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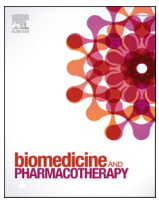

Review

Iron chelators as mitophagy agents: Potential and limitations

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ABSTRACT

Mitochondrial autophagy (mitophagy) is very important process for the maintenance of cellular homeostasis, functionality and survival. Its dysregulation is associated with high risk and progression numerous serious diseases (e.g., oncological, neurodegenerative and cardiovascular ones). Therefore, targeting mitophagy mechanisms is very hot topic in the biological and medicinal research. The interrelationships between the regulation of mitophagy and iron homeostasis are now becoming apparent. In short, mitochondria are central point for the regulation of iron homeostasis, but change in intracellular cheatable iron level can induce/repress mitophagy. In this review, relationships between iron homeostasis and mitophagy are thoroughly discussed and described. Also, therapeutic applicability of mitophagy chelators in the context of individual diseases is comprehensively and critically evaluated.

Eukaryotic cells, unlike prokaryotic cells, are defined by the existence of organelles separated by endomembranes. This intricate structure enables precise regulation of signal transduction and enzymatic reactions, thereby enhancing cellular efficiency. Mitochondria, a which serve as cellular powerhouse and signalling hub, maintain their own DNA (mtDNA), ribosomes, and two distinct membranes - the inner and outer (IMM and OMM). These two membranes are separated by an intermembrane space (IMS). [1,2] Mitochondria play a pivotal role in basal metabolism as a bearer of Krebs cycle, Lynen spiral, and respiratory chain as well as a site of heme and Fe-S cluster biosynthesis, crucial for iron homeostasis and metabolism. [1] In addition, mitochondria play a crucial role in redox signalling by generating reactive oxygen species (ROS). This process regulates various cellular activities such as the cell cycle, stress response mechanisms, inflammation signals, and even triggers cell death, including apoptosis. Efficiently functioning mitochondria are vital for the optimal performance of cells and the overall health of an organism. [3]

For instance, the OMM plays a crucial role in various intracellular signalling pathways, including the mitochondria-dependent apoptotic pathway. [4] Under normal conditions, the apoptotic proteins BAK and BAX are kept inactive by binding to the antiapoptotic BCL-2 protein. However, the loss of BCL-2, which can occur following the loss of the IMM potential ($\Delta\Psi m$), allows for the activation of BAX and BAK. This activation leads to pore formation in the OMM and the subsequent release of cytochrome c (Cyt c) into the cytosol. Once liberated, Cyt c activates caspases, initiating apoptosis. Other IMM proteins, such as Smac/DIABLO and Omi/HtrA2, can also participate in this process by targeting inhibitor of apoptosis proteins. [5–7] Additionally, Endonuclease G, apoptosis-inducing factor (AIF), and Omi/HtrA2 contribute to caspase-independent cell death. [7–10]

IMS proteins play crucial role in various functions, including the transport of proteins, lipids, and metabolites, protein folding, and maintaining the integrity of the respiratory chain. [11] The primary role of the mitochondrial matrix is the biosynthesis of ATP through oxidative

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phosphorylation, which relies on the proton gradient across the IMM. Within the mitochondrial matrix, the Krebs cycle (also known as the tricarboxylic acid cycle), in combination with oxidative phosphorylation, constitutes as the final step in the catabolism of amino acids, carbohydrates, and saccharides, ultimately leading to ATP production. [12] Furthermore, certain mitochondrial metabolites are involved in chromatin control processes, such as DNA methylation and histone modification. [13]

However, mitochondrial dysfunction is a phenomenon associated with numerous pathological conditions. These include aging, the development of cancer, and the onset of various chronic diseases. Dysfunctional mitochondria produce less ATP, exhibit a reduced (ΔΨm, and generate increased levels of ROS. [2] On the other hand, the mechanisms of mitochondrial quality control (MQC) play a crucial role in preventing or alleviating pathological consequences. [14] As mitochondria are the primary source of ROS in cells, one of the key functions of MQC is to protect against ROS-induced damage. Under normal physiological conditions, ROS detoxification is efficiently maintained. [15] It is worth noting that ROS, particularly H_2O_2, can also serve as a signalling molecule in redox signalling and the regulation of cellular functions via reversible oxidation of cysteine thiol groups.

During stressful conditions, such as elevated levels of ROS, oxidative damage to mitochondrial biomolecules, including mitochondrial DNA (mtDNA), can occur. To preserve proper mitochondrial function, MQC mechanisms are activated. At the molecular level, the DNA repair system can be activated; however, the efficiency of DNA repair in mitochondria is typically lower than in nuclear DNA, particularly under conditions of heightened oxidative stress due to increased mitochondrial ROS levels. [16,17] In cases of protein damage, mitochondrial chaperones, such as heat shock proteins HSP60, HSP70, and HSP90, are responsible for monitoring and correcting protein folding processes, as well as triggering the degradation of dysfunctional proteins via the ubiquitin-proteasome system (UPS). [18,19] If mitochondrial damage cannot be repaired at the molecular level, organelle-level MQC mechanisms, including mitophagy and the fusion/fission processes, are activated to maintain mitochondrial integrity and functionality. [14]

Mitochondria are highly dynamic organelles that exist either as a connected mitochondrial reticulum or as individual vesicles. They are constantly engaged in fusion and fission processes. This dynamism is linked with mitochondrial biogenesis, which includes mtDNA replication, and is paralleled by the autophagic removal of dysfunctional mitochondria. [20] Defective or damaged mitochondria undergo asymmetric fission, resulting in two mitochondria, one of which retains normal function, while the defective one is subsequently eliminated [21] by mitochondria-specific autophagy, more commonly referred to as mitophagy, thereby maintaining a healthy mitochondrial pool. [22,23] A basal level of mitophagy is essential as it ensures an adequate number of mitochondria for metabolic demands. [24] Under pathological conditions, this balance is disrupted, leading to abnormal mitochondrial accumulation, as observed in mouse models of obesity and diabetes. [25]

Therefore, the regulation of mitochondrial dynamics and mitophagy is of paramount importance for the maintenance of cell survival and functionality, and any disturbance can have serious pathological consequences.

Importantly, iron metabolism and homeostasis play a significant role in the control of mitophagy. For instance, a decrease in intracellular iron levels can induce mitophagy. This review is focused on investigating the role of intracellular iron in the control of mitophagy. Additionally, we will discuss the prospects and limitations of using iron chelators as mitophagy agents in the treatment of oncological, neurodegenerative, cardiovascular, and other diseases.

1. Mitophagy mechanism

The most common and widely known mitophagy mechanism is based on the PINK1/Parkin pathway (Fig. 1.). [26,27] In normal polarized mitochondria, PINK1 forms complex with TIM23 (part of transmembrane protein transporter) at the IMM, [28,29] subsequently its transmembrane region, including kinase domain is clipped off by presenilin-associated rhomboid protease (PARL) and liberated into cytosol. [30,31] In the next step, free transmembrane region is ubiquitinated and degraded by the proteasome. [29] Nevertheless, in the mitochondria with lower ΔΨm, PINK1 forms a complex with TOM in OMM and its activity remains preserved. [29,32,33] Accumulated PINK1 is activated by autophosphorylation in the kinase domain (S228 and S402, human sequence) and most probably through dimerization. [33–37] Activated PINK1 stimulates Parkin E3 ligase activity and initiates its mitochondrial recruitment via phosphorylation of Parkin (Ub-like domain). [38–40]

Ubiquitin chains of OMM proteins bind and activate autophagy adaptor proteins, known as autophagy receptor proteins. These include p62 (SQSTM1), NBR1, TAX1BP1 and especially optineurin (OPTN), and NDP52 (CALCOCO2). [41–43] They are not localized on OMM. Their structure contains **LC3 i**nteraction **r**egions (LIR) for the binding LC3, or GABARAP subfamily members. Their interaction with LC3-II initiated autophagosome formations.

