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The role of iron in viral infections

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1. ABSTRACT

Crucial cellular processes such as DNA synthesis and the generation of ATP require iron. Viruses depend on iron in order to efficiently replicate within living host cells. Some viruses selectively infect iron – acquiring cells or influence the cellular iron metabolism via Human hemochromatosis protein (HFE) or hepcidin. During infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) iron overload is associated with poor prognosis for the patient and enhanced progression of the disease. Recent findings still lack to fully describe the viral interaction with the host iron metabolism during infection. This review summarizes the current knowledge of the viral regulation on the host cell iron metabolism in order to discuss the therapeutic option of iron chelation as a potential and beneficial adjuvant in antiviral therapy.

2. INTRODUCTION

2.1. Human iron homeostasis

Iron is an essential nutrient for humans with critical functions in many cellular processes (1), including DNA – synthesis, replication, repair and transcription (2). Iron deficiency affects the activity of iron - dependent enzymes and disrupts the proper function of different cellular processes (3). Iron functions as a redox catalyst and occurs as ferrous (Fe^{2+}) or ferric (Fe^{3+}) iron inside the cell.

Viruses depend on host cell survival during replication. The cellular metabolism is enhanced in order to support the necessary factors for replication and protein synthesis (2). These processes also require iron and therefore, iron chelation could improve antiviral treatment.

Iron uptake functions through divalent metal – iron transport protein 1 (DMT1) in the proximal duodenum or the heme carrier protein 1 (HCP1) in the jejunal enterocytes (4). In the duodenum ferric iron is reduced by ferric reductases present in the apical brush border of enterocytes. The correct subcellular location relies on a transport mechanism via ferritin. On the basolateral side the iron export is controlled by the membrane transporter ferroportin (FPN1) (5–7). In

the extracellular space iron is oxidized to ferric iron by the ferroxidase. By binding to transferrin (Tf), ferric iron can then be transported to special target cells. The iron loaded transferrin enters the target cells via receptor-mediated endocytosis. Inside the cells iron takes part in the biosynthesis of heme in mitochondria. Its tetrapyrrole form can serve either as a prosthetic group for metalloenzymes or as oxygen – binding part of hemoglobin. Furthermore, ferritin can also act as a storage for cellular iron (1).

The cellular level of iron is regulated by iron regulatory proteins (IRP1/IRP2), which bind to iron – response elements (IRE). IREs are RNA hairpin structures in the untranslated region (UTR) of several cellular mRNAs like in the mRNA encoding ferritin or DMT1 (8). Systemically the peptide hormone hepcidin, which is itself produced in the liver, regulates the activity of FPN1 by binding to it and therefore inhibiting the cellular iron export. During an iron overload the hepcidin synthesis is increased leading to the internalization and degradation of FPN1. Despite the cellular homeostasis hepcidin also controls the export of iron into the plasma (9) (Figure 1).

2.2. Iron and the immune system

Hence pathogens require iron as a nutrient, iron deprivation serves as an innate immune mechanism against invading pathogens (1). One of the most important regulators is hepcidin, which is upregulated during inflammation by pro inflammatory cytokines, Toll like receptors (TLR) and the induction of endoplasmatic reticulum unfolded response. Hepcidin limits the extracellular iron through the internalization and degradation of FPN1 (10).

The iron homeostasis regulating cytokines either function via hepcidin or directly modulate iron metabolism in immune cells, e.g. pro inflammatory cytokines like IFN–γ downregulate transferrin receptor (TfR1) expression in macrophages, leading to a decrease of intracellular iron in these immune cells (11, 12).

In the reticuloendothelial system macrophages acquire iron through TfR – mediated endocytosis of holo – Tf from senescent erythrocytes (1). Macrophages and other immune cells like neutrophils are capable of regulating the iron homeostasis via hepcidin (13). Through downregulating TfR, macrophages limit the iron intake in order to reduce iron availability to intracellular pathogens (1). In addition, via pattern recognition receptor (PRR) binding and induction of pro inflammatory cytokines, the TfR expression is decreased in phagocytes during infection. Additionally, DMT1 expression is increased, directing the cellular iron into the late endosomes and lysosomes, to induce cell death.

The two glycoproteins haptoglobin and hemopexin also play a role in iron limitation by scavenging liberated hemoglobin and heme (1). Furthermore, free extracellular iron is limited by binding to transferrin with high affinity. If the capacity for binding free iron is exceeded, iron is as well able to bind to other plasma proteins like albumin, citrate and amino acids (14). Besides the named proteins lactoferrin has a high affinity for binding free iron, which is being released at infectious sites. Because of its pH – optimum in low levels lactoferrin takes function in acidotic infectious foci (15).

