This is a preproof accepted article for *Animal Nutriomics*
This version may be subject to change during the production process
DOI: 10.1017/anr.2025.10013

Ferroptosis in viral infections: overview and regulation by nutritional interventions

Aimin Wu[a, b, #], Tingting Zhang [a, b, #], Daiwen Chen [a, b,*]

[a]*Institute of Animal Nutrition, Sichuan Agricultural University, Chengdu 611130, China;*

[b]*Key Laboratory for Animal Disease-resistance Nutrition of China Ministry of Education, Sichuan Agricultural University, Chengdu 611130, China.*

[#]These authors contributed equally to this work.

[*]To whom correspondence should be addressed: Daiwen Chen; E-mail address: dwchen@sicau.edu.cn;

Abstract: Cell death is a defense strategy employed by host cells to combat viral invasion. Viruses can manipulate the host cell death process to facilitate their own dissemination or evade immune surveillance. Ferroptosis, characterized by excessive iron accumulation and lipid peroxidation, is one crucial form of such cell death. Although ferroptosis is primarily associated with tissue/organ damage and tumorigenesis, accumulating evidence suggests that ferroptosis is closely linked to viral infections and their pathogenic mechanisms. This article systematically reviews the metabolic processes associated with ferroptosis, mainly including amino acid metabolism, iron metabolism, lipid peroxidation, and mitochondrial metabolism, it discusses in detail the interaction between viral infections and ferroptosis, and it highlights how viruses exploit the mechanisms of ferroptosis for their own infection and replication. Additionally, the impact of nutritional regulation of ferroptosis on the progression of viral infections is explored. Therefore, understanding the interaction between cellular ferroptosis and viral infections not only provides valuable insights for developing effective antiviral therapeutic strategies but also offers references for the prevention and control of viral infections in animals.

Keywords: Viral infection, Cell death, Ferroptosis, Iron metabolism, Lipid peroxidation

Introduction

Over the past decade, while we have achieved remarkable progress in the prevention and control of infectious diseases, the incidence rate of emerging and re-emerging viral infections remains concerning. Various epidemics or pandemics caused by viral infections pose a serious threat to human health, such as the coronavirus disease (COVID-19) (Choi 2021), Middle East respiratory syndrome coronavirus (MERS-CoV) (Li and Du 2019), influenza A virus (IAV) (Du et al. 2023), and Ebola virus (EBOV) (Chen and Whitehead 2021). Additionally, some animal viruses, such as porcine reproductive and respiratory syndrome virus (PRRSV) (Guo et al. 2021), African swine fever virus (ASFV) (Li et al. 2022), porcine epidemic diarrhea virus (PEDV) (Zhao et al. 2024), and transmissible gastroenteritis virus (TGEV) (Wu et al. 2020), have also caused significant economic losses in the industry. Numerous studies have confirmed that viral infections can trigger or evade cell death, with distinct mechanisms (Verburg et al. 2022). During viral infections, cell death acts as a double-edged sword (Wang et al. 2022). On one hand, virus-induced cell death facilitates viral clearance; on the other hand, certain viruses can exploit cell death pathways to evade host immune defenses (Tummers and Green 2022). Therefore, exploring the mechanisms of cell death during viral infections is crucial for developing novel antiviral therapeutics.

Iron is essential for maintaining the physiology of host cells and the effective replication of viruses, making it a necessary trace element in the intense competition between hosts and viruses. Certain viruses can modulate the host's antioxidant defense system and iron metabolism pathways, while others can directly utilize iron transport proteins as entry receptors (Wang et al. 2022). Notably dysregulation of systemic iron homeostasis (including both iron deficiency and overload) can facilitate infection by specific viruses, ultimately leading to pathological cell death, such as ferroptosis, characterized by accumulation of lipid peroxidation products and collapse of the antioxidant system (Ganz and Nemeth 2015). Ferroptosis is a newly discovered form of cell death characterized by excessive iron accumulation and lipid peroxidation (Dixon et al. 2012). When the rate of reactive oxygen species (ROS) production within cells exceeds the cell's ability to eliminate them, it induces ferroptosis. Currently, the role of ferroptosis in cancer and tissue/organ damage has garnered much attention, but its role in pathogen infections has been severely underestimated (Lei et al.

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

2022). In fact, the latest evidence suggests that processes such as the transmission, pathogenicity, or immune evasion of viral infections are closely related to ferroptosis (Wang et al. 2022). This review provides a comprehensive analysis of iron absorption, transport, metabolism, and its regulatory networks, with particular emphasis on ferroptosis induction during viral infections. The manuscript details the mechanisms by which pathogens hijack ferroptotic pathways to enhance viral replication and dissemination, while concurrently contributing to disease progression. Additionally, we evaluate promising nutritional-based therapeutic approaches that modulate ferroptosis for the prevention and clinical management of virus-associated diseases.

Ferroptosis

The Characteristics of Ferroptosis

Ferroptosis is a newly discovered type of cell death characterized by iron-dependent production of ROS and the accumulation of lipid peroxides to lethal levels (Chen et al. 2021). Compared to common types of cell death, ferroptosis exhibits significant differences in morphological characteristics and biochemical markers (Xie et al. 2016). In terms of morphological features, apoptosis is characterized by chromatin condensation, formation of apoptotic bodies, and disintegration of the cytoskeleton. Notably, mitochondrial morphology remains unaltered throughout this process (Li et al. 2020). The morphology of necrosis is defined by plasma membrane rupture and the spillover of cellular components into the microenvironment (Dixon et al. 2012). Pyroptosis is often accompanied by the formation of pyroptotic bodies prior plasma membrane rupture (Yuan, Najafov, et al. 2016). In contrast, the main morphological features of ferroptosis include mitochondrial membrane shrinkage, increased membrane density, reduced volume, and blurred cristae (Chen et al. 2021). Biochemically, ferroptosis is marked by elevated levels of intracellular free iron (Fe^{2+}), inducing a large production of ROS. Additionally, there is a decrease in glutathione (GSH) content and the activity of glutathione peroxidase 4 (GPX4, a selenoprotein that reduces lipid hydroperoxides), leading to a substantial accumulation of the lipid peroxidation product malondialdehyde (MDA), a terminal product and biomarker of lipid peroxidation (Park and Chung 2019b). Based on the unique features of ferroptosis in cell morphology and biochemistry, these indicators are typically used to assess ferroptosis (Martinez et al. 2020).

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

Regulatory Mechanisms of Ferroptosis

Ferroptosis is triggered by the catalytic oxidation of polyunsaturated fatty acids (PUFAs) on the cell membrane by Fe^{2+} or lipoxygenases (LOX, non-heme iron-dependent dioxygenases that directly peroxidize PUFAs). Various molecules involved in the regulation of amino acid metabolism, iron metabolism, lipid metabolism and mitochondrial metabolism are key regulators of ferroptosis (Fig. 1).