Nevertheless, functionality of OPTN, NDP52, and SQSTM1 can be also controlled by their phosphorylation via TBK1. [27,42] It has been reported, that PINK1/Parkin signalling triggers TBK1 activation leading to the subsequent recruitment of adaptor proteins. On the other hand, during PINK1/Parkin mitophagy, autophagy adaptors such as OPTN (via TBK1 binding) and NDP52 recruit kinase complexes, such as PI3KC3 and ULK1/2, respectively. TBK1 and OPTN also recruit ATG9A, thereby initiating autophagy formation on the surface damaged mitochondria (Fig. 2.). Additionally, NDP52 and ATG8, and most probably their mammalian homologs (LC3 proteins) are recruited through the accumulation of mitochondrial matrix proteins such as NIPSNAP 1/2 on the mitochondrial surface, further enhancing autophagy. [44] OPTN and NDP52 mitophagy functionality can be strongly amplified by ATG8. [45] ATG8s play an important role in facilitating the fusion of autophagosomes with lysosomes to degrade their mitochondrial cargo. [46, 47] The mammalian ATG8 orthologues (MAP1LC3A/B/C and GABARAP/L1/L2; are ubiquitin (UB)-like proteins) activated through conjugation to phosphatidylethanolamine. [48–50] This posttranslational modification causes their translocation to lysosomes, facilitating their role in autophagy.

In addition to Parkin, several other ubiquitin E3 ligases (e.g., Gp78, SIAH1, MUL1, and ARIH1,) are activated by PINK1, contributing to mitophagy regulation. [51–55]. PINK1 also phosphorylates S65 in ubiquitin conjugated to OMM proteins such as mitofusins 2 (MFN2) and the mitochondrial Rho GTPases 1/2 (Miro 1/2) thus regulating mitochondrial transport. [56–60] Mfn1/2 is ubiquitinated by Parkin to prevent mitochondrial fission. [61] On the other hand, deSUMOylation/OM translocation of mitochondrial fission 1 protein (Fis1, K149) can induce mitophagy. [62] Accordingly, defective mitophagy was observed in Fis1 null worms and Fis1 knock out mammalian cells. This is accompanied, for example, by the accumulation of large LC3 aggregates in PINK1-dependent manner. [63]

Some proteins localized in OMM (called mitophagy receptors) such as B-cell lymphoma 2 nineteen kilodalton interacting protein 3 (BNIP3), Nix, Bcl-2-like protein 13 (Bcl2-L-13; mammalian Atg32 homologue) [64] and FUND1 can activate mitophagy depending on cell type and physiological conditions (Fig. 3). [65–69] The binding of these receptors to LC3/GABARAP proteins is essential for the recognition and targeting of damaged or dysfunctional mitochondria to the autophagosome for degradation.

At low oxygen levels (i.e. hypoxia), non-canonical mitophagy can be activated to prevent mitochondrial stress. For example, HIF-1α stimulates the expression of BNIP3 and NIX. [70] BNIP3 (initially known as "NIP3") Nix and (also called BNIP3L) are apoptotic proteins belonging to the Bcl-2 family. These full-length proteins that consist of an

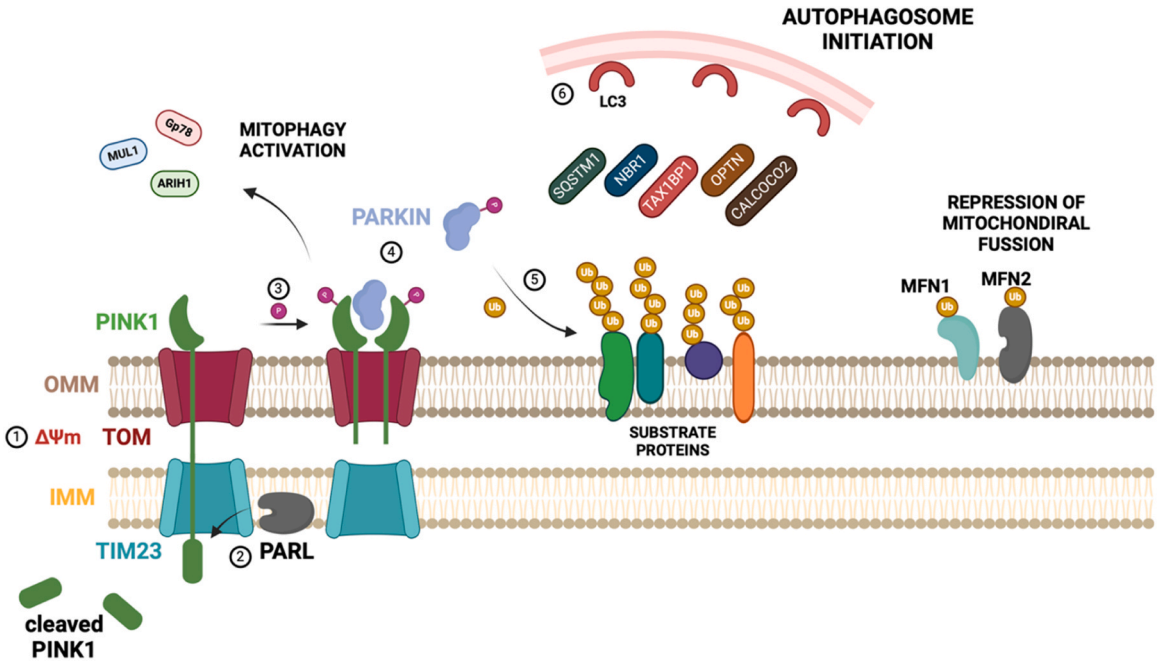

Fig. 1. Mechanism of PINK1/PARKIN pathway in mitophagy. 1) Mitochondrial dysregulation or disturbance can lead to a decrease in ΔΨm. 2) Lower ΔΨm does not support PINK1's mitochondrial localization and subsequent degradation via PARL, leading to PINK1 accumulation on the OMM through interaction with the TOM complex. 3) An increase in PINK1 levels leads to self-activation via autophosphorylation and dimerization. 4) PINK1 phosphorylates/activates PARKIN, and stimulates its mitochondrial recruitment; other ubiquitin E3 ligases such as Gp78, MUL1, and ARIH1 are also activated. 5) PARKIN ubiquitinates OMM proteins. Parkin also represses mitochondrial fusion by mediating the degradation of MFN1 and MFN2, thereby segregating depolarized mitochondria from healthy mitochondria. 6) Autophagy adaptor proteins (SQSTM1, NBR1, TAX1BP1, OPTN, and CALCOCO2) bind to ubiquitinated OMM proteins and initiate autophagosome formation through LC3 binding (Created with Biorender.com).

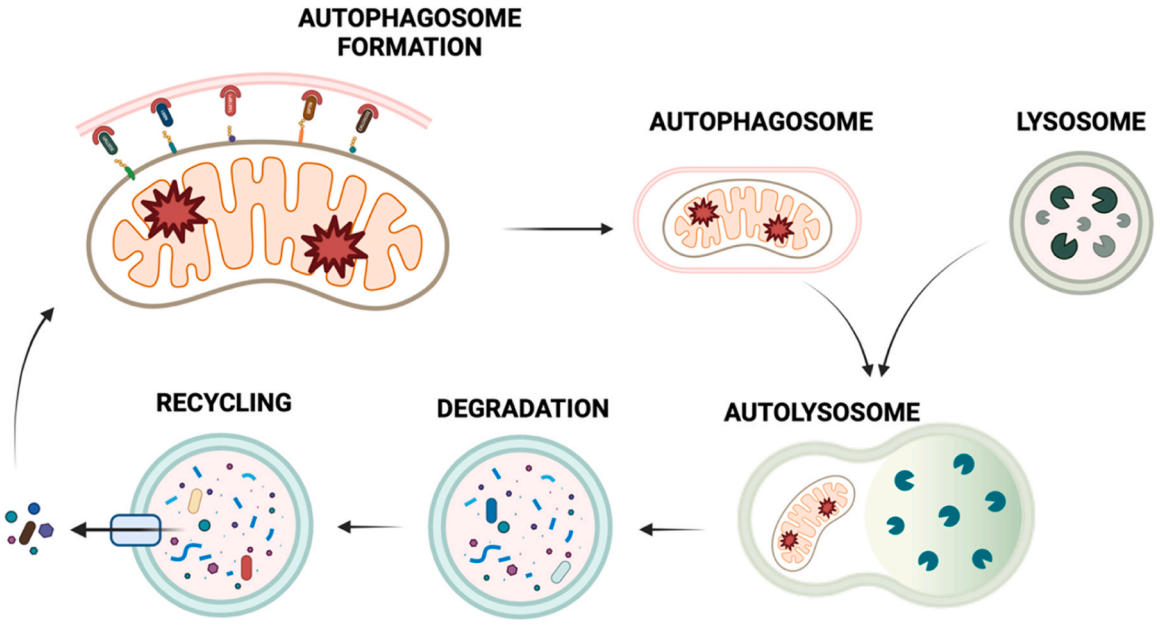

Fig. 2. Lysosomal digestion of the mitochondria through the mitophagy. Autophagy adaptor proteins facilitate the connection between ubiquitinated OMM proteins and palmitoylated LC3-II, which binds to the lipid bilayer. This process leads to the formation of an autophagosome around the mitochondria. The fusion of the autophagosome with a lysosome results in the formation of an autolysosome. Within the autolysosome, the mitochondria are digested, and the recycled components are released into the cytosol for reuse (Created with Biorender.com).