2.3. Damaging effects of cellular iron

Despite being an essential nutrient, iron also bears damaging potential for the cell. During the Fenton reaction hydroxyl radicals are being generated by reducing ferrous to ferric iron. The generated hydroxyl radicals damaging lipids, DNA and proteins (1). Iron accumulation and overdose therefore also leads to increased oxidative stress and DNA damage, genetic instability and carcinogenesis (16). The reactive oxygen species (ROS) produced at high levels of cellular iron or rather hydroxyl radicals lead to destabilization and breakdown of the phospholipid membrane. This process leads to ferroptosis, an iron-dependent cell death mechanism (17, 18). ROS can attack cellular components and are further able to induce systemic damage like hepatic, cardiovascular and pancreatic dysfunctions (19, 20).

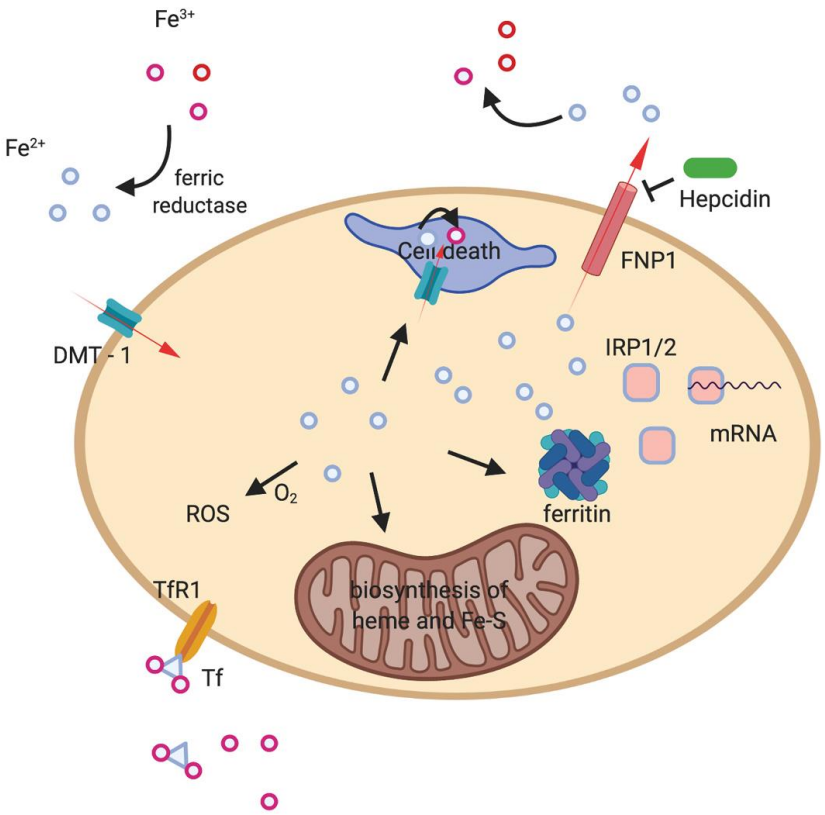

Figure 1. Iron Homeostasis. Iron uptake functions through the divalent metal – iron transport protein 1 (DMT1). In the duodenum ferric iron is reduced by ferric reductases present in the apical brush border of enterocytes. The correct subcellular location relies on a transport mechanism via ferritin. On the basolateral side the iron export is controlled by the membrane transporter ferroportin (FPN1). In the extracellular space iron is oxidized to ferric iron by the ferroxidase. By binding to transferrin (Tf), ferric iron can be transported to special target cells. Inside the cells iron takes part in the biosynthesis of heme in mitochondria. Iron can be transported into endosomes via DMT-1. Furthermore, ferritin also acts as a storage for cellular iron. The peptide hormone hepcidin regulates the activity of FPN1 by binding to it and therefore inhibiting the cellular iron export. Intracellularly Iron responsive proteins control iron metabolism by binding to iron – response elements (IRE).

3. IRON IN VIRAL INFECTIONS

3.1. Role of iron in HBV infection

The *hepatitis B virus* (HBV) is a partially double - stranded DNA – virus (21, 22), and belongs to the family of *Hepadnaviridae* (23). HBV causes chronic liver diseases, like chronic hepatitis B (CHB), liver cirrhosis (LC) and hepatocellular carcinoma (HCC). Approximately 240 million people are affected by hepatitis B infections and associated diseases worldwide (24, 25).

In 40% of patients with CHB elevated levels of iron in liver tissue were detected and linked to severity of the corresponding liver disease (26). Higher serum iron levels correlated with worse outcomes and prognosis for patients with CHB (27).