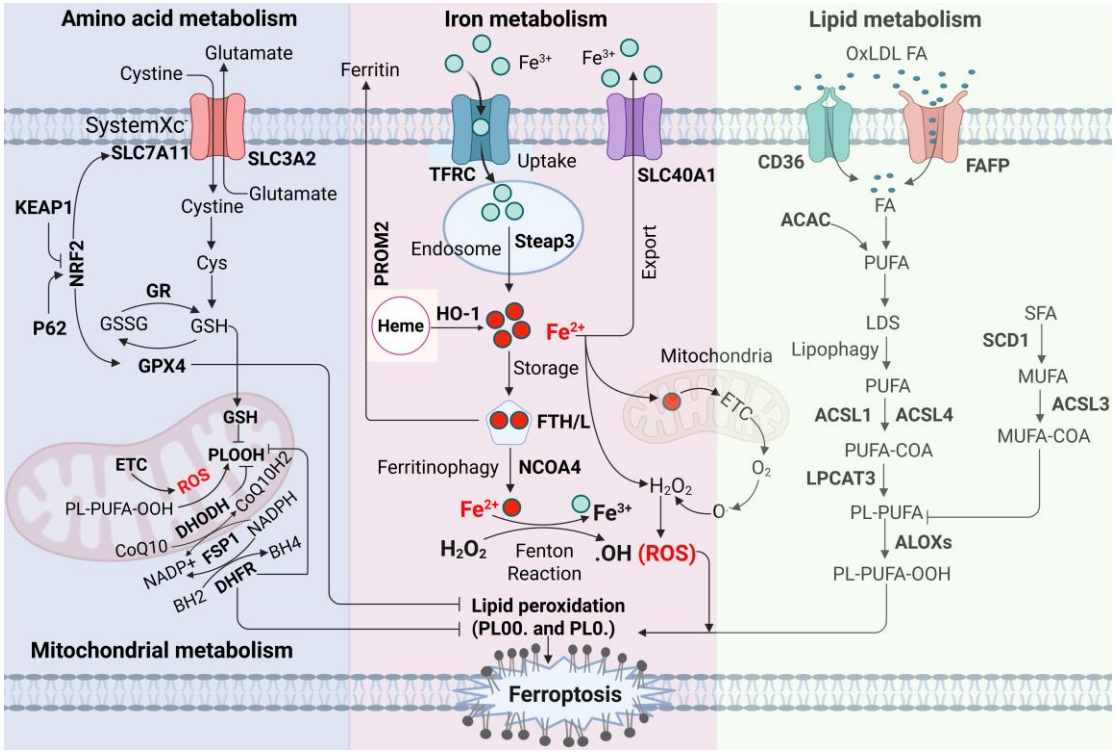

Figure 1 Core pathways of ferroptosis regulation. The pathways triggering ferroptosis ultimately converge on membrane lipid peroxidation as a common endpoint, with multiple metabolic processes involved, including amino acid metabolism, mitochondrial metabolism, iron metabolism and lipid metabolism. As a plasma membrane receptor, the system Xc^- (SLC7A11 and SLC3A2) imports cystine into cells for GSH synthesis, the substrate of GPX4, thereby inhibiting ferroptosis. The keleh-like ECH-associated protein 1 (KEAP1)-P62- nuclear factor erythroid 2-related factor 2 (NRF2) pathway regulates the expression of various anti-ferroptotic proteins, including system Xc^- and GPX4. When cells are deficient in reducing agents such as cysteine, cellular metabolism—particularly oxidative metabolism in mitochondria—leads to ROS accumulation and promotes ferroptosis. Additionally, coenzyme Q10 (CoQ10) and tetrahydrobiopterin (BH4) can suppress ferroptosis independently of GSH. Iron metabolism plays a critical role in ferroptosis activation, primarily involving iron uptake (via transferrin receptor 1, TFRC), storage (in ferritin heavy/light chains, FTH/L), export (via ferroportin, Fpn, SLC40A1), and recycling (through

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy and HO-1-mediated heme degradation). These processes regulate intracellular Fe^{2+} levels. Elevated Fe^{2+} reacts with H_2O_2 via the Fenton reaction, generating excessive ROS and ultimately triggering ferroptosis. Furthermore, lipogenesis involves fatty acid uptake (mediated by CD36 and fatty acid-binding protein, FABP) and the synthesis of polyunsaturated fatty acid-containing phospholipids (PUFA-PLs, key substrates for peroxidation), catalyzed by enzymes such as acyl-CoA synthetase long-chain family member 4 (ACSL4). The activation of Acyl-CoA synthetase long-chain family Member 1 (ACSL1), ACSL4, lysophosphatidylcholine acyltransferase 3 (LPCAT3), and lipoxygenases (LOXs) promotes lipid peroxidation, contributing to ferroptosis progression. Figure created with Biorender.

Amino acid Metabolism

The cystine/glutamate transport system (XC^-), a crucial amino acid transport and antioxidant system, is located on the cell membrane. This system consists of solute carrier family 7 member 11 **(**SLC7A11) and solute carrier family 3 member 2 (SLC3A2) subunits linked through disulfide bonds, forming a functional heterodimer that mediates the 1:1 exchange of extracellular cystine for intracellular glutamate (Sato et al. 1999). SLC7A11 serves as the specific transporter for cystine uptake, whereas SLC3A2 plays an essential role in stabilizing the complex and ensuring proper membrane localization of SLC7A11 (Sato et al. 1999; Koppula et al. 2018; Nakamura et al. 1999). GSH, composed of cysteine, glutamate, and glycine, can bind to toxic free radicals and serves as the substrate for GPX4-catalyzed reactions, converting toxic phospholipid hydroperoxides (PLOOH) to non-toxic phospholipid alcohols phospholipid alcohols (PLOH), thereby clearing lipid ROS and reducing the occurrence of ferroptosis (Yang 2014). Erastin, a canonical ferroptosis inducer, directly inhibits XC^- system activity (Reina and De Pinto 2017). This inhibition comprises cystine uptake, resulting in sustained depletion of intracellular GSH, attenuation of GPX4 activity, and ultimately triggering ferroptosis.

GPX4 is the only known mammalian enzyme that can catalyze the reduction of PLOOH to phospholipid alcohol (Seiler et al. 2008). GPX4 can utilize GSH as a substrate to specifically reduce hydroperoxidized phospholipids and fatty acids, thereby protecting the body from PLOOH-mediated oxidative damage and inhibiting ferroptosis (Ursini and Maiorino 2020). Therefore, GPX4 is a key target for regulating ferroptosis. RSL3 is a GPX4

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

inhibitor that can covalently bind to GPX4, resulting in its inactivation (Yang 2014). In addition to RSL3, several compounds including ML162, DPI, FIN56, and FINO2 have also been identified as GPX4 inhibitors (Cheff et al. 2023).

NRF2 serves not only as an upstream regulator of GPX4, but also as a master transcription factor governing cellular antioxidant responses, playing a pivotal role in activating the antioxidant defense system. p62-mediated degradation of Keleh-like ECH-associated protein 1 (KEAP1) facilitates NRF2 activation in cellular ferroptosis, thereby activating downstream regulatory genes such as *SLC7A11*, quinone oxidoreductase 1 (*NQO1*), heme oxygenase 1 (*HO-1*), and ferritin heavy chain 1 (*FTH*, an iron-sequestering protein), which confer resistance to ferroptosis by altering iron metabolism and lipid peroxidation (Sun et al. 2016).

Therefore, the core amino acid metabolic basis of ferroptosis primarily involves: System Xc^- dysfunction directly impairs glutathione (GSH) biosynthesis, consequently reducing GPX4 activity and its capacity to scavenge lipid peroxides, while the KEAP1-p62-NRF2 signaling pathway transcriptionally regulates both system Xc^- and GPX4 expression to modulate ferroptosis.

Iron Metabolism

Disruption of iron metabolism is a fundamental characteristic of ferroptosis. The body's iron comes from the absorption of exogenous iron and the reutilization of endogenous iron. Dietary iron primarily exists in the form of Fe^{3+}, which is reduced to Fe^{2+} by duodenal cytochrome B (DcytB, a brush border ferrireductase) in the intestine, and then absorbed into intestinal epithelial cells (IECs) by the divalent metal transporter 1 (DMT1). The iron can either be directly utilized or stored in ferritin (FTH/L). The iron that enters the IECs is transported into the bloodstream via ferroportin (Fpn, SLC40A1, the only known iron exporter) on the basolateral side. About 60% to 70% of the body's iron is found in the hemoglobin of red blood cells. Aging red blood cells are phagocytosed by macrophages, where heme oxygenase 1 (HO-1) degrades heme in lysosomes, releasing iron bound to heme(Wu et al. 2021). The released free iron is pumped out of macrophages by Fpn, re-entering the bloodstream and becoming a major source of endogenous iron(Fleming 2008). Once exogenous or endogenous iron enters the bloodstream, it binds to transferrin (TF) and is

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

transported to various tissue cells, where it binds to transferrin receptors (TFR1) on the cell membrane, allowing it to enter the cells and perform its physiological functions(Guan et al. 2021). The iron that enters the cells not only meets the needs of various cellular physiological activities but also binds to FTH/L to sequester free iron(Park and Chung 2019a). Unbound iron poses significant oxidative risk by catalyzing ROS formation. These ROS species then initiate a cascade of free radical chain reactions with PUFAs, ultimately driving their conversion into lipid peroxides. When cellular iron uptake increases while iron storage decreases or efflux becomes impaired, the consequent accumulation of free Fe^{2+} disrupts intracellular iron homeostasis. Excessive free Fe^{2+} not only drives oxidative stress but also compromises mitochondrial function, triggering overproduction of ROS. This leads to nuclear DNA and mitochondrial damage, ultimately resulting in cellular injury, degeneration, and ferroptosis(Jiang et al. 2021).