LC3-interacting region (LIR), and a putative short linear motif (SLiM, also called MER; essential for the activity of NIX)) and a C-terminal transmembrane (TM) domain, facilitating outer mitochondrial membrane (OMM localization) [71–74]. A PEST sequence (rich in proline [P], glutamic acid [E], serine [S], threonine [T]), which probably serves as a marker for rapid protein degradation, is localized in the N-terminal region. [74] They can also activate mitochondrial autophagy via an atypical BH3 domain (binding BCL-2 proteins). [71,73,74]

Moreover, under hypoxic conditions, both participate in the suppression of mitochondrial ROS and mitophagy induction. [75] These

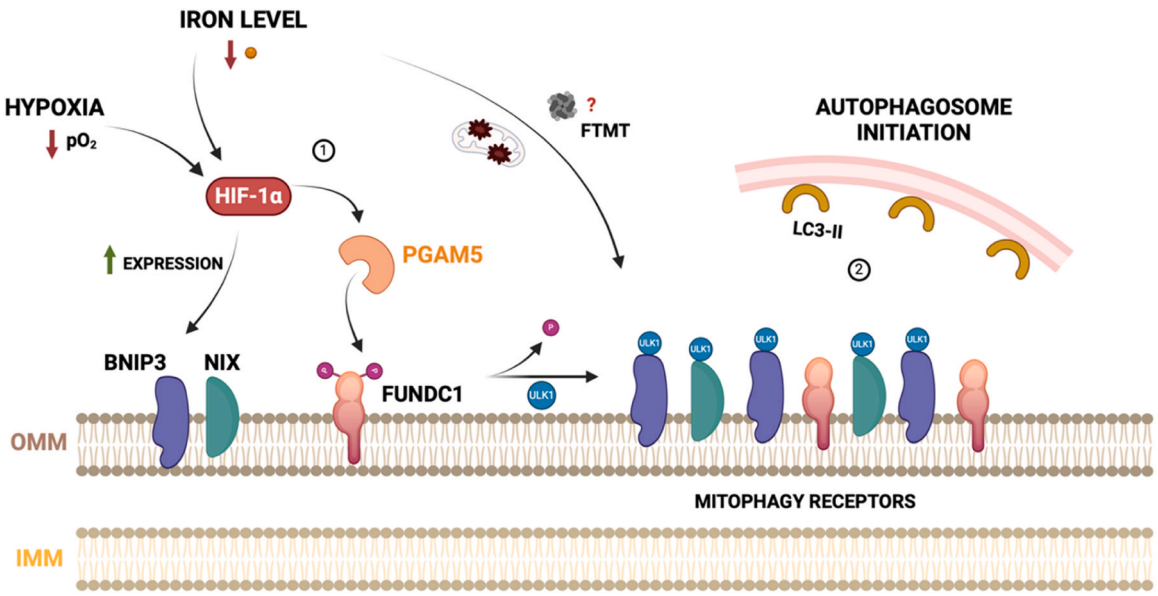

Fig. 3. 1) During hypoxia, which can also be induced by iron loss, in a dependent phenotype and condition, HIF-1α triggers the expression of BNIP3 and NIX while activating FUNDC1 through the dephosphorylation process mediated by PGAM5. Mitochondrial damage or reduced mitochondrial iron levels, potentially influenced by FTMT, result in the accumulation of mitophagy receptors such as BNIP3, NIX, and FUNDC1 on the OMM. ULK1 boosts the binding affinity of BNIP3 and NIX for LC3-II. 2) Mitophagy receptors, such as BNIP3, NIX, and FUNDC1, initiate autophagosome formation by binding to LC3-II. The autophagosome formed then fuses with a lysosome, resulting in the creation of an autolysosome where mitochondria are degraded through the process of mitophagy (Created with Biorender.com).

proteins form very stable dimers, which display significantly higher affinity for the GABARAP family proteins such as LC3. [76–78] Phosphorylation is another crucial modification controlling their activity.

It is well known, that the phosphorylated form of BNIP3 (Ser17 and **24 by ULK1**) and NIX (Ser35 and **34 by ULK1**) display significantly higher affinity for LC3. [79–81] Nevertheless JNK1/2 (c-Jun N-terminal kinase 1/2) can phosphorylate BNIP3 at Ser 60/Thr 66 and thereby increase its stability and interaction with LC3. [82] Similarly, it was reported, that NIX Ser81 phosphorylation is necessary for the mitophagy induction. [83] Whereas, BNIP3 dephosphorylation by PP1/2 A (protein phosphatase 1/2 A) induces its proteasomal degradation and represses mitophagy. [82] BNIP3 also induces mitochondrial translocation of the activator of mitochondrial fission, Drp-1, which significantly participates in NIP3-mediated mitophagy. Nevertheless, Mfn1 overexpression represses BNIP3-dependent mitophagy. [84] Zhang et al. reported, that BNIP3 represses PINK1 cleavage and supports accumulation of the full-length PINK1 at the mitochondrial outer membrane. [85] On the other hand, loss of Parkin ubiquitin ligase can repress BNIP3 autophagy activity. [84] However, it was reported, that Nix can restore mitophagy activity in absence of PINK1/Parkin-mediated pathway. [86]

In hypoxia conditions, the process of mitophagy is triggered, primarily through the dephosphorylation of FUNDC1 in LIR motif (Tyr18 and Ser-13- PGAM5) [87,88], leading to its activation and subsequent binding to LC3, thereby initiating mitophagy. In the normoxia, FOUNDC1 is deactivated by kinases Src (Tyr18) and CK2 (Ser13). [88, 89] However, PGAM5 activity is supressed by Bcl-xL binding (in BH3 domain). [90] Nevertheless, in hypoxia, the Bcl-xL protein level is significantly decreased. [90] Alternatively, PGAM5 may form multimers and dissociate from the Bcl-xL complex and induce mitophagy. [91] This multimerized form of PGAM5 can also activate Bcl-xL (dephosphorylation at Ser62) leading to inhibition of apoptosis. [91] PARL, a rhomboid protease can cleave PGAM5 and the truncated form of PGAM5 can also dephosphorylate FUNDC1. [92] Depletion of FUNDC1 inhibits Parkin-mediated mitophagy. Stx17 and PGAM5 are also required for PINK1/Parkin-mediated mitophagy. In addition, it was reported that FUNDC1 may participate in the inhibition of HIF1-α ubiquitination. [93]

The above suggests a profound link between the control of autophagy/mitophagy and cell survival. Another factor that participates in the regulation of both apoptotic and autophagy pathways is mammalian sterile 20-like kinase 1 (Mst1). [94,95] Mst1 (serine threonine kinase; component of the “Hippo” signalling pathway), can be activated by a caspase-dependent mechanism, or by Ras association domain family 1 isoform A (Rassf1A). [96,97] It has been reported, that Mst1 phosphorylates Beclin1 (Thr108 in the BH3 domain) to form a Beclin1 homodimer. [94] Beclin1, together with Vps34-p150, plays a significant role in autophagosome formation and autolysosome fusion by forming a heterodimeric complex of Atg14 and UVRAG (UV irradiation resistance-associated gene; mammalian homologue of Vps38). [98] Nevertheless, the interaction between Beclin1 and Vps34-p150, along with their phosphatidylinositide 3-kinase activity promoting mitophagy, is repressed by Bcl-2 family proteins. Phosphorylated Beclin1 (via Mst1) has a higher affinity for the Bcl-2 and Bcl-xL. [94] In addition, liberated Bax can activate apoptosis. On the other hand, Mst1 stimulates FOXO3a signalling, [99,100] which can trigger PINK1, or BNIP3/BNIP3L dependent mitophagy. [101–104]