Wei *et al*. showed that serum iron levels were lower in HBV – related HCC patients compared to CHB and HBV – related LC – patients. In the named study iron levels negatively correlated with tumor size. It was suggested that the concentration of functional iron in the peripheral blood is low or normal, while the concentration of functional iron in tissue is high. Elevated iron levels were associated with enhanced progression of chronic HBV – infection and poor prognosis for the patient. Therefore, it was recommended to investigate iron chelation as a novel adjuvant for HCC therapy (28). Additionally, a study performed in 2016, showed that

the combination of Sorafenib with the iron chelator deferasirox led to a higher rate of apoptosis in HCC, compared to single drug treatment (29).

A study by Felton *et al*. in 2006 also showed that elevated serum iron levels are associated with a higher prevalence of HBV infection (30). Gao *et al*. found in 2018 that serum iron and serum ferritin levels were elevated in patients with CHB. In this study they saw decreased serum transferrin levels and total binding capacity and increased transferrin saturation, findings that were supported by several other studies (22, 23, 28, 29). It was postulated that increased iron release from infected and damaged hepatocytes is responsible for that. Additionally, persistent HBV carriers showed significantly higher levels of serum iron compared to patients with cleared viral infection (33).

Ohkoshi *et al*. showed in 2008 that in patients with HBV and LC the success of lamivudine treatment correlated with reduction in serum ferritin levels. The findings also showed that a successful antiviral therapy resolved the illness-related iron overload in these patients (34). Supporting Mao *et al*., 2015 found a positive correlation between serum iron, ferritin and alanine aminotransferase (ALT) levels. It was suggested that in cirrhotic patients HBV related liver injury, but not the HBV infection itself may be cause changes in serum iron markers (32). Furthermore, mean hepcidin levels were elevated in patients with CHB, leading to iron overload (35, 36). In patients with CHB iron overload could be due to liver injury (30), viral activity (30, 37), micro ribonucleic acid -122 (38), ROS (39), IL-6 (35) or other inflammatory factors (35). Mutations in the hemochromatosis gene (*HFE*), which lead to the following amino acid changes C282Y and H63D have shown deleterious effects in patients with CHB, causing iron overload and leading to steatosis and liver fibrosis (40).

The depletion of iron in HepG2 cells shows a decrease in HBV production (41). The question whether iron is promoting or inhibiting HBV replication is highly controversial. Several studies have shown the promoting effects of iron on HBV replication (42, 43), while others have shown detrimental effects (44, 45). The differing effects of iron could rely on the different stages of liver disease focused in the listed studies (Figure 2).

3.2. Role of iron in HCV infection

The *hepatitis C virus* (HCV), a member of the *Hepacivirus C* species, is a small, enveloped, positive-sense single-stranded RNA virus of the family *Flaviviridae* (46). HCV is the cause of hepatitis C and several types of cancer such as HCC and lymphomas (47, 48) affecting approximately 177 million people worldwide (49).

Iron liver deposits have been observed in 7 – 61% of patients with chronic hepatitis c (CHC) and are associated with severity of the liver disease (50–52). Studies suggest, that a high level of iron in the liver plays a crucial role in the progression of liver disease and increasing the risk for liver cancer (53). Additionally, elevated iron levels were associated with poor response to interferon and ribavirin therapy (54). Effective interferon therapy has been shown to be capable of a significant decrease in iron liver deposits (51). Further the reduction of excess liver iron and body iron storages by phlebotomy ameliorated the course of chronic HCV among patients incapable of receiving interferon therapy (55). Phlebotomy was an approved antiviral therapy in the United States and Japan before the emerge of direct – acting antiviral agents (56–58).

Furthermore, a study by Di Bisceglie *et al*. in 1992 showed that HCV patients displayed elevated levels of serum ferritin, correlating with iron overload and inflammation of the liver (59). Ferritin levels have been described as strong predictors of severe liver fibrosis and steatosis and necro-inflammatory activity (54, 60). Studies showed, that high ferritin levels are correlated with ALT, aspartate transaminase (AST) and gamma-glutamyl transferase (GGT) levels (61). Iron supplementation in hemodialysis patients with HCV infection significantly increased transaminase levels after three months of therapy (62, 63).

Mesenchymal hepatic iron overload in the course of HCV infection has been suggested to be caused by hepatocyte necrosis, leading to the release of ferritin and iron uptake of macrophages and Kupffer cells (55). These events may contribute