The liver is both a major storage site for iron and a key organ for secreting the iron-regulating hormone hepcidin (Bloomer and Brown 2021). Hepcidin regulates serum iron levels by binding to Fpn on the surfaces of macrophages and IECs, leading to its degradation, thereby inhibiting the absorption of exogenous iron or the release of endogenous iron, playing an important role in systemic iron metabolism (Nemeth and Ganz 2021). At the molecular level, iron metabolism is primarily regulated by iron regulatory proteins (IRPs) and iron response elements (IREs) to maintain intracellular iron homeostasis (Gao, Li, et al. 2019). The two work in coordination to maintain the homeostasis of iron metabolism in the body, and any abnormalities in iron metabolism can induce ferroptosis.

Cytosolic labile iron accumulation−resulting from either promoting iron uptake or suppressing iron storage−can trigger ferroptosis initiation (Rochette et al. 2022). For instance: NCOA4-mediated ferritinophagy degrades FTH/L, releasing stored iron and elevating labile iron levels (Park and Chung 2019a); HO-1 overexpression induces heme breakdown (generating biliverdin/bilirubin, CO, and Fe^{2+}), which risks intracellular iron overload; Hepcidin induces degradation of Fpn (SLC40A1), blocking iron export and causing iron retention. Conversely, downregulating iron homeostasis factors (DMT1, transferrin, TFR1, FTH) reduces cellular Fe^{3+} influx and alleviates ferroptosis(Liu et al. 2025). Thus, the core

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

iron dysregulation in ferroptosis−LIP accumulation−directly catalyzes ROS formation and initiates PUFA peroxidation cascades, ultimately driving iron-dependent lipid peroxidation and ferroptosis.

Lipid Metabolism

Ferroptosis is also triggered by the accumulation of lipid ROS. PUFAs can increase membrane fluidity, playing important roles in cellular substance transport, energy conversion, cell recognition, and immunity. Fatty acyl-CoA synthetase long-chain family member 4 (ACSL4, a PUFA-preferring esterification enzyme) and lysolipid acyltransferase 3 (LPCAT3) are important lipid metabolic enzymes responsible for synthesizing phospholipids containing PUFAs (PL-PUFAs)(Yuan, Li, et al. 2016; Hashidate-Yoshida et al. 2015). In the presence of Fe^{2+}, PL-PUFAs can be converted into PLOOH through both enzymatic and non-enzymatic lipid peroxidation reactions. PLOOH is a specific type of ROS, and its significant accumulation can disrupt the integrity of the lipid bilayer, ultimately affecting the functionality of the cell membrane and leading to ferroptosis(Kagan et al. 2017). In brief, ferroptosis is driven by PLOOH accumulation: ACSL4 and LPCAT3 synthesize PL-PUFAs, which are catalyzed by Fe^{2+} into PLOOH, disrupting lipid bilayer integrity to execute cell death.

Mitochondrial Metabolism

The role of mitochondria in ferroptosis is highly controversial, and whether dysfunction itself can initiate cellular ferroptosis, as well as whether mitochondrial function in ferroptotic cells depends on the environment, remains debated (Battaglia et al. 2020). On one hand, mitochondria are the primary site for iron utilization and a major regulator of oxidative metabolism, serving as a significant source of ROS (Murphy 2009). Mitochondrial glutamine catabolism, the electron transport chain (ETC) can induce ferroptosis by promoting cysteine deprivation(Gao, Yi, et al. 2019). On the other hand, cells lacking mitochondrial DNA exhibit sensitivity to ferroptosis similar to that of cells with intact mitochondrial DNA (Dixon et al. 2012); Cells undergoing mitophagy remain susceptible to ferroptosis inhibition by ferrostatin-1 (Fer-1), a radical-trapping compound, even in the absence of functional mitochondria. This demonstrates that mitochondria are dispensable for ferroptosis execution (Gaschler et al. 2018).

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

Ferroptosis suppressor protein 1 (FSP1, also known as flavoprotein apoptosis-inducing factor mitochondria-associated 2, AIFM2) has been identified as a glutathione-independent inhibitor of ferroptosis (Bersuker et al. 2019). FSP1 functions as an NADH/NADPH-dependent coenzyme Q10 reductase, consuming NAD(P)H to reduce coenzyme Q10 (CoQ10, ubiquinone) to coenzyme Q10H2 (CoQ10-H2, ubiquinol). CoQ10 is a lipophilic molecule primarily found in the inner mitochondrial membrane, while CoQ10-H2, as a lipophilic antioxidant, can capture free radicals and prevent lipid peroxidation. It can also indirectly regenerate another antioxidant (α-tocopherol), capturing free radicals to inhibit ferroptosis (Li, Liang, et al. 2023). The FSP1–CoQ10–NAD(P)H pathway exists as an independent parallel system that cooperatively suppresses ferroptosis alongside GPX4-GSH (Doll et al. 2019).

Dihydroorotate dehydrogenase (DHODH), localized on the outer surface of the inner mitochondrial membrane (IMM), operates in parallel with mitochondrial GPX4 (but independently of cytosolic GPX4 or FSP1) by reducing CoQ to CoQH2, which then reduces mitochondrial membrane PLOOH to PLOH, thereby inhibiting ferroptosis (Mao et al. 2021).

Tetrahydrobiopterin (BH4), an essential redox cofactor, plays critical roles in nitric oxide biosynthesis and aromatic amino acid metabolism. Its de novo synthesis is initiated by GTP cyclohydrolase 1 (GCH1), which catalyzes the conversion of guanosine triphosphate (GTP) to BH4 in the rate-limiting step of this pathway (Xu et al. 2007). Beyond its classical enzymatic functions, BH4 is an effective free radical-capturing antioxidant that can independently protect lipid membranes from auto-oxidation and works synergistically with vitamin E (Soula et al. 2020). Notably, GCH1 overexpression has been shown to confer protection against both lipid peroxidation and ferroptosis (Hu et al. 2022). Mitochondrial dysfunction promotes ferroptosis (e.g., via ETC-mediated cysteine deprivation) and supports anti-ferroptotic pathways (FSP1/DHODH/BH4). However, mitochondrial essentiality in ferroptosis remains contentious.

Ferroptosis and the Relationship with Viral Infections

Viruses rely on host cells for survival, and their replication is associated with the intensity of cellular metabolism. The viral life cycle can be divided into four stages: entry, replication, assembly, and release, with specific details varying by virus type (Chen, Fu, et al. 2023).

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

Various types of cell death, such as apoptosis, necrosis, or autophagy, are considered important strategies used by hosts to defend against viral infections (Wang et al. 2022). Ferroptosis has been increasingly linked to the pathogenesis of viral infections, with viruses modulating key cellular targets and regulatory pathways, as illustrated in Fig. 2 and Table 1.