BCL2-like 13 (BCL2L13/Bcl-rambo) is a member of the pro-apoptotic BCL2 family with BH domain and LIR sequence. Its functionality (mitochondrial fragmentation and subsequently mitophagy and apoptosis) depends on its OMM localization. [64] BH domains are important for the fragmentation, while the WXXI induces mitophagy. Murakawa et al. reported, [105] that the three-molecular complex of BCL2 like 13 (BCL2L13) with LC3B, and ULK1 (most probably interacts through LIR motif of Bcl2-L-13) is required for Bcl2-L-13-dependent mitophagy in mammalian cells. Mitochondrial membrane depolymerization induces Bcl2-L-13 expression and S272 phosphorylation in LIR motif, probably by ULK1. [64,105] In the A172 cells with BCL2L13 overexpression, the expression of NDP52, PINK1, Parkin, Optineurin, BNIP3L/NIX and BNIP3 was also increased. [106]

It should also be considered, that mitophagy regulation is a complex process strongly dependent on the cell type. In the Nucleus pulposus, HIF-1α induces mitophagy through the mitochondrial translocation of BNIP3. Surprisingly, however, loss of HIF-1α did not decrease mitophagy flux but a compensatory increase in NIX and PINK1-Parkin pathways. [107]

1.1. Mitophagy in the context of mitochondrial dynamics

Besides mitophagy, mitochondrial homeostasis is dynamically regulated by mitochondrial fission and mitochondrial fusion. [108] These processes are not isolated phenomena but are part of the complex interconnected system of maintaining mitochondrial functionality. Mitochondrial fission can lead to mitochondria with different ΔΨm. [21, 109] Daughter mitochondria with ΔΨm can recover and subsequently rejoin the mitochondrial network by fusion. Nevertheless, mitochondria with persistently low ΔΨm cannot fusion and they are eliminated through mitophagy.

A member of the dynamin family of GTPases, dynamin-related protein 1 (DRP1, called also dynamin-1-like protein (DNM1L)) is a key factor controlling mitochondrial fission. [110,111] Drp1-dependent mitochondrial fission is mediated by the endoplasmic reticulum. It can be induced by mitochondrial dysfunction associated with higher level of oxidative stress and apoptosis. Mitochondrial fission can be induced by cell cycle modulators such as ERK1/2 and cyclin B1/CDK1, which activate Drp1 by phosphorylation (serine 616) and initiate its transport from cytoplasm to the mitochondrion. [112,113] During fission, DRP1 is recruited by OMM proteins such as mitochondrial fission factor (MFF), mitochondrial fission protein 1 (FIS1), mitochondrial dynamics protein 49 (MiD49) and mitochondrial dynamics protein 51 (MID51) to the mitochondrial surface. [114] In the next step, Drp1 forms oligomers and subsequently a ring structure (in the OMM), which encircles mitochondrion [111]. And finally, mitochondria are cleaved into two daughter mitochondria by DRP1, which constricts and cleaves mitochondrial membranes in a GTP-dependent manner. Inhibition of its GTPase activity represses mitochondrial fission.

However, MTP18 (IMM proteins, PIK3 dependent [115]) also play significant roles in the mitochondrial fission, changes of mitochondrial morphology from filamentous to fragmented spherical one. On the other hand, MTP18 knockdown stimulates mitochondrial fusions. [115,116] Similarly, it was found, that overexpression of MTP18 and Drp1 in the Drp1 and MTP18 did not stimulate mitochondrial fission. [117]

Mitochondrial fusion is initiated by the tethering of mitochondria [20], followed by the fusion of the OMM and subsequently the IMM. The most important proteins (in this case of mammalian cells) that participate in OMM and IMM fusion are mitochondrial fusion protein 1/2 (MFN1/2) and optic atrophy 1 protein (OPA1), respectively. [118,119] In the OMM, MFN1 forms homo-, or hetero-helix (with MFN2), which connects two interacting mitochondria and supports transmembrane protein binding. [120]Then, MFN1 (not MFN2) causes OMM structural change via its GTPase activity and thereby initiates its fusion. This process can be controlled by ROS via MFN2. [121] In mitochondrial oxidative stress, reduced glutathione (GSH) is oxidised via ROS to glutathione disulphide (GSSG). GSSG stimulates the oxidation of MFN2-SH groups (C-terminal domain) localized in the IMS, resulting in disulfide bridge formation with other OMM proteins, including MFN1.

In the next step, OPA (kinesin-related GTP), namely its two isoforms long-OPA1 (L-OPA1) and short-OPA1 (S-OPA1) initiate IMM fusion depending on ΔΨm. In the normal (active ΔΨm) state, IMM fusion is mediated by L-OPA1 by cardiolipin interaction. [119] In this case, IMM depolarization occurs when L-OPA1 is hydrolysed to S-OPA1, which induces IMM fusion.

However, it has been neglected that mitophagy proteins can also participate in the mitochondrial fission or fusion and vice versa. It has been reported, that mutations in the PINK1 and Parkin could be compensated by upregulation of Drp1 or downregulation of MFN1/2 and OPA1. [122,123] Tanaka et al. found, that Parkin participates in the degradation of MFN1/2 via p97. [124] On the other hand, phosphorylated MFN2 (at Thr111 and Ser442 by PINK1) is Parkin receptor, whereas non-phosphorylated MFN2 acts as a mitochondrial fusion protein. [60,125] Nevertheless, the overexpression of Mfn2 induces the expression of LC3-II, which is associated with mTOR inhibition. [126] In contrast, MFN2 silencing decreases LC3-II protein level. In this line it should be mentioned, that repression of fission cannot block mitophagy. [127] Stopping the fission process, causes increased mitochondrion damage and subsequently activating mitophagy. However, without the production of healthy daughter mitochondria (normal/active ΔΨm) via fission, as a consequence, the mitochondrial pool is depleted.

The possible role of MTP18 in the mitophagy was described by Panigrahi et al. [117] They reported, that MTP18-induced mitochondrial fission is followed by mitophagy through interaction with LC3. Nevertheless, MTP18 is an IMM protein, therefore OMM rupture is required for the interaction of MTP18 and LC3 to promote mitophagy. However, in the FaDu cells (exposed to CCCP; carbonyl cyanide m-chlorophenyl hydrazone), the PINK1/Parkin pathway did not promote mitophagy, but OMM degradation was induced.

2. Iron metabolism and homeostasis

Iron is a redox-active heavy metal that can catalyze Fenton reaction through redox cycling thereby aggravating oxidative stress and triggering cell damage and even the specific type of cell death called ferroptosis. [20] On the other hand, activity and functionality of many enzymes and regulation factors are controlled by iron ions. [128] Cellular iron level is controlled by several factors, such as iron transporter Transferrin (Tf), Tf-Receptor 1 (TfR1), iron storage proteins such Ferritins (FTs), Mitochondrial Ferritin (FTMT) and Frataxin (FXN) and iron regulatory proteins IRP1 and IRP2 (IRPs) **(**Fig. 4**)**. [129,130] Tf is a glycoprotein, which serves as extracellular iron transporter (in the Fe^{3+} form). Iron-transporting Tf displays different conformation from iron-free TF and only iron-loaded Tf can and interact with TFR1 at the cell membrane. [131] The complex Tf-TfR1 is taken up into the cell via endocytosis. In the endosome, the complex is disassembled and Tf and TfR1 are recycled (into blood and cell surface, respectively) [84,86] Fe^{3+} is reduced to Fe^{2+} and transported into the cytosol by DMT1. Excess iron can be excluded from the cell via ferroportin 1 (FPN1). In the cell, iron is stored in FT. FT is composed of 24 subunits, heavy and the light chain (H- and L-chain, respectively) and one FT can bind approximately 4500 iron atoms. [132]

IRPs (iron regulatory proteins) are cytosolic RNA-binding proteins that are the main regulatory factors controlling iron homeostasis. [133] In the majority of tissues, IRP1 is expressed in two forms, RNA binding protein and aconitase that binds iron in its oxidized form at iron depleted conditions. IRP2 is expressed (iron response element binding protein 2) in the brain and small intestine. IRPs bind the iron-responsive element (IRE) of mRNA of iron metabolic proteins. When the iron level is low, IRPs stabilize TfR1 and DMT1 mRNA via binding their IRE sequence at 3'-UTR, and inhibits translation of FT and FPN1 mRNA. [131,134,135] On the other hand, at high iron level iron-sulphur-cluster (ISC) protein (4Fe–4S) binds iron regulatory protein (IPR), which cannot bind/activate TFR1 and DMT1 mRNAs, while FT and FPN1 are translated. It results in the stimulation of iron storage and transport and suppression of iron uptake.