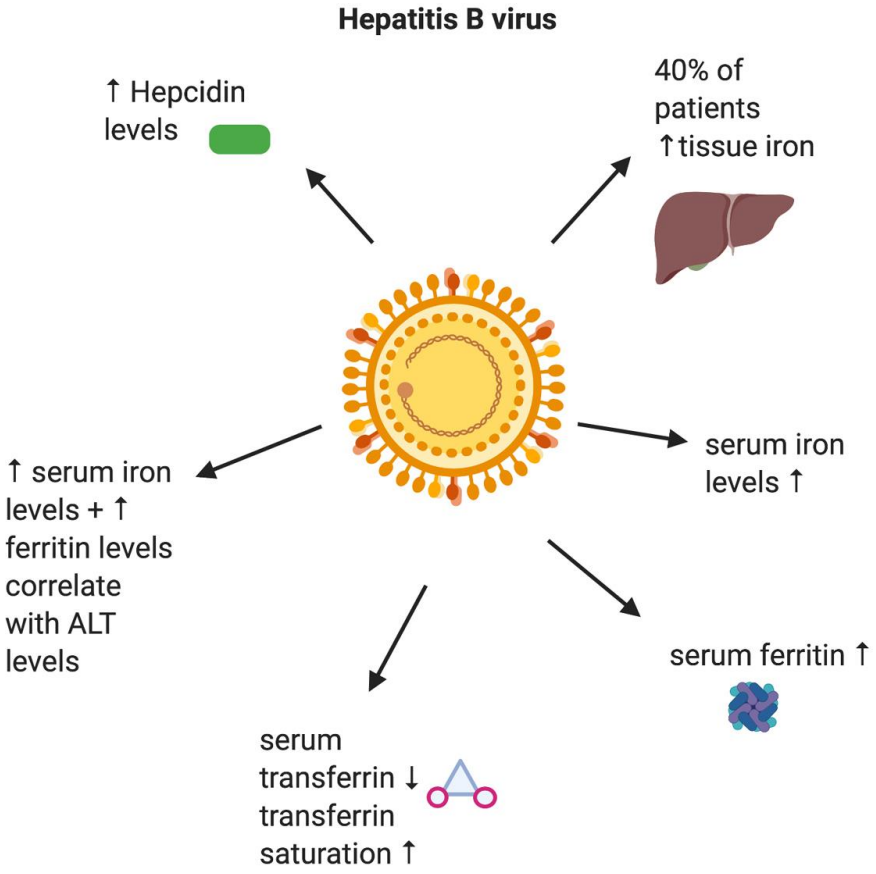

Figure 2. Iron and Hepatitis B virus. 40% of patients with CHB displayed elevated tissue iron. Furthermore, studies found elevated serum iron levels and elevated serum ferritin levels in infected patients. Additionally, studies found decreased serum transferrin level and elevated transferrin saturation. Several studies investigated the correlation between elevated serum iron and ferritin levels and ALT levels. Furthermore, patients with CHB had elevated Hepcidin levels.

to cytokine release triggering inflammation and fibrosis of the liver (53).

On a cellular level, the hemochromatosis gene (*HFE*) seems to play a role in promoting iron overload in HCV infected patients. Studies found, that homozygous and heterozygous mutations in *HFE* C282Y caused hepatic iron overload promoting steatosis and liver fibrosis in HCV – infected patients (40, 64–66).

Recent works have shown the beneficial role of iron on HCV translation in different HCV genotypes (67), but it remains unclear whether iron is suppressing or promoting HCV replication. By enhancing the function of the eukaryotic initiation factor elf3 and the La protein, iron seems to promote the translation of HCV mRNA (67, 68).

It was also investigated, that HCV is able to reduce the level of hepcidin through its core proteins E1, E2, NS3, NS4A, NS4B and NS5A by signal transduction and activation of the transcription, mitogen – activated protein kinase (MAPK), Bone morphogenetic proteins (BMP)/SMAD signaling pathways and an increased histone deacetylase (HDAC) activity (69, 70). These findings are further supported by Tumban *et al*., 2009 showing that the HCV – genome contains a RNA – structure mimicking iron responsive elements on its internal ribosome entry site, indicating that HCV has the ability to modulate the cellular iron metabolism (71). Low hepcidin levels lead to an increased ferroportin activity in the duodenum, upregulating intestinal iron

absorption (72). In conclusion, HCV proteins seem to directly increase iron absorption, macrophage iron release and hepatic iron accumulation (73).

Recent discussions elucidate whether iron is a promoting factor for HCV replication in liver cells. Several studies have found that HCV replication is enhanced in iron overloaded macrophages compared to physiological iron level. This could be the result of high oxidative stress in the macrophages and an impaired immune function (74). A study by Kakizaki *et al*., 2000 showed that $FeSO_4$ in concentrations of 50 – 100µM enhanced HCV replication 10-fold in cultured human hepatocytes within 48 hours respectively to the untreated control (75). Nevertheless, other studies working with the neoplastic cell line Huh7 found that supra-physiologic iron concentrations induced by halmin inhibited HCV replication by inactivating RNA – polymerase NS5B (76, 77). Fillebeen *et al*., showed that HCV infection caused cellular iron depletion in Huh7 cells by increasing IRP activity and suppressing TfR1 and DMT -1 expression (78) (Figure 3).