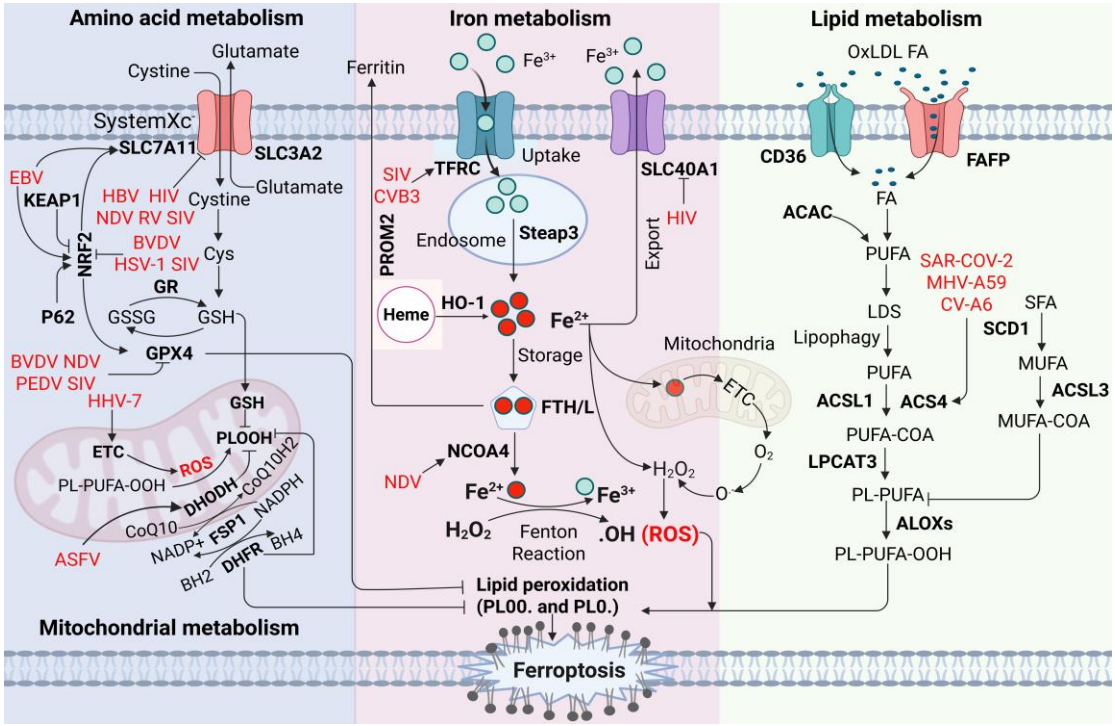

Figure 2. An overview of the relationship between ferroptosis and viral infections. Viruses often exploit ferroptosis to facilitate their replication. For instance, epstein-Barr virus (EBV), hepatitis B virus (HBV), human Immunodeficiency Virus (HIV), newcastle disease virus (NDV), rotavirus (RV), and swine influenza virus (SIV) inhibit the cystine/glutamate antiporter (system Xc^-), leading to GSH depletion and subsequent ferroptosis. Meanwhile, EBV also indirectly disrupts ferroptosis by upregulating NRF2 to suppress GPX4. In contrast, other viruses (e.g., bovine viral diarrhea virus (BVDV), NDV, porcine epidemic diarrhea virus (PEDV), and SIV) directly induce ferroptosis by downregulating GPX4. Additionally, SIV and coxsackievirus B3 (CVB3) bind to TFRC to enter cells, resulting in iron accumulation and ferroptosis. Notably, NDV infection triggers ferritinophagy mediated by NCOA4. Other mechanisms—such as iron level modulation (e.g., HIV inhibiting SLC40A1)—also influence viral pathogenesis. Furthermore, coxsackievirus A6 (CV-A6), mouse hepatitis virus strain A59 (MHV-A59), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) promote ferroptosis via ACSL4-dependent lipid peroxidation. Figure created with Biorender.

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

The Promoting Relationship Between Viruses and Host Cellular Ferroptosis

Ferroptosis can provide a favorable environment for the survival, replication, and evasion of viruses. Some viruses can inhibit ferroptosis by affecting the host cell's iron metabolism, lipid metabolism, and mitochondrial metabolism, thereby promoting their own replication and spread. Ferroptosis in host cells can exacerbate viral infections, and inhibiting ferroptosis with ferroptosis inhibitors can reduce the extent of viral infection in host cells.

Viruses Inducing Ferroptosis by Regulating Iron Metabolism

Iron is one of the essential raw materials for basic metabolism and is a target of competition between the host and the virus (Mancinelli et al. 2020). Iron is required for viral genome replication and protein synthesis, so viruses must obtain sufficient iron from the host to proliferate within host cells (Wang et al. 2022). Studies have indicated that the expression of iron transport proteins inhibits HIV-1 transcription. In THP-1 cells, hepcidin is associated with enhanced HIV-1 transcription, reduced expression of iron transport proteins, and accumulation of intracellular iron (Mancinelli et al. 2020). Coxsackievirus B3 (CVB3) infection upregulates the expression of TFR1, leading to a large influx of iron into cells, which subsequently causes ferroptosis (Yi et al. 2022).

Table 1 Targets and regulatory mechanisms in viral infections and ferroptosis

Virus	Mechanism	Targeted cells	Function	References
ASFV	Brequinar inhibiting DHODH activity to activats ferroptosis	PAMs	Brequinar inhibits ASFV replication by activating ferroptosis	(Chen et al. 2023)
BVDV	BVDV promotes ferroptosis by inhibiting Nrf2 to downregulate mitochondrial GPX4	MDBK cells	Enhance viral replication Cause the impairment of mitochondria.	(Li et al. 2024)
CVB3	TFR1 was enhanced by CVB3 infection, leading to the release of large quantities of free iron, which promoted lipid peroxidation and ferroptosis	HeLa cells	Promote virus replication	(Yi et al. 2022)
CV-A6	Viruses recruit ACSL4 for RO formation and promote lipid peroxidation	RD cells	Promote virus replication	(Kung et al. 2022)
EBV	EBV infection activates the p62-Keap1-NRF2 pathway and upregulates GPX4 expression in	Akata cels NPC cells	GPX4 promotes proliferation and colony formation in NPC cells	(Yuan et al. 2022)

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

	NPC cells			
	TFP was a strong inducer of ferroptosis in EBV-infected gastric cancer cells and that such effects were achieved by inhibiting NRF2/HO-1 signaling	AGS cells, MKN45 cells	Unknown	(Kong et al. 2024)
HBV	HBV X protein (HBx) facilitates ferroptosis in acute liver failure (ALF) via EZH2/H3K27me3-mediated SLC7A11 suppression	Hepatocytes	Exacerbating ALF.	(Liu et al. 2021)
SIV	SIV infection disrupts intracellular iron and redox homeostasis. Meanwhile, SIV infection inhibits the system Xc^{-}/GPX4 axis	A549 cells	Lead to inflammatory cytokine secretion or even excessive inflammatory reactions	(Cheng et al. 2022)
HHV7	HHV-7 induces ferroptosis by upregulation COX4I2 expression, which increases intracellular free iron level and triggers an increase in ROS in mitochondrial	Schwann cells	Virus infection triggers ferroptosis within cells	(Chang et al. 2021)
HIV	Inhibiting SLC7A11 and SLC40A1 expression to activate ferroptosis	Human macrophages	Unknown	(Rabinowitz et al. 2021)
HSV-1	HSV-1 infection activates ferroptosis by enhancing the ubiquitin-mediated degradation of NRF2.	Human astrocytes microglia cells	Contributes to viral encephalitis	(Xu et al. 2023)
MHV-A59	Upregulating ACSL1 expression to promote ferroptosis	murine macrophages	Result in a typical cell–cell fusion named syncytia	(Xia et al. 2021)
NDV	Inhibiting the XC^{-}/GSH/GPX4 axis and inducing ferritinophagy	U251 glioma cells	Induce cell death	(Kan et al. 2021)
PEDV	RSL3 inhibits PEDV replication by regulating GPX4 to induce ferroptosis and modulate intracellular lipid and ROS levels	Vero cells	Contributes to PEDV replication	(Li, et al. 2023)
RV	RV infection triggers ferroptotic cell death via AS1/xCT axis	HT-29 cells	Promote virus propagation	(Banerjee et al. 2024)
SAR-COV-2	Upregulating ACSL4 expression to promote ferroptosis	RD cells	Promote virus replication	(Kung et al. 2022)

Viruses Inducing Ferroptosis by Regulating Lipid Metabolism

ACSL1 is a ferroptosis-activating factor. Research has found that mouse hepatitis virus strain A59 (MHV-A59) can induce ferroptosis in mouse macrophages by promoting the

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

expression of ACSL1; conversely, the ACSL1 inhibitor Triacsin C can inhibit macrophage ferroptosis, thereby protecting the host from MHV-A59 infection (Xia et al. 2021). ACSL4 is an enzyme that esterifies CoA to specific PUFAs and is a key regulator of lipid metabolism and ferroptosis. Further studies have demonstrated that ACSL4 participates in the biogenesis of replication organelles during Coxsackievirus A6 (CV-A6) and SARS-CoV-2 infections, while simultaneously promoting virus-induced ferroptosis. Notably, specific ferroptosis inhibitors (Fer-1, TRO (troglitazone), ROSI (rosiglitazone), and PIO (pioglitazone)) have been shown to significantly restore cellular viability following infection by these viruses (Kung et al. 2022).