Haem (porphyrin-iron complexes) serve as prosthetic groups in many haemoproteins (e.g., haemoglobin, myoglobin, and cytochromes), a large class of metalloproteins, which play an important role in oxygen transport, oxidative reaction, and electron transfer. [136]

Iron in the form of inorganic sulphur (ISC), including [2Fe–2S] and [4Fe–4S], serves as a cofactor in electron transfer (e.g. ferredoxins), non-redox catalysis (e.g. fumarase A and B), gene regulation (IRP1), and DNA glycosylation (MutY/MUTYH). [137–140] ISCs production occurs mainly in mitochondria, nevertheless ISC is required for the maturation of cytosolic and nuclear proteins. [141] For example, Fe-S clusters play a very important role in ribosome biogenesis, which is essential for cell survival. [141,142]

Enzymes can also use iron in the form of ions as cofactors such as Fe^{2+}/2-oxoglutarate-dependent oxygenases (prolyl hydroxylases, TET protein and Jumonji C (JmjC) domain-containing demethylases). [139] For example, prolyl hydroxylases 2 (PHD2) regulate the stability and

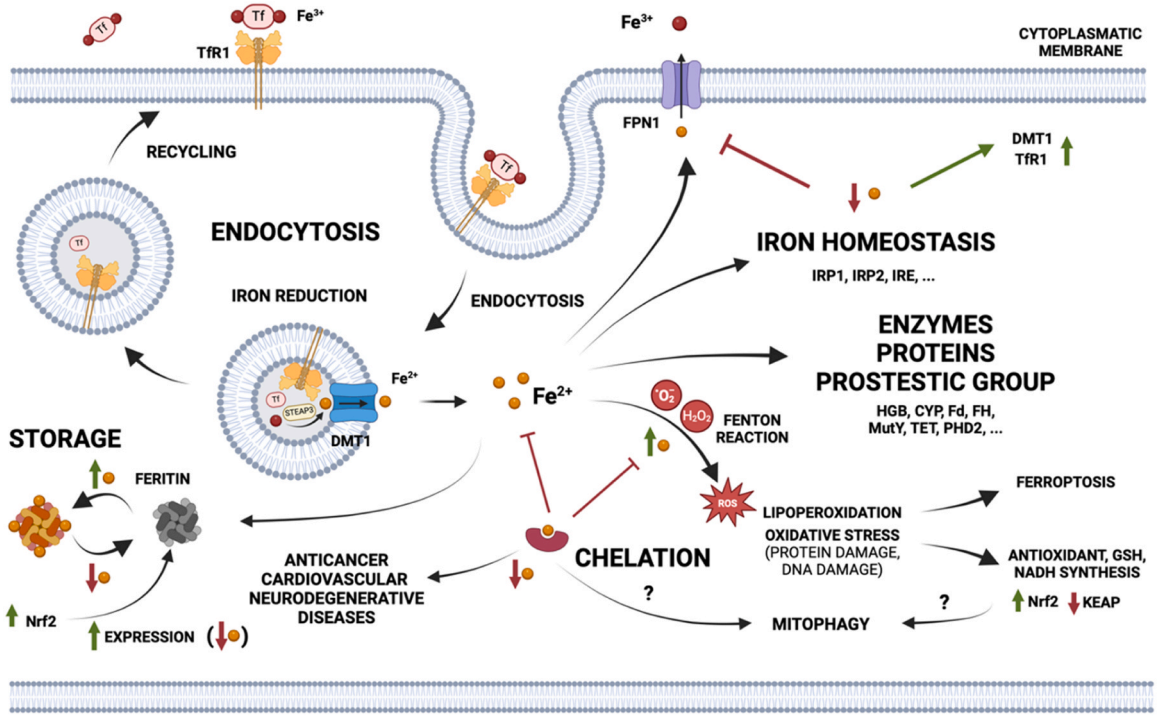

Fig. 4. Intracellular iron homeostasis. Transferrin carries Fe^{3+} ions that bind to TfR1, forming a complex that enters cells via endocytosis. Within the endosome, Tf and TfR1 are recycled, while iron ions are reduced and transported into the cytoplasm via DMT1. Iron is primarily stored in ferritin within cells, and excess iron is exported by FPN1. The regulation of iron homeostasis, involving Nrf2, is a complex process crucial for cellular function. Iron ions are essential for numerous enzymes and factors. Fe^{2+} ions also play a role in controlling gene expression through IRA. Excessive iron levels can lead to oxidative damage and ferroptosis, associated with serious conditions like cancer, neurodegenerative, and cardiovascular diseases. Recent observations suggest that the therapeutic benefits of iron chelators may be linked to inducing mitophagy (Created with Biorender.com).

therefore the protein level of the hypoxia-inducible factor (HIF-1, composed of two subunits, HIF-1α and HIF-1β) by proline hydroxylation using iron and oxygen as cofactors. [143,144] Under normal concentrations of oxygen and iron, HIF-1α is hydroxylated by PHD, which leads to the polyubiquitylation of HIF-1α and its proteasomal degradation. However, low concentrations of oxygen or iron lead to a decrease in PHD activity and maintenance of HIF-1 activity. HIF-1 stimulates the expression of various genes participating in iron homeostasis (Tf, TfR, DMT-1 and FPN1)[144], or mitophagy. However, high levels of HIF-1α do not always correlate with high levels of mitophagy. [145] It should also be mentioned, that 2OG oxygenase can be stimulated by L-ascorbic acid (LAA). LAA reduces excessive Fe^{3+} ions back into the Fe^{2+} ions, [146] and thereby can decrease /repress the inhibitory effect of chelation.

TET proteins (TET1, TET2 and TET3) modulate gene expression by successive oxygenation reactions in DNA, e.g. by converting 5-methylcytosine into 5-hydroxymethylcytosine, 5-formylcytosine, and 5-carboxycytosine. [147] At the molecular level, their activity is directly stimulated by Fe^{2+} ions, α-ketoglutarate (α-KG), O_2, and vitamin C. On the other hand, some products of mitochondrial metabolism (succinate, fumarate and 2-hydroxyglutarate) repress their enzymatic activity. [148,149] Some high impact papers suggest, that TET proteins could play a significant role in the regulation of iron metabolism. [150,151] Mild anaemia and increase of serum iron and ferritin levels (131 vs 160 ug/dL and 104 vs 329 ng/ml, respectively) were observed in the Tet2-knockdown mice compared to the wild type. [150] Erythroblasts analysis showed, that the Tet2-knockdown decreased haem concentration (most probably via Hmox1 downregulation) and increased the level of mitochondrial FT (FTMT). Nevertheless, applications of acetylating and de-methylating agents (the opposite effect of TET protein knockdown) activated FTMT expression in K562 and HeLa cells. [152]

JmJC domain-containing demethylases are the largest group of histone demethylases, mostly lysine specific demethylases. [153,154] In histone pattern, di- and trimethylation at H3K4 are linked to increased gene expression, whereas methylation at H3K9, H3K27 and H4K20 is associated with gene repression. [155] After treatment with VLX600, tri-methylation of H3K4, H3K9, H3K27 and H4K20 was observed [156]

2.1. *Iron homeostasis and mitochondria*

Iron ions are transported into mitochondria through OMM by mitochondrial DMT1, DMT2 and by mitoferrins Mfrn1 and Mfrn2 through IMM. [157–159] In yeast, Mmt1, Mmt2 and Mtm1 serve as iron exporters. [160,161]

It should be mentioned that only the role of Mfrns as iron transport proteins has been studied in more detail. [162] In the mitochondria, Fe^{2+} ions are used for ISC and hem production, or they are stored in FTMT. [163,164], which is highly expressed in tissues at high oxygen consumption. [165] It was found, that FTMT could have protective effects against iron-induced ROS. [152,166–168]

Frataxin (FXN) is another regulator, which controls iron metabolism (e.g., ISC biogenesis, haem biogenesis, iron binding/ storage, ferroxidase activity and iron chaperone). [140,169,170] Downregulation of FXN expression causes mitochondrial accumulation of iron and decreases iron levels in the cytosol. [171,172] A significant increase in HIF-1α protein levels by approximately one-third was found in the *Fxn* knockout mice (10-weeks old), although the increase in its mRNA concentration was sometimes higher (~8 fold). [173] In this case, a strong reduction in Ftl1, Fth1 and Ftmt was observed.