3.3 Role of iron in HCMV infection

The *human cytomegalovirus* (HCMV) is an enveloped, double – stranded DNA – virus and belongs to the group of *β – Herpesviruses* (79). HCMV remains a major health burden with the world´s seroprevalence ranging between 40 – 99% depending on the geographical and socioeconomic background (80). Whereas HCMV infections remain mostly asymptomatic or display only mild symptoms in immunocompetent hosts, severe life – threatening symptoms are described for patients with an impaired adaptive immune system (81).

Studies have shown that the HCMV replication could be inhibited by the iron chelators deferoxamine (DFO) and calcium trinatrium diethylenetriaminepentaacetic acid (DPTA) (82, 83). A study by Sun *et al*. discovered a correlation between the HCMV protein pUL38 and the prevention of premature cell death due to antagonization of cellular stress response. It was shown that HCMV influences the iron metabolism in order to ensure cellular survival during viral replication. Through activating the ubiquitin – specific protease 24 (USP24), and thus reducing the release of free iron, pUL38 suppresses ferritinophagy. The cell death induced by infection with pUL38 – deficient HCMV could be inhibited by treatment with iron chelators like ciclopirox olamine or tiron (84).

Furthermore, another study found a connection between HCMV – infection and the nonclassical class I major histocompatibility complex molecule HFE. *HFE* is mutated in autosomal recessive iron overload disease hereditary hemochromatosis leading to a reduced iron intake via the transferrin receptor (85). The expression of the HCMV protein US2 interferes with the stability and assembly of hHFE complexes. US2 targets HFE specifically for proteasomal degradation leading to a decreased iron uptake. It remains unclear if this viral mechanism is used to alter cellular metabolism in order to escape immune response (86).

However, a study by Kaptein *et al*., 2006 identified the anti – malaria drug artesunate as a potential new antiviral drug, suggesting that its antiviral activity is enhanced by increased intracellular iron concentrations. Iron overload increases the production of reactive oxygen intermediates (ROI) and negatively influences signal transduction pathways like NF-κB which are crucial for HCMV's replication (87) (Figure 4).

3.4. Role of iron in HIV infection

Even after the establishment of highly active antiretroviral therapy (HAART), HIV – infections remain a major cause of mortality worldwide (88). The United Nations estimate that currently 33 million individuals are infected with HIV worldwide (2).

Iron is important for DNA synthesis and repair (89). During an HIV – infection the body is set into a systemic inflammatory state (90, 91). HIV modulates cellular and systemic iron homeostasis (12, 92, 93), leading to lower hemoglobin (Hb) levels (94). Findings by Banjoko *et al*., in 2009 described elevated iron levels in antiretroviral therapy ART – naive HIV – positive patients (95), leading to the question whether HIV alters the iron homeostasis.