Viruses Inducing Ferroptosis by Regulating Mitochondrial Metabolism

Human herpesvirus 7 (HHV-7) is a type B herpesvirus that can invade the nervous system. Once it enters the central nervous system, it can replicate and trigger immune and inflammatory responses associated with related encephalopathies (Foiadelli et al. 2021). The mitochondrial electron transport chain serves as a primary source of cellular ROS, with cytochrome c oxidase (COX) functioning as the terminal electron acceptor in this system. As an essential component of oxidative phosphorylation, COX plays an indispensable role in ATP generation in cells (Pajuelo Reguera et al. 2020). Emerging evidence indicates that HHV-7 induces ferroptosis in rat Schwann cells by upregulation COX4I2 expression, ultimately causing peripheral facial nerve damage (Chang et al. 2021). Bovine viral diarrhea virus (BVDV) represents a major global threat to both domestic livestock and wild cattle populations worldwide, causing significant economic losses in the cattle industry through its immunosuppressive effects and persistent infections. BVDV can induce ferroptosis through mitochondrial metabolism, primarily by inhibiting the protein levels of NRF2 and downregulating the protein expression of mitochondrial GPX4, leading to ferroptosis in infected cells (Li et al. 2024).

Viruses Inducing Ferroptosis by Inhibiting the XC^-/GPX4 System

Swine influenza (SI), an acute respiratory disease caused by the influenza A virus (IAV), poses significant challenges to the swine industry. Cheng and colleagues demonstrated that infection with H1N1 subtype swine influenza virus (SIV) induced excessive iron uptake and storage, inhibited the XC^-/GPX4 axis, reduced SLC7A11 levels, led to GSH depletion,

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

decreased GPX4 activity and expression, and resulted in the accumulation of lipid peroxidation products, triggering ferroptosis and enhancing viral replication (Cheng et al. 2022). Hepatitis B virus (HBV) remains a major global health challenge, affecting approximately 257 million individuals worldwide and contributing to an estimated 887,000 annual deaths from HBV-related complications (Gentile et al. 2023). HBx is a protein associated with HBV and is indispensable in HBV replication and infection (Wang et al. 2023). HBx can also sensitize hepatocytes to ferroptosis by inhibiting SLC7A11 (Liu et al. 2021). Rotavirus (RV), which causes viral-associated gastroenteritis in infants, can reduce intracellular GSH and enhance lipid peroxidation, triggering ferroptosis through the SLC7A11-AS1/ XC^- axis, thereby facilitating RV replication and the spread of viral particles (Banerjee et al. 2024). Newcastle disease virus (NDV) is an RNA virus that can cause highly infectious poultry diseases, causing significant economic losses in the global poultry industry. NDV promotes cellular ferroptosis by inhibiting the XC^-–GSH–GPX4 axis, activating p53, and inducing ferritinophagy (Kan et al. 2021).

Viruses Promoting Ferroptosis by Regulating NRF2

Herpes simplex virus type 1 (HSV-1) is a DNA virus belonging to the Herpesviridae family. Studies have shown that HSV-1 infection enhances the ubiquitin-mediated degradation of NRF2. This degradation leads to marked downregulation of NRF2-dependent antioxidant genes, ultimately disrupting cellular redox homeostasis (Xu et al. 2023). Recent research indicates that H1N1 can induce ferroptosis and glutamine catabolism in human nasal epithelial progenitor cells via the KEAP1-NRF2-GCLC signaling pathway, leading to inflammation in the nasal mucosa (Liu et al. 2023).

The Inhibitory Relationship Between Viruses and Host Cell Ferroptosis

Cell death represents a fundamental host defense mechanism wherein infected cells are selectively eliminated to protect uninfected tissues and maintain organismal homeostasis. Pathogens often inhibit cell death to allow for their replication and promote their spread (Ashida et al. 2011). After a virus infiltrates the host cell, it can reduce the sensitivity of host cells to ferroptosis by regulating GPX4, NRF2, XC^-, iron metabolism, and other factors.

Viruses Inhibiting Ferroptosis by Upregulating SLC7A11/GPX4 and Promoting Their Own Replication

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

It has also been reported that HBx mediates the upregulation of heat shock protein family A member 8 (HSPA8) expression and stimulates HBV replication, with HSPA8 suppressing ferroptosis in liver cancer cells by upregulating SLC7A11/GPX4 expression and reducing the accumulation of Erastin-mediated ROS and Fe^{2+} in cells, thereby promoting the proliferation of liver cancer cells (Kuo et al. 2020; Wang et al. 2023). Porcine epidemic diarrhea virus (PEDV) is a α-coronavirus, primarily infecting intestinal and villous cells in pigs, rapidly spreading and causing diarrheal diseases characterized by vomiting, diarrhea, and dehydration, with a high mortality rate reaching up to 100% in newborn piglets, resulting in significant economic losses in the swine industry (Lin et al. 2022). Research has shown that overexpression of GPX4 can inhibit ferroptosis and promote PEDV proliferation. Conversely, inhibiting GPX4 expression with RSL3 and activating ferroptosis suppresses PEDV replication. This indicates that cellular ferroptosis can affect the infection and replication of PEDV in Vero cells (Li, Bao, et al. 2023).

Viruses Reducing Cellular Sensitivity to Ferroptosis by Activating the Keap1-p62-NRF2 Signaling Pathway

Epstein-Barr virus (EBV) is a DNA herpesvirus associated with many human cancers, including nasopharyngeal carcinoma (NPC) (Young and Murray 2003). Li et al. (Yuan et al. 2022) reported that EBV infection reduces NPC cells' sensitivity to ferroptosis by activating the Keap1-p62-NRF2 signaling pathway and upregulating the expression of SLC7A11 and GPX4. Other studies have shown that EBV dynamically sensitizes B cells to ferroptosis (Burton et al. 2022). Thus, it is evident that the effects of the same virus on ferroptosis can differ across different cell types.

Activation of Ferroptosis via the DHODH Pathway Can Inhibit Viral Infection

African swine fever virus (ASFV) infection does not inherently induce cellular ferroptosis; however, brequinar (a DHODH inhibitor) can suppress ASFV replication by activating cellular ferroptosis (Chen, Guo, et al. 2023). Influenza viruses are highly infectious, with a multitude of subtypes and frequent mutations, which limits the development of effective broad-spectrum antiviral strategies. One study showed that metastable iron-sulfur (FeS) relies on Fe^{2+}, inducing high levels of lipid peroxidation and free radical production in conserved viral envelopes, leading to viral ferroptosis and resulting in the loss of infectivity and

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

pathogenicity of the influenza virus (Miao et al. 2023). Other studies have indicated that high concentrations of iron within host cells can inhibit viral infections, including herpes simplex virus type 1 (HSV-1), hepatitis C virus (HCV) and bovine viral diarrhea virus (BVDV) (Bartolomei et al. 2011; Terpiłowska and Siwicki 2017).

The Role of Nutrient Regulation in Ferroptosis During Viral Infections

Adequate nutrition helps organisms achieve optimal immune function, reducing the adverse effects of pathogen infections. Impaired nutritional status can increase susceptibility to and severity of viral infections.

