosis and discovering new inducers have revealed the role of metabolites and cellular organelles in ferroptosis. Viruses have been known to disrupt cell metabolism and organelles, leading to conditions that may favor ferroptosis. Further investigations in cellular metabolism during viral infections and how it may facilitate ferroptosis can also provide a new understanding. An increased focus on how ferroptosis occurs in viral infections and understanding the role of microbiota in iron uptake during viral infections may lead to discovering new therapeutic targets.

Furthermore, therapeutics of iron metabolism may serve as potential drugs to inhibit viral infection exacerbation caused by cell death. Currently, there are many types of medicines regulating ferroptosis by enzyme inhibition, ion chelation and redox response [143]. Canonical antioxidants, like butylated hydroxytoluene or vitamin E, are recognized as both modulators of ferroptosis and supplements fighting against SARS-CoV-2, HSV, HIV, etc. [144–146]. Among these iron-dependent drugs, most of them variously show antiviral activity for certain viral species. However, the precise antiviral mechanism still need further investigations to provide significant research data. Increasing discoveries prove that ferrous-reactive endoperoxides like artemisinin, arterolane, and artefenomel also have an antiviral function [147–149]. The pharmacological intervention of the ferropotosis pathway indicates promising therapeutics for virus infection prevention and control. The decipherment of the regulatory process of ferroptosis is still critical and can ultimately facilitate the development of new antiviral drugs.

(JLU-STIRT) [2017TD-05]; CAMS Innovation Fund for Medical Sciences (2020-12M-5-001). This review should not be taken as evidence of ferroptosis in viral infection but can be referenced for investigations in these or any related areas. The mentioned viruses are not the only viruses that can increase the likelihood of ferroptosis in host cells. The authors' views are of the authors and should not be interpreted as expressions or implications of the affiliated institutes.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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