Iron also serves as a cofactor in important metabolic processes localized to mitochondria such as oxidative phosphorylation (OXPHOS) and Krebs cycle, lipid metabolism, and mtDNA replication and repair. [163,164] For example, iron is essential for the activity of certain mitochondrial enzymes such as cytochrome *c*, cytochrome *c* oxidase I

(COX1), succinate dehydrogenase, aconitase, and isocitrate dehydrogenase. [174–176] It should be also mentioned, that iron level can participate in the control of mitochondrial epigenome. For example, the presence of TET proteins (Fe^{2+} dependent DNA methylcytosine dioxygenases) has been observed in the mitochondria. [177,178]

On the other hand, mitochondrial iron significantly participates in mitochondrial oxidative stress via the Fenton reaction. [179,180] Some Krebs cycle enzymes, such as aconitase, α-ketoglutarate, and succinate dehydrogenases, are inactivated by excessive oxidative stress. [181] Mitochondrial dynamics can also be dysregulated by iron overload, which stimulates fission and can repress fusion. [182] Some products of the Krebs cycle (e.g., acetyl CoA, succinate, fumarate and α-KG) can also control nuclear epigenome, thereby modulating gene expression. [183] Therefore, higher iron levels can cause mitochondrial dysfunction, such as downregulating ΔΨm and thereby contributing to the development of many serious diseases. [179,180]

2.2. Iron homeostasis and ferroptosis

Ferroptosis, a distinct form of programmed cell death, alongside necrosis and apoptosis, results from the dysregulation of iron homeostasis. [184] Elevated levels of intracellular free iron can instigate the ROS production and lipid peroxidation, leading to cellular damage. Disruption in iron regulation, such as increased ferritin degradation, enhanced activity of IREB2, and heightened intracellular iron uptake, can initiate the ferroptosis cascade. [185] Conversely, heat shock protein beta-1 (HSPB1), also known as mouse HSP25 or human HSP27, has been identified as a suppressor of ferroptosis through the downregulation of TFR1 expression. [186,187]

ROS, generated through the Fenton reaction involving iron ions, particularly hydroxide radicals (·OH), oxidize polyunsaturated fatty acids (PUFA) within phospholipids of the cell membrane. The resulting lipoperoxides are highly reactive and propagate oxidative stress within cellular membranes, leading to membrane deterioration and ultimately cell death. [188] This process involves lipid peroxidases (LOXs), non-heme iron-containing dioxygenases that catalyse the oxidation of PUFA double bonds. [189] While LOXs typically target free PUFA, studies have shown that 15LO1 and 15LO2 can interact with phosphatidylethanolamine-binding protein 1 (PEBP1; respective its phosphorylated form), redirecting their selectivity towards phosphatidylethanolamine PUFA. [190] This interaction has been associated with ferroptosis in MLE cells and HT22 cells, a phenomenon that was inhibited by anti-PEBP1 antibody.

Furthermore, the downregulation of acyl-CoA synthetase 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3), enzymes involved in the incorporation of PUFA into phospholipids, can reduce cell susceptibility to ferroptosis. [191,192].

Glutathione plays a crucial role in regulating ferroptosis sensitivity by acting as a reducing agent (GSG) that donates electrons to reactive molecules like ROS, converting to its oxidized form (GSSG). [193]

Approximately 10–15 % of cellular glutathione is localized in mitochondria, where it protects the inner mitochondrial membrane, particularly cardiolipin, from oxidative stress. [194] Due to their small volume, the concentration of mitochondrial GSH is usually higher than that in the cytosol.

Depletion of glutathione can lead to ROS accumulation and subsequent cardiolipin oxidation, but NADPH can restore GSSG to its reduced GSH state. [195] Additionally, the functionality of glutathione can be replenished by System Xc^-, an amino acid antiporter that exports glutamate in exchange for extracellular cystine, a precursor of cysteine, which is essential for glutathione biosynthesis. [196]

Moreover, glutathione serves as a cofactor for Glutathione peroxidase 4 (GPX4), which converts lipid peroxides into alcohols. [197] GPX4 exists in three variants - mitochondrial (mGPX4), nuclear (nGPX4), and cytosolic (cGPX4) - each with distinct functions based on their intracellular localization. While mGPX4 acts as a mitochondrial anti-apoptotic enzyme by providing antioxidative protection of cardiolipin and also functions as a structural protein in sperm, [198–200] nGPX4 protects chromatin integrity and fertility, [201–204] and cGPX4 inhibits cell death by targeting lipid peroxidation. [205] Nevertheless, cytosolic form can also be present in other organelles, such as mitochondria.

Methylation of the GPX4 promoter under chronic stress can lead to ROS accumulation and ferroptosis by repressing GPX4 transcription. [205–207] Conversely, histone 3 lysine 4 trimethylation (H3K4me3) and histone 3 lysine 27 acetylation (H3K27ac) are associated with elevated GPX4 protein levels in cells. [206]

Additionally, Ferroptosis Suppressor Protein 1 (FSP1), also known as Apoptosis-Inducing Factor Mitochondria-Associated 2 (AIFM2), plays a protective role against ferroptosis independently of GPX4 and glutathione. [208] However, the functionality of FSP1 is reliant on N-Myristoyltransferase 2 (NMT2), a NADPH-dependent enzyme. [209] Myristoylation of FSP1 facilitates its translocation to the plasma membrane, where it converts CoQ10 to its reduced form ubiquinol, a lipophilic antioxidant that scavenges free radicals. [208–210]

3. Iron and mitophagy

Dysregulation of iron metabolism and mitophagy control can cause redox imbalance and participate in numerous hematological, metabolic, neurodegenerative and aging-related diseases.[211,212] Currently, the deep connection between mitophagy and iron metabolism is starting to be discussed more and more. Several crucial signalling proteins are involved in both the regulation of mitophagy and iron metabolism.

An example is the Nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor that plays a pivotal role in cellular defense against toxic and oxidative insults, controlling both iron metabolism and mitophagy mechanism. [213] Under quiescent conditions, the activity of nuclear factor erythroid 2-related factor 2 (Nrf2) is repressed by its binding partner, Kelch-like ECH-associated protein 1 (KEAP1) [214] KEAP1 also promotes the proteasomal degradation of Nrf2 as part of the KEAP1-CUL3 complex. [215,216] Oxidation of KEAP1's cysteine thiol groups during oxidative stress prevents Nrf2 binding. [214] The E3 ubiquitin ligase activity of the KEAP1-CUL3 complex is suppressed by the thiol modification of specific cysteine residues (Cys273 and Cys288) [217] Additionally, the accumulation of mitochondrial metabolites like fumarate and succinate can covalently modify KEAP1, thereby diminishing its affinity for Nrf2. [218,219] This leads to the accumulation of Nrf2 in the nucleus and initiates the transcription of antioxidative enzymes. [213] Nevertheless, glycogen synthase kinase 3 beta (GSK-3β) can impede the nuclear translocation and cytoplasmic accumulation of Nrf2, [220], which may increase the free iron pool and the cell's sensitivity to ferroptosis [221] However, application of iron chelators can activate PTEN, which, in turn, inhibits the PI3K/AKT/GSK-3β signalling pathway. [222]