How Nutrients activate Ferroptosis in the Context of Viral Infection

Emerging evidence indicates that intracellular iron homeostasis modulates neonatal piglet susceptibility to porcine epidemic diarrhea virus (PEDV) infection through TFR1-mediated mechanisms. Iron overload, induced by ammonium ferrous citrate (FAC) supplementation, was shown to attenuate PEDV infectivity in both in vitro and in vivo models, likely through competitive inhibition of TFR1- the established cellular receptor for PEDV (Zhang et al. 2020). Tremella fuciformis polysaccharides (TFP) are active components of Tremella mushrooms, with significant antioxidant and anti-inflammatory properties (Ruan et al. 2018). Approximately 10% of gastric cancer cases are associated with EBV, EBV-infected cells exhibit heightened susceptibility to ferroptosis. The ferroptosis inducer TFP promotes this process through dual inhibitory mechanisms: both suppressing NRF2-mediated transcription of HMOX1 (encoding heme oxygenase-1, HO-1) and GPX4, and downregulating xCT (SLC7A11) to impair glutathione (GSH) biosynthesis. Collectively, these actions induce GPX4 dysfunction, triggering lethal phospholipid peroxidation that ultimately eliminates EBV-infected cells (Kong et al. 2024). Rhein is a naturally occurring anthraquinone extracted from the roots of palm trees, known for its neuroprotective, anticancer, antibacterial, antiviral, antioxidant, and lipid-regulating pharmacological effects. HBx alleviates cell death by inhibiting ferroptosis, whereas rhein can attenuate HBx-induced hepatic stellate cell activation via a GPX4-dependent pathway and diminish HBx-mediated cell death suppression via a GPX4-independent pathway, mitigating hepatic stellate cell fibrosis (Kuo et al. 2020).

How Nutrients Inhibit Ferroptosis in the Context of Viral Infection

Proanthocyanidins (PAs) are flavonoids found in safflower, known for their antioxidant

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

and antiviral properties. Infection with influenza A virus (IAV) can provoke acute lung injury. While PAs do not inhibit IAV replication, they significantly decrease the levels of MDA and ACSL4 while upregulating GSH, GPX4, and SLC7A11, which can alleviate IAV-induced acute lung injury by inhibiting cellular ferroptosis (Lv et al. 2023). Excessive death of normal liver cells may lead to severe liver damage, even liver cancer. Selenocysteine (Sec), an essential catalytic residue for GPX4 enzymatic activity, is incorporated into its catalytic center through selenium supplementation, which enhances GPX4 activity, and selenium donors can regulate GPX4 expression and reduce iron-induced ferroptosis in liver cells via the Na2SeO3‑GPX4 axis, thereby mitigating acute liver injury mediated by HBx infection in normal liver cells (Shi et al. 2023).

Conclusions

Viral infections are one of the leading causes of global morbidity and mortality. Cellular ferroptosis is a form of cell death that is closely related to viral infections. Some viral infections and ferroptosis have a mutually promoting relationship, where viral infections can induce ferroptosis in cells, and ferroptosis can, in turn, facilitate viral infections; furthermore, inhibiting cellular ferroptosis can also suppress viral infections to some extent. Conversely, some viral infections and ferroptosis have an inhibitory relationship. However, not all viruses interact with cellular ferroptosis. It is well known that viruses exhibit high variability and can frequently mutate, leading to the evolution of many variants, which results in limited vaccine efficacy. Many viruses, including PEDV (Lin et al. 2022) and EBV (Borghol et al. 2024), still lack effective vaccines or treatments, posing a significant threat to public health worldwide. Cellular ferroptosis can create a favorable environment for viral survival, replication, and immune evasion (Wang et al. 2022). Therefore, targeting ferroptosis may represent a promising antiviral therapeutic strategy.

Adequate nutrition helps enhance the immune response, and certain nutrients are closely related to some key factors in the cellular ferroptosis mechanism. To date, research on the role of nutrients in alleviating viral infections and regulating cell death has been extensive; however, studies on how nutrients regulate cellular ferroptosis during viral infections are relatively scarce. Because the interactive effects between different viruses and ferroptosis can vary, it remains uncertain whether any interaction exists between many viruses and

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

ferroptosis, or what the nature of those interactions might be. Research examining the interactive effects between various viral infections and host cell ferroptosis, along with the regulatory effects of nutrients, may help in developing antiviral strategies by manipulating cellular ferroptosis to fend off viral infections, treat related diseases, and mitigate the harm posed by viruses to humans and animals.

Author contributions

AMW and TTZ conceived and wrote the review, DWC provided the writing guidance and revised the paper.

Financial support

This work was supported by the Joint Funds of the National Natural Science Foundation of China (Grant No. U22A20513) and National Natural Science Foundation of Sichuan Province (Grant No. 24NSFSC0279).

Reference

Ashida H, Mimuro H, Ogawa M *et al.* 2011. "Cell Death and Infection: A Double-Edged Sword for Host and Pathogen Survival." *Journal of Cell Biology* 195 (6):931-42.

Banerjee S, Sarkar R, Mukherjee A *et al.* 2024. "Rotavirus-Induced Lncrna Slc7a11-As1 Promotes Ferroptosis by Targeting Cystine/Glutamate Antiporter Xct (Slc7a11) to Facilitate Virus Infection." *Virus research* 339:199261.

Bartolomei G, Cevik R E, and Marcello A. 2011. "Modulation of Hepatitis C Virus Replication by Iron and Hepcidin in Huh7 Hepatocytes." *Journal of general virology* 92 (9):2072-81.

Battaglia A M, Chirillo R, Aversa I *et al.* 2020. "Ferroptosis and Cancer: Mitochondria Meet the “Iron Maiden” Cell Death." *Cells* 9 (6):1505.

Bersuker K, Hendricks J M, Li Z *et al.* 2019. "The Coq Oxidoreductase Fsp1 Acts Parallel to Gpx4 to Inhibit Ferroptosis." *Nature* 575 (7784):688-92.

Bloomer S A, and Brown K E. 2021. "Hepcidin and Iron Metabolism in Experimental Liver Injury." *The*

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

American journal of pathology 191 (7):1165-79.

Borghol A H, Bitar E R, Hanna A *et al.* 2024. "The Role of Epstein-Barr Virus in Autoimmune and Autoinflammatory Diseases." *Critical reviews in microbiology*:1-21.

Burton E M, Voyer J, and Gewurz B E. 2022. "Epstein–Barr Virus Latency Programs Dynamically Sensitize B Cells to Ferroptosis." *Proceedings of the National Academy of Sciences* 119 (11):e2118300119.

Chang B, Guan H, Wang X *et al.* 2021. "Cox4i2 Triggers an Increase in Reactive Oxygen Species, Leading to Ferroptosis and Apoptosis in Hhv7 Infected Schwann Cells." *Frontiers in Molecular Biosciences* 8:660072.

Cheff D M, Huang C, Scholzen K C *et al.* 2023. "The Ferroptosis Inducing Compounds Rsl3 and Ml162 Are Not Direct Inhibitors of Gpx4 but of Txnrd1." *Redox biology* 62:102703.

Chen C C, and Whitehead A. 2021. "Emerging and Re-Emerging Infections in Children: Covid/Mis-C, Zika, Ebola, Measles, Varicella, Pertussis... Immunizations." *Emergency Medicine Clinics of North America* 39 (3):453.

Chen J, Fu J, Zhao S *et al.* 2023. "Free Radical and Viral Infection: A Review from the Perspective of Ferroptosis." *Veterinary Sciences* 10 (7):456.

Chen X, Li J, Kang R *et al.* 2021. "Ferroptosis: Machinery and Regulation." *Autophagy* 17 (9):2054-81.

Chen Y, Guo Y, Chang H *et al.* 2023. "Brequinar Inhibits African Swine Fever Virus Replication in Vitro by Activating Ferroptosis." *Virology journal* 20 (1):242.

Cheng J, Tao J, Li B *et al.* 2022. "Swine Influenza Virus Triggers Ferroptosis in A549 Cells to Enhance Virus Replication." *Virology journal* 19 (1):104.

Choi Y K. 2021. "Emerging and Re-Emerging Fatal Viral Diseases." *Experimental & Molecular*

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

Medicine 53 (5):711-12.