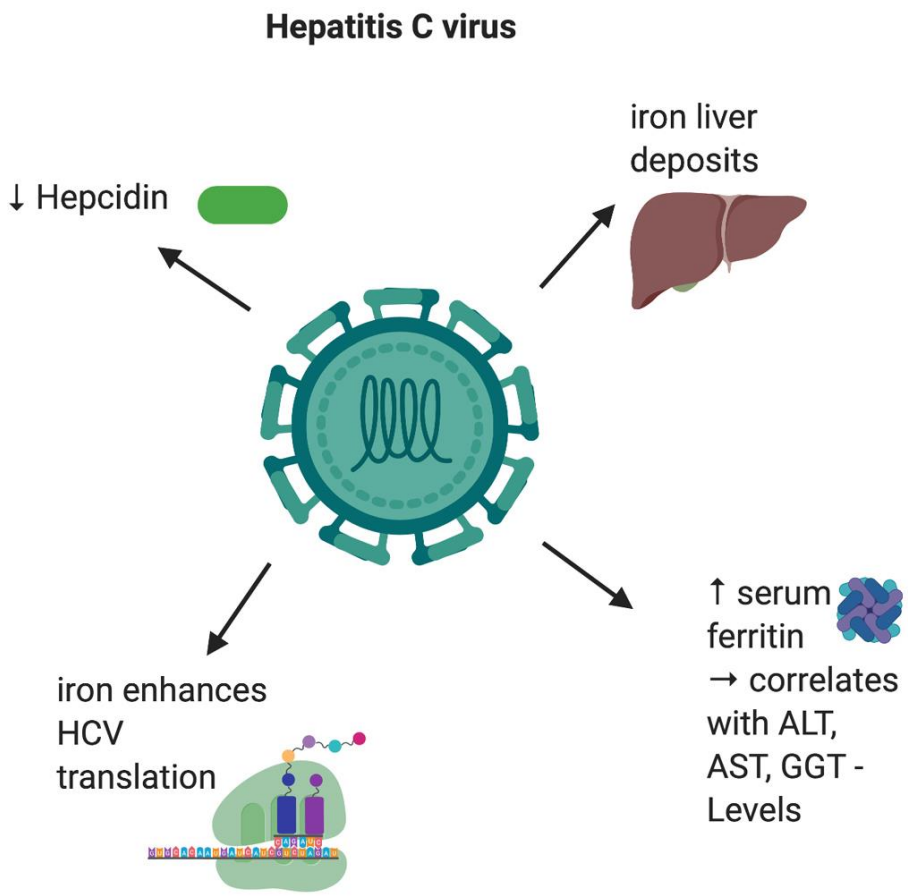

Figure 3. Iron and Hepatitis C virus. Studies found iron liver deposits in infected patients. Furthermore, patients showed elevated serum ferritin level positively correlating with ALT, AST, GGT – level. Studies found that iron enhances HCV translation. Patients with CHC displayed lower levels of Hepcidin.

Studies have shown that anemia is associated with worse outcomes of HIV – infection (2). In contrast to that iron overload is also a risk factor for rapid progression of the disease (96). High cellular iron levels in macrophages lead to an increased HIV – transcription (97, 98). A study by Sappey *et al*. in 2009 revealed that the treatment with the iron chelator DFO led to a downregulation of NFκB in monocytes. The downregulation of NF-κB correlates with a decrease in HIV-1 reactivation probably caused by emerging oxidative stress (99). However, this effect was not seen in other studies examining the effect of iron chelation on NFκB – expression (100).

A different mechanism examined is the inhibition of the cyclin dependent kinases 2 (CDK2)/ Cyclin E complex axis, in order to describe the relation between iron deficiency and reduced HIV replication, although it couldn't be verified (101).

A study by Chang *et al*., 2014, showed that HIV – replication was enhanced in presence of higher iron levels. Iron supplementation increased viral replication and release. A decrease in cellular iron was protective against HIV – infection. Transferrin – receptor 1 (TfR-1) mRNA levels were increased due to HIV – infection, which led to an increased iron uptake and higher level of cellular iron. To examine whether ART was able to alter the cellular iron level, cells were treated with the protease inhibitor darunavir and nucleoside reverse transcriptase inhibitor tenofovir. The treatment increased TfR-1 levels and decreased ferroportin (FPN – 1) levels