Nrf2 plays a significant role in the up-regulation of the PINK1 and p62 genes, which are involved in the regulation of iron homeostasis and mitochondrial functionality, as evidenced by the overexpression of genes such as FTN2, FTMT, and FXN [120,223,224] Conversely, the aberrant accumulation of p62/SQSTM1 can disrupt the KEAP1-NRF2 complex. Phosphorylation of p62 at Ser349, most likely by mTORC1, markedly increases its affinity for KEAP1, resulting in the liberation of Nrf2 [225,226] Presently, the modulation of Nrf2 is being intensively studied as a treatment strategy for oncological, neurodegenerative, and cardiovascular diseases. [214,227–229]

Also, siRNA targeting genes involved in the mitochondrial ISCs assembly (ISCU, FXN, NFS1 and ISD11) activated mitophagy in HeLa cells. [230] This finding could be explained by IRP1 binding to Bcl-xL mRNA (5' untranslated region) and suppressing its translation. Treatment with DFO and knockdown of ISCU (scaffold protein for the ISC assembly) decreased Bcl-xL levels. However, IRP1 knockdown could stabilize Bcl-xL, even under low iron levels. Bcl-xL is a repressor of PGFAM5,

which catalyses dephosphorylation/activation of FUNDC1 [90], and its loss can sensitize cells to hypoxia-induced mitophagy. [90] Similarly, it was reported, that DFO and mitoDFO decreased ACO1 activity in the breast cancer cells. [231]

FTMT knockdown by siRNA repressed DPP induced mitophagy in the Huh7 and HepG2 cells. [232] Iron loss (via the HIF-1α/SP1 axis) can also increase FTMT expression (most exactly its precursors), which can display OMM co-localization. In the OMM, FTMT can interact with NCOA4 (a selective cargo receptor)[233] and thereby induce mitophagy. [232] In normal conditions, FTMT precursors are processed in mitochondria. Nevertheless, NCOA4 depletion increases IRP2 protein levels after DFO application. [233] In this line, it should also be mentioned that FTMT overexpression can stimulate HIF-1α expression. [234] On the other hand, it was reported, that HIF-1α can repress FTMT expression.

Iron loss (DFP treatment in Hela cells) increases SENP3 via repression of ubiquitin ligase STUB1/CHIP and thereby inhibiting the proteasomal degradation of SENP3. [62] SENP3 or FIS1 depletion repress DFP induced mitophagy. On the other hand, the expression of constitutive deSUMOylated FIS1 causes mitophagy in SENP3 depleted cells. It is noteworthy to mention that SENP3, through the degradation of SQSTM1/p62, can inhibit both basal and starvation-induced autophagy. [235]

It cannot be excluded, that chelator treatment can induce mitophagy by targeting other organelles. In U-251 GM cells, VLX600 induces ribosomal dysfunction (most probably via ISC deficit) associated with nuclear stress. [156] Nuclear stress associated with ribosomal dysfunction has previously been linked to autophagy. [236] For example, p73 (homolog of p53, activated by nuclear stress)[237] can support autophagy by increasing ATG5 transcription. [238] It was also found, that DFX application stabilizes p73, and promotes apoptosis and cell cycle arrest in a p53-independent manner. [239] Also p53 (stabilized by iron deficit) plays a significant role in autophagy control, depending on intracellular localization. [240–242] In the nucleus, it activates the expression of autophagic target genes, such as DRAM, Sestrin1, Sestrin2 and ISG20L1. [243–245] In addition, Funauchi et al. reported, that p53 stimulates ISCU expression through binding to an intronic p53-binding site. [246] In the cytoplasm, p53 represses autophagy by suppressing AMPK and activating the mTOR-dependent pathway. [240]

It should be mentioned, that p53 can directly affect mitochondrial functionality. [241] Cytosolic p53 can translocate to the mitochondria (under stress condition) and can induce apoptosis via interaction/inhibition of Bcl-2 [247] and Bax OMM translocation and activation [248,249]. On the other hand, p53 can interact with TFAM and support its role in maintaining mtDNA integrity. [250,251] Besides, Wang et al. reported, that Bnip3 is transcriptionally regulated by p53. [252]

The ATP13A2 gene (also known as PARK9, controlled by HIF-1α promotor) encodes a lysosomal transmembrane type 5 ATPase pump, which controls the homeostasis of Zn^{2+}, Fe^{2} ions. [253] Deletion of ypk9 (the yeast homolog of ATP13A2) increases sensitivity to heavy metals (e.g., cadmium, manganese, selenium, and nickel). [254,255] In dopaminergic neuronal cells, loss of ATP13A2 functionality decreases cell viability via disturbance of lysosomal ability for iron storage. [256] Caenorhabditis elegans with catp-6 mutant (ortholog of human ATP13A2) display defects in early autophagosome formation (decrease cleaved form of LGG-1) and iron metabolism, such as lower mRNA levels of aco-1, aco-2, mfn-1 and ftn-2 and lower mitochondrial potentials compared to wild type worms. [257] The catp-6(ok3473) mutant worms also display higher sensitivity to rotenone (a mitochondrial toxin), but Ca-EDTA (iron chelator calcium-EDTA), urolithin A (mitophagy inductor)[258] decreased rotenone toxicity. [257]

In the case of TET proteins, their effect on mitophagy is not unambiguous. TET2 knockout increases the protein level of FTMT, [150] which could play a significant part in iron loss mitophagy. On the other hand, TET proteins can activate the expression of Foxp3 (mitophagy activator via PINK1, or BNIP3/BNIP3L)[101–104]. [259,260] Nevertheless, it has been reported that FOXO3A (in pancreatic β-cells at the diabetic stress) represses PINK1/Parkin dependent mitophagy by inhibition of the Plk3-mtROS-PINK1 signal pathway. [261]

A brief overview of the proteins involved in mitophagy and iron metabolism is given in Table 1.

3.1. Ferroptosis in the context of autophagy machinery

Ferroptosis primarily hinges on intracellular free iron levels and cellular redox homeostasis. Recent studies have suggested that autophagy factors may also contribute to ferroptosis. [290]

It is essential to recognize that ferroptosis is a complex process regulated by numerous factors, including p53, AMPK, HIFs, and Nrf2, [291–294] all of which are also involved in the regulation of autophagy and mitophagy (chapter 3).

The transcription of spermidine/spermine N1-acetyltransferase 1 (SAT1) is positively regulated by p53. [291] Ou et al. reported that SAT1 stimulates the expression of 15-lipoxygenase (15-LOX), thereby enhancing the ferroptosis sensitivity of cells. [295] This process, albeit significantly slower, was also observed with the mutant protein $p53^{3KR}$, which has reduced acetylation functionality.

Another enzyme regulated by p53 is glutaminase 2 (GLS2), which hydrolyses glutamine to glutamate. [296] p53 can stimulate GLS2 expression under both normal and stressed conditions. GLS2 activity is correlated with increased levels of GSH, glutamate, α-KG (a substrate of TET proteins)[147], enhanced mitochondrial respiration, and decreased ROS levels. [296] However, GLS2 activity has also been associated with the induction of ferroptosis in isolated rat hearts under conditions of cysteine starvation. [297] p53, similar to $p53^{3KR}$ but not $p5^{34KR}$ (which has lost acetylation functionality), acts as a transcriptional repressor of the cystine transporter solute carrier family 7 member 11 (SLC7A11; part of System Xc^{-}) [298,299], which promotes antioxidative cellular protection. [300]

Moreover, p53 can repress ferroptosis by downregulating dipeptidyl-peptidase 4 (DPP4) activity and inducing p21 expression. [301] Loss of p53 prevents the nuclear accumulation of DPP4 and triggers the formation of a complex with NOX in the plasma membrane, which is responsible for lipid peroxidation. The enzymatic activity of DPP4 (peptide cleavage) [302] was found not to be essential for inducing ferroptosis. [301] p21, a transcriptional target of p53, increases the expression of System Xc^{-}, thereby maintaining glutathione levels. [303]

Nrf2 is a key regulatory factor that plays a crucial role in the regulation of iron homeostasis (primarily by reducing the free iron pool), maintenance of GSH levels (e.g., by increasing SLC7A11 expression and NADPH production), and ROS detoxification (through the expression of GPX4 and FSP1). [304,305] Generally, Nrf2 expression is associated with protection against ferroptosis.