Dixon S J, Lemberg K M, Lamprecht M R *et al.* 2012. "Ferroptosis: An Iron-Dependent Form of Nonapoptotic Cell Death." *Cell* 149:1060-72.

Doll S, Freitas F P, Shah R *et al.* 2019. "Fsp1 Is a Glutathione-Independent Ferroptosis Suppressor." *Nature* 575 (7784):693-98.

Du R, Cui Q, Chen Z *et al.* 2023. "Revisiting Influenza a Virus Life Cycle from a Perspective of Genome Balance." *Virologica Sinica* 38 (1):1-8.

Fleming M D. 2008. "The Regulation of Hepcidin and Its Effects on Systemic and Cellular Iron Metabolism." *Hematology Am Soc Hematol Educ Program*:151-8. https://doi.org/10.1182/asheducation-2008.1.151.

Foiadelli T, Rossi V, Paolucci S *et al.* 2021. "Human Herpes Virus 7-Related Encephalopathy in Children." *Acta Bio Medica: Atenei Parmensis* 92 (Suppl 4):e2021415.

Ganz T, and Nemeth E. 2015. "Iron Homeostasis in Host Defence and Inflammation." *Nature Reviews Immunology* 15 (8):500-10.

Gao G, Li J, Zhang Y *et al.* 2019. "Cellular Iron Metabolism and Regulation." *Brain iron metabolism and CNS diseases*:21-32.

Gao M, Yi J, Zhu J *et al.* 2019. "Role of Mitochondria in Ferroptosis." *Molecular cell* 73 (2):354-63. e3.

Gaschler M M, Hu F, Feng H *et al.* 2018. "Determination of the Subcellular Localization and Mechanism of Action of Ferrostatins in Suppressing Ferroptosis." *ACS chemical biology* 13 (4):1013-20.

Gentile G, Arcaini L, Antonelli G *et al.* 2023. *Hbv and Lymphoma*. Vol. 13. Frontiers Media SA.

Guan W, Xia M, Ji M *et al.* 2021. "Iron Induces Two Distinct Ca(2+) Signalling Cascades in Astrocytes."

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

Commun Biol 4 (1):525. https://doi.org/10.1038/s42003-021-02060-x.

Guo J, Liu Z, Tong X *et al.* 2021. "Evolutionary Dynamics of Type 2 Porcine Reproductive and Respiratory Syndrome Virus by Whole-Genome Analysis." *Viruses* 13 (12):2469.

Hashidate-Yoshida T, Harayama T, Hishikawa D *et al.* 2015. "Fatty Acid Remodeling by Lpcat3 Enriches Arachidonate in Phospholipid Membranes and Regulates Triglyceride Transport." *Elife* 4 https://doi.org/ARTN 0632810.7554/eLife.06328.

Hu Q, Wei W, Wu D *et al.* 2022. "Blockade of Gch1/Bh4 Axis Activates Ferritinophagy to Mitigate the Resistance of Colorectal Cancer to Erastin-Induced Ferroptosis." *Frontiers in cell and developmental biology* 10:810327.

Jiang X, Stockwell B R, and Conrad M. 2021. "Ferroptosis: Mechanisms, Biology and Role in Disease." *Nat Rev Mol Cell Biol* 22 (4):266-82. https://doi.org/10.1038/s41580-020-00324-8.

Kagan V E, Mao G W, Qu F *et al.* 2017. "Oxidized Arachidonic and Adrenic Pes Navigate Cells to Ferroptosis." *Nature Chemical Biology* 13 (1):81-90. https://doi.org/10.1038/ Nchembio.2238.

Kan X, Yin Y, Song C *et al.* 2021. "Newcastle-Disease-Virus-Induced Ferroptosis through Nutrient Deprivation and Ferritinophagy in Tumor Cells." *Iscience* 24 (8)

Kong W, Liu X, Zhu H *et al.* 2024. "Tremella Fuciformis Polysaccharides Induce Ferroptosis in Epstein-Barr Virus-Associated Gastric Cancer by Inactivating Nrf2/Ho-1 Signaling." *Aging (Albany NY)* 16 (2):1767.

Koppula P, Zhang Y, Zhuang L *et al.* 2018. "Amino Acid Transporter Slc7a11/Xct at the Crossroads of Regulating Redox Homeostasis and Nutrient Dependency of Cancer." *Cancer communications* 38:1-13.

Kung Y-A, Chiang H-J, Li M-L *et al.* 2022. "Acyl-Coenzyme a Synthetase Long-Chain Family Member

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

4 Is Involved in Viral Replication Organelle Formation and Facilitates Virus Replication Via Ferroptosis." *Mbio* 13 (1):e02717-21.

Kuo C-Y, Chiu V, Hsieh P-C *et al.* 2020. "Chrysophanol Attenuates Hepatitis B Virus X Protein-Induced Hepatic Stellate Cell Fibrosis by Regulating Endoplasmic Reticulum Stress and Ferroptosis." *Journal of pharmacological sciences* 144 (3):172-82.

Lei G, Zhuang L, and Gan B. 2022. "Targeting Ferroptosis as a Vulnerability in Cancer." *Nature Reviews Cancer* 22 (7):381-96.

Li F, and Du L. 2019. *Mers Coronavirus: An Emerging Zoonotic Virus*. Vol. 11. MDPI.

Li J, Cao F, Yin H-l *et al.* 2020. "Ferroptosis: Past, Present and Future." *Cell death & disease* 11 (2):88.

Li W, Liang L, Liu S *et al.* 2023. "Fsp1: A Key Regulator of Ferroptosis." *Trends in molecular medicine* 29 (9):753-64.

Li Y, Bao Y, Li Y *et al.* 2023. "Rsl3 Inhibits Porcine Epidemic Diarrhea Virus Replication by Activating Ferroptosis." *Viruses* 15 (10):2080.

Li Z, Chen W, Qiu Z *et al.* 2022. "African Swine Fever Virus: A Review." *Life* 12 (8):1255.

Li Z, Zhao B, Zhang Y *et al.* 2024. "Mitochondria-Mediated Ferroptosis Contributes to the Inflammatory Responses of Bovine Viral Diarrhea Virus (Bvdv) in Vitro." *Journal of Virology* 98 (2):e01880-23.

Lin F, Zhang H, Li L *et al.* 2022. "Pedv: Insights and Advances into Types, Function, Structure, and Receptor Recognition." *Viruses* 14 (8):1744.

Liu C, Wu X, Bing X *et al.* 2023. "H1n1 Influenza Virus Infection through Nrf2-Keap1-Gclc Pathway Induces Ferroptosis in Nasal Mucosal Epithelial Cells." *Free Radical Biology and Medicine* 204:226-42.

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

Liu G-Z, Xu X-W, Tao S-H *et al.* 2021. "Hbx Facilitates Ferroptosis in Acute Liver Failure Via Ezh2 Mediated Slc7a11 Suppression." *Journal of biomedical science* 28:1-13.

Liu Y, Wang Q, Hou Z *et al.* 2025. "Electroacupuncture Inhibits Ferroptosis by Modulating Iron Metabolism and Oxidative Stress to Alleviate Cerebral Ischemia-Reperfusion Injury." *J Mol Neurosci* 75 (2):63. https://doi.org/10.1007/s12031-025-02355-2.

Lv Y-w, Du Y, Ma S-s *et al.* 2023. "Proanthocyanidins Attenuates Ferroptosis against Influenza-Induced Acute Lung Injury in Mice by Reducing Ifn-Γ." *Life Sciences* 314:121279.

Mancinelli R, Rosa L, Cutone A *et al.* 2020. "Viral Hepatitis and Iron Dysregulation: Molecular Pathways and the Role of Lactoferrin." *Molecules* 25 (8):1997.

Mao C, Liu X, Zhang Y *et al.* 2021. "Dhodh-Mediated Ferroptosis Defence Is a Targetable Vulnerability in Cancer." *Nature* 593 (7860):586-90.

Martinez A M, Kim A, and Yang W S. 2020. "Detection of Ferroptosis by Bodipy™ 581/591 C11." *Immune Mediators in Cancer: Methods and Protocols*:125-30.