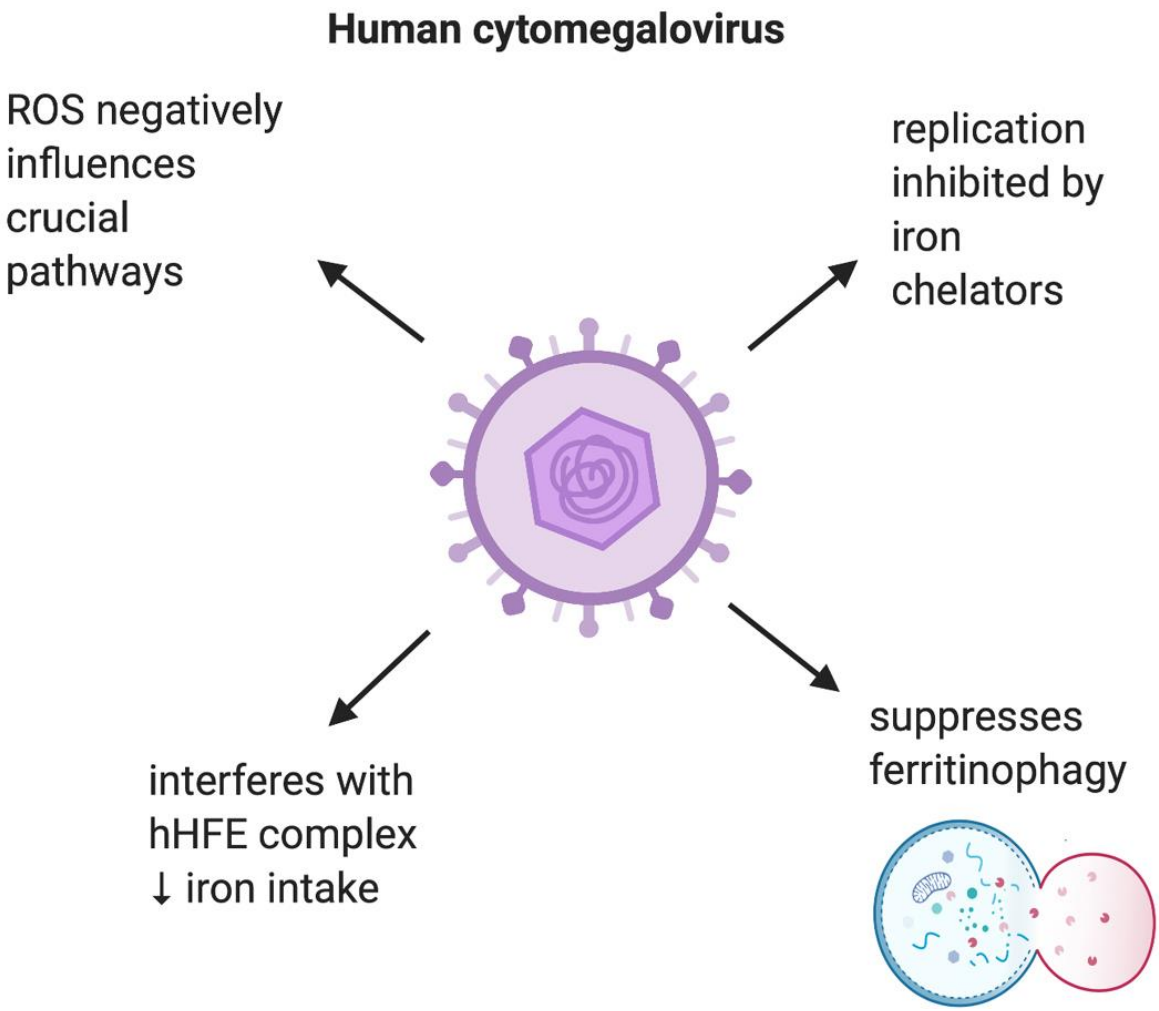

Figure 4. Iron and Human cytomegalovirus. Studies found, that HCMV replication could be inhibited by iron chelators. Furthermore, HCMV seems to be able to suppress ferritinophagy. The virus interferes with the stability of the hHFE complex, therefore, suppressing iron intake. A study claimed, that ROS negatively influences crucial pathways for the HCMV.

(88). Tenofovir also targets the mitochondrial DNA – polymerase γ, leading to induced oxidative stress by altered iron levels (102, 103). In contrast the non – nucleoside reverse transcriptase inhibitor evafirenz didn't alter cellular iron levels or the expression of iron regulatory genes (88).

In HIV – positive blood samples a significant increase in serum iron levels, transferrin saturation and a decrease in unsaturated binding capacity was examined. These effects even persisted under ART (88). Although other studies have shown that the overexpression of HIV – 1 Nef protein impaired the recycling of TfR-1 to the cell surface, which is therefore leading to reduced cellular iron uptake and iron deficiency (104, 105). This could be a strain – specific effect (106). Especially the influence of HIV on hepcidin levels has to be further investigated. Several studies have shown increased hepcidin levels during an HIV infection leading to reduced serum iron levels (88). Even though other studies have shown decreased hepcidin levels in HIV – positive women, which could be due to increased iron release into the circulation (107).

A recent study showed that HIV – infected

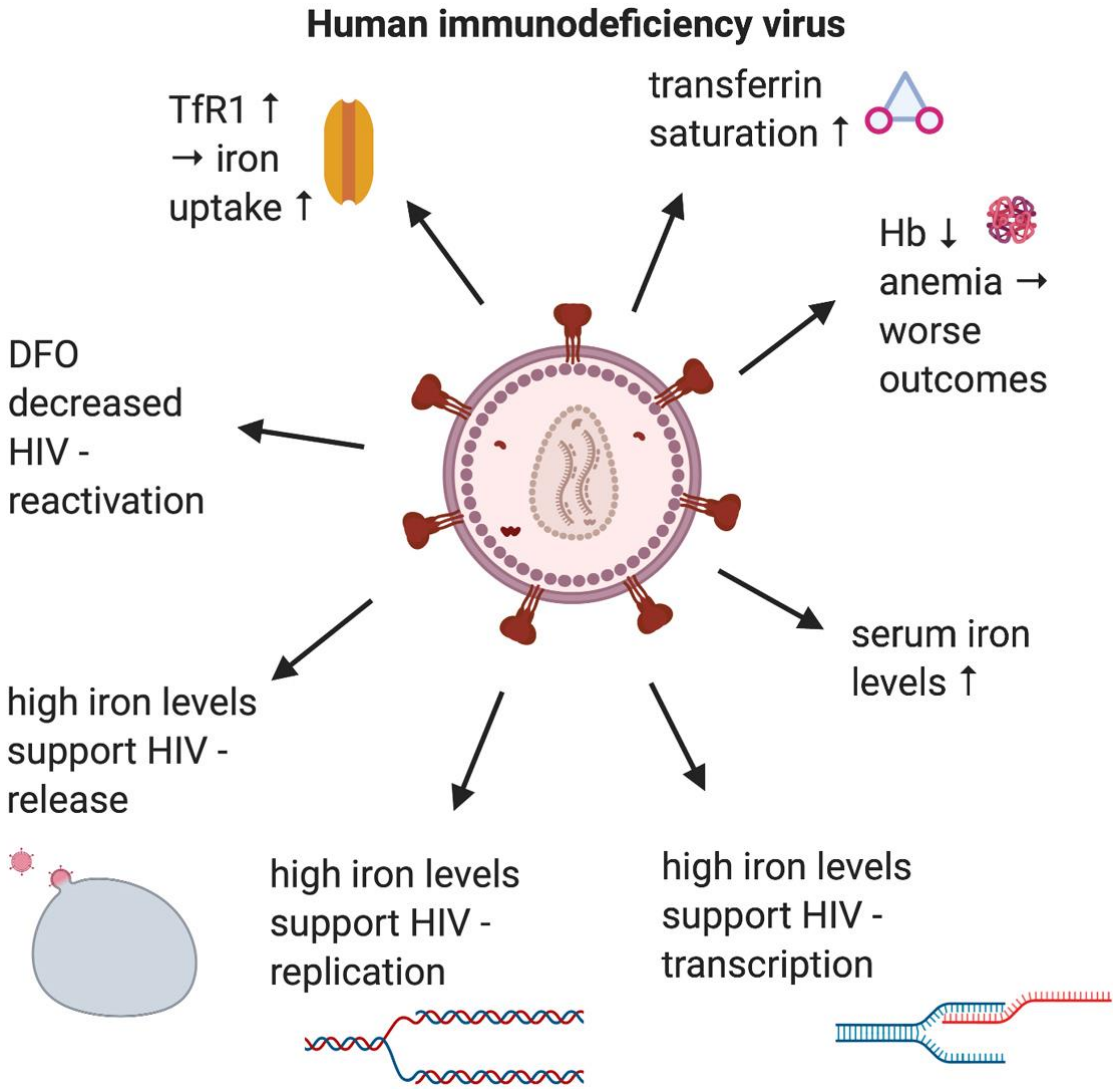

Figure 5. Iron and Human immunodeficiency virus. In some studies, HIV – positive patients showed lower Hb – levels, which correlated with worse outcomes. Nevertheless, iron excess is also predictor for a progression of the disease. Studies found elevated serum iron levels, increased transferrin saturation, increased Transferrin - receptor 1 levels, leading to a higher iron intake. High iron level seems to support HIV – transcription, replication and release. A study investigated, that the iron chelator DFO decreased HIV – reactivation.

adults have a disrupted CNS iron transport, leading to mitochondrial degradation, owed to the fact that cellular iron is an important co – factor for mitochondrial biogenesis (108) (Figure 5).

4. CONCLUSION

The above discussed studies indicate the detrimental effects of iron overload in the setting of viral infections. The viruses discussed in this review are postulated to be able of altering the iron homeostasis in infected individuals. The viruses seem to prosper in the presence of iron overload; therefore, iron chelation appears to be a potential and logical beneficial adjuvant therapy for viral infections in an era of multidrug resistant viruses. However, further studies are needed to examine the precise interactions between iron homeostasis and viral proteins in order to improve actual and develop new therapeutic strategies.

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Abbreviations: HBV: hepatitis B virus, HCV:

hepatitis C virus, HCMV: human cytomegalovirus, HIV: human immunodeficiency virus, DNA: desoxyribonucleic acid, ATP: adenosine triphosphate, HFE: hemochromatosis protein, DMT - 1 : divalent metal - iron transport protein 1 , HCP - 1 : heme carrier protein 1, FNP1 : ferroportin , Tf: transferrin, IRP1/IRP2: iron regulatory proteins, IRE: iron response elements, RNA: ribonucleic acid , UTR: untranslated region, mRNA: messenger ribonucleic acid, TLR: Toll like receptor, IFN-γ : Interferon gamma, TfR1: Transferrin receptor 1, PRR: Pattern recognition receptor, ROS: reactive oxygen species , CHB: chronic hepatitis B, LC: liver cirrhosis, HCC: hepatocellular carcinoma, ALT: alanine aminotransferase, IL-6: Interleukin 6, CHC: chronic hepatitis C, AST: aspartate transaminase, GGT: gamma-glutamyl transferase, MAPK: mitogen-activated protein kinase , BMP: bone morphogenetic proteins, HDAC: histone deacetylase , IRP: iron responsive proteins, DFO: deferoxamine , DPTA: calcium trinatrium diethylenetriaminepentaacetic acid, USP24: ubiquitin - specific protease 24, HAART: highly active antiretroviral therapy, Hb: hemoglobin, ART: antiretroviral therapy, CDK2: cyclin dependent kinase 2

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