Miao X, Yin Y, Chen Y *et al.* 2023. "Bidirectionally Regulating Viral and Cellular Ferroptosis with Metastable Iron Sulfide against Influenza Virus." *Advanced Science* 10 (17):2206869.

Murphy M P. 2009. "How Mitochondria Produce Reactive Oxygen Species." *Biochemical journal* 417 (1):1-13.

Nakamura E, Sato M, Yang H *et al.* 1999. "4f2 (Cd98) Heavy Chain Is Associated Covalently with an Amino Acid Transporter and Controls Intracellular Trafficking and Membrane Topology of 4f2 Heterodimer." *Journal of Biological Chemistry* 274 (5):3009-16.

Nemeth E, and Ganz T. 2021. "Hepcidin-Ferroportin Interaction Controls Systemic Iron Homeostasis." *International journal of molecular sciences* 22 (12):6493.

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

Pajuelo Reguera D, Čunátová K, Vrbacký M *et al.* 2020. "Cytochrome C Oxidase Subunit 4 Isoform Exchange Results in Modulation of Oxygen Affinity." *Cells* 9 (2):443.

Park E, and Chung S W. 2019a. "Ros-Mediated Autophagy Increases Intracellular Iron Levels and Ferroptosis by Ferritin and Transferrin Receptor Regulation." *Cell Death Dis* 10 (11):822. https://doi.org/10.1038/s41419-019-2064-5.

Park E, and Chung S W. 2019b. "Ros-Mediated Autophagy Increases Intracellular Iron Levels and Ferroptosis by Ferritin and Transferrin Receptor Regulation." *Cell death & disease* 10 (11):822.

Reina S, and De Pinto V. 2017. "Anti-Cancer Compounds Targeted to Vdac: Potential and Perspectives." *Current Medicinal Chemistry* 24 (40):4447-69.

Rochette L, Dogon G, Rigal E *et al.* 2022. "Lipid Peroxidation and Iron Metabolism: Two Corner Stones in the Homeostasis Control of Ferroptosis." *International Journal of Molecular Sciences* 24 (1)https://doi.org/10.3390/ijms24010449.

Ruan Y, Li H, Pu L *et al.* 2018. "Tremella Fuciformis Polysaccharides Attenuate Oxidative Stress and Inflammation in Macrophages through Mir - 155." *Analytical Cellular Pathology* 2018 (1):5762371.

Sato H, Tamba M, Ishii T *et al.* 1999. "Cloning and Expression of a Plasma Membrane Cystine/Glutamate Exchange Transporter Composed of Two Distinct Proteins." *Journal of Biological Chemistry* 274 (17):11455-58.

Seiler A, Schneider M, Förster H *et al.* 2008. "Glutathione Peroxidase 4 Senses and Translates Oxidative Stress into 12/15-Lipoxygenase Dependent-and Aif-Mediated Cell Death." *Cell metabolism* 8 (3):237-48.

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

Shi J, Liu Z, Li W *et al.* 2023. "Selenium Donor Inhibited Hepatitis B Virus Associated Hepatotoxicity Via the Apoptosis and Ferroptosis Pathways." *Analytical Cellular Pathology* 2023 (1):6681065.

Soula M, Weber R A, Zilka O *et al.* 2020. "Metabolic Determinants of Cancer Cell Sensitivity to Canonical Ferroptosis Inducers." *Nature chemical biology* 16 (12):1351-60.

Sun X, Ou Z, Chen R *et al.* 2016. "Activation of the P62-Keap1-Nrf2 Pathway Protects against Ferroptosis in Hepatocellular Carcinoma Cells." *Hepatology* 63 (1):173-84.

Terpiłowska S, and Siwicki A K. 2017. "Chromium (Iii) and Iron (Iii) Inhibits Replication of DNA and Rna Viruses." *Biometals* 30:565-74.

Tummers B, and Green D R. 2022. "The Evolution of Regulated Cell Death Pathways in Animals and Their Evasion by Pathogens." *Physiological reviews* 102 (1):411-54.

Ursini F, and Maiorino M. 2020. "Lipid Peroxidation and Ferroptosis: The Role of Gsh and Gpx4." *Free Radical Biology and Medicine* 152:175-85.

Verburg S G, Lelievre R M, Westerveld M J *et al.* 2022. "Viral-Mediated Activation and Inhibition of Programmed Cell Death." *PLoS Pathogens* 18 (8):e1010718.

Wang M-p, Joshua B, Jin N-y *et al.* 2022. "Ferroptosis in Viral Infection: The Unexplored Possibility." *Acta Pharmacologica Sinica* 43 (8):1905-15.

Wang Y, Zhao M, Zhao L *et al.* 2023. "Hbx-Induced Hspa8 Stimulates Hbv Replication and Suppresses Ferroptosis to Support Liver Cancer Progression." *Cancer Research* 83 (7):1048-61.

Wu A, Feng B, Yu J *et al.* 2021. "Fibroblast Growth Factor 21 Attenuates Iron Overload-Induced Liver Injury and Fibrosis by Inhibiting Ferroptosis." *Redox Biol* 46:102131. https://doi.org/10.1016/j.redox.2021.102131.

Wu A, Yu B, Zhang K *et al.* 2020. "Transmissible Gastroenteritis Virus Targets Paneth Cells to Inhibit the Self-Renewal and Differentiation of Lgr5 Intestinal Stem Cells Via Notch Signaling." *Cell death & disease* 11 (1):40.

Xia H, Zhang Z, and You F. *Inhibiting Acsl1-Related Ferroptosis Restrains Murine Coronavirus Infection. Viruses. 2021; 13: 2383*.

Xie Y, Hou W, Song X *et al.* 2016. "Ferroptosis: Process and Function." *Cell Death & Differentiation* 23 (3):369-79.

Xu J, Wu Y, Song P *et al.* 2007. "Proteasome-Dependent Degradation of Guanosine 5′-Triphosphate Cyclohydrolase I Causes Tetrahydrobiopterin Deficiency in Diabetes Mellitus." *Circulation* 116 (8):944-53.

Xu X-Q, Xu T, Ji W *et al.* 2023. "Herpes Simplex Virus 1-Induced Ferroptosis Contributes to Viral Encephalitis." *Mbio* 14 (1):e02370-22.

Yang W. 2014. "Sri Ramaratnam R, Welsch Me, Et Al. Regulation of Ferroptotic Cancer Cell Death by Gpx4." *Cell* 156 (1-2):317-31.

Yi L, Hu Y, Wu Z *et al.* 2022. "Tfrc Upregulation Promotes Ferroptosis in Cvb3 Infection Via Nucleus Recruitment of Sp1." *Cell death & disease* 13 (7):592.

Young L S, and Murray P G. 2003. "Epstein–Barr Virus and Oncogenesis: From Latent Genes to Tumours." *Oncogene* 22 (33):5108-21.

Yuan H, Li X M, Zhang X Y *et al.* 2016. "Identification of Acsl4 as a Biomarker and Contributor of Ferroptosis." *Biochemical and Biophysical Research Communications* 478 (3):1338-43. https://doi.org/10.1016/j.bbrc.2016.08.124.

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press

Yuan J, Najafov A, and Py B F. 2016. "Roles of Caspases in Necrotic Cell Death." *Cell* 167 (7):1693-704.

Yuan L, Li S, Chen Q-Y *et al.* 2022. "Ebv Infection-Induced Gpx4 Promotes Chemoresistance and Tumor Progression in Nasopharyngeal Carcinoma." *Cell Death and Differentiation* 29:1513 - 27.

Zhang S, Cao Y, and Yang Q. 2020. "Transferrin Receptor 1 Levels at the Cell Surface Influence the Susceptibility of Newborn Piglets to Pedv Infection." *PLoS Pathogens* 16 (7):e1008682.

Zhao Y, Fan B, Song X *et al.* 2024. "Pedv-Spike-Protein-Expressing Mrna Vaccine Protects Piglets against Pedv Challenge." *Mbio* 15 (2):e02958-23.

https://doi.org/10.1017/anr.2025.10013 Published online by Cambridge University Press