Depending on the cell phenotype and experimental conditions, hypoxia can either repress or activate ferroptosis. [293] For instance, in glioma cells, HIF-1α upregulates SLC7A11 expression via PI3K activation. [306] Similarly, HIF-1α stimulates the expression of GPX4 and SLC7A11 in oral squamous cell carcinoma. [307] In rat hippocampus tissues under hypoxic-ischemic injury conditions, an increase in the expression of glucose-6-phosphate dehydrogenase (NADPH production), GPX4, and SLC7A11 was observed. [308]

On the other hand, chronic intermittent hypoxia, as studied in the hippocampus, liver, and cardiomyocytes, can induce ferroptosis by upregulating ACSL4 and decreasing the expression of SLC7A11, TRX-1, GPX4, and Nrf2. [309–311] Hypoxia also stimulates ROS production via mitochondrial complex III in RPE cells, facilitating the Fenton reaction. [312] Similarly, in renal clear cell carcinoma, HIF2α activation selectively enriches polyunsaturated lipids. [313]

Induction of AMPK, whether through glucose starvation or AICAR AMPK activator, leads to a reduction in GPX4 expression and GSH levels. This results in increased p53 and iron levels, enhancing ferroptosis

Table 1
Overview of proteins related to mitophagy and iron metabolism.

Name	Functions
Signalling factor	
AMPK [262–268]	**Cytosol** ULK1-formation of autophagosomes, MFF dependent mitochondrial fission (via Drp1) decrease in mTOR, FoxO3 and Pink1, ULK1(Parkin? in the next step) **Activation:** LKB1, CaMKKβ, TAK1, AMP/ATP ratio and ROS
(HIF−1α)	Expression of mitophagy receptors (BNIP3, BNIP3L) **Activation:** iron depletion (via inhibition of prolyl hydroxylases), FTMT
FoxO3 [101–104,266]	autophagy (ULK1, Beclin1) and mitophagy (BNIP3, BNIP3L), PINK1 (via LPS/ATP?) **Activation:** AMPK, LPS/ATP
Nrf2[213]	PINK1 or p62 dependent mitophagy and regulation of iron metabolism Induction: **oxidative stress.**
Mitophagy	
Atg12–Atg5-Atg16 complex [269]	**Pre-autophagosomal structure** stimulate formation of
(LC3I)	LC3-II from LC3-I
(LC3II, LC3-PE)	Cytosolic form of LC3 (LC3A/B-I) is conjugated to PE (called LC3A/B-II) and recruited to autophagosomal membranes. LC3B interact with aptamer proteins/ mitophagy receptors and enable transport of ubiquitinated protein and organelles.
Parkin [268,270]	Ubiquitination of OMM proteins, recognition of autophagy adaptor (OPTN, TAX1BP1 and CALCOCO2/ NDP52) **Represor:** TOMM40 **Activation**: Pink1a and ULK1
PINK1 [37]	Mitochondrial serine/threonine protein kinase (Parkin activator), after decrease in ΔΨm can form complex with TOMM20 (in OMM). **Induction**: Nrf2 and AMPK
Mitophagy receptor	Recruiting LC3-II to OMM
BNIP3[85,271,272]	Stabilization of PINK1, increase of PINK1/Parkin pathway via cleavage PINK1-**OMM** **Activation:** hypoxia (p38 and JNK, MAPK via ROS?) and ROS
NIX (BNIP3L and BNIP3a,)[273]	**Induction**: hypoxia and p53, FOXO3
FUNDC1 [274,275]	Activation of mitochondrial fission via Drp1 **Activation**: PGAM5 and Drp1 **Repressor**: OPA1, SRC kinase and CK2
Autophagy adaptor	Interaction with ubiquitinated proteins (UBA domains) and autophagosome (LIR domains)
p62/SQSTM1 [2,49, 225,276]	Activation of Nrf2 **Induction:** Nrf2
NDP52 [277]	PtdIns3K activation via ULK1/2 complex recruitment
OPTN[277]	PtdIns3K activation via TBK1 and subsequently ATG13 (ULK1/2 complex) recruitment
Mitochondrial dynamic	
Drp [37,278]	**OMM:** mitochondrial fission via Fis1 and Miff, MiD49
MFN2 [120]	**OMM:** mitochondrial fusion **Induction:** Nrf2
MFN1 [279]	**OMM:** mitochondrial fusion via Opa1 **Induction:** HDAC6 (glucose starvation)
OPA1 [280]	**IMM:** inner mitochondrial membrane fusion protein prevents cytochrome *c* release-induced apoptosis, mitophagy prevention **Activation**: SIRT3:(induced via oxidative stress)
MTFP1 (MTP18)[281, 282]	**IMM**: Mitochondrial fission, repression opening mitochondrial permeability transition pore, OXPHOS regulation, mitophagy induction (via MAP1LC3) **Induction:** mTORC1 via 4E-BP inhibition?
Transport proteins	
(Tom20 and Tom22) [283]	**OMM:** parts of TOM complex, protein import recognition of hydrophobic and cationic residues, respectively
(Timm50) [283]	**IMM:** Protein transport from TOM to Tim23, part of TIM23 channel
Timm23 [283]	**IMM:** Protein transport though IMM, part of TIM23 channel
Iron Metabolisms	
FECH [284,285]	**MM:** Insertion of ferrous iron into protoporphyrin IX, reduction mitochondrial free iron pool **Induction:** HIF−1α
FPN [131]	**CM:** Transmembrane iron exporter **Induction:** Iron
FXN [140,169,170,223]	**MM:** assembly of Fe-S clusters, control ROS and iron level **Induction:** NRF2
FTH [131]	**Cytosol:** Iron storage protein-heavy chain **Induction:** Nrf2
FTL [131]	**Cytosol:** Iron storage protein-light chain **Induction:** Nrf2, hypoxia
FTMT [150,152,224, 234]	**MM:** Decrease in cytosol and mitochondrial labile iron pool, hem and Fe-S cluster, Increase in HIF−1α expression **OMM:** (induce mitophagy?) **Induction:** Nrf2, TET2 protein, DNA demethylation and histone deacetylation (5-azacytidine and sodium butyrate,) iron deficit **Repression**: HIF−1α
HMOX1 [286,287]	**MM others:** hem degradation and CO production, increase in labile iron pool **Induction:** Nrf2, HIF−1α
ISCU [246,288]	**MM:** Enzyme cofactors, iron homeostasis, metabolisms and oxidative stress response **Induction:** p53
(TFR1) [131,289]	**CM:** Recognition and capturing of plasma iron-carrier proteins (transferrin and ferritin) **Induction:** iron deficiency

Cytoplasmic membrane (CM); IMM (Inner mitochondrial membrane); Mitochondrial matrix (MM); Outer mitochondrial membrane (OMM)
5' AMP-activated protein kinase (AMPK); Autophagy related 5 (ATG5); Autophagy related 7 (ATG7); Bcl-2 interacting protein (BNIP3); BCL2 Interacting Protein 3 Like (BNIP3L, BNIP3a, NIX); Calcium/calmodulin-dependent-kinase kinase β (CaMKKβ); Protein kinase casein kinase-2 (CK2) dynamin-related protein (Drp1); DNM1L (Dynamin 1 Like; c-Jun N-terminal kinase (JNK); Eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1); Ferrochelatase (FECH); ferroportin (FPN); Forkhead box O3 (FOXO3); Frataxin (FXN); Ferritin heavy chain (FTH); Ferritin heavy chain (FLH); Ferritin Mitochondrial (FTMT); FUNDC1 FUN14 Domain Containing 1; Hypoxia-inducible factor-1α (HIF-1α); Histone deacetylase 6 (HDAC6); Mitogen activated kinase (MAPK); Microtubule-associated protein 1 light chain 3 (MAP1LC3); Microtubule-associated protein 1 A/1B-light chain 3 (LC3I), LC3-phosphatidylethanolamine conjugate (LC3II, LC3-PE); Liver kinase B1 (LKB1); Lipopolysaccharide (LPS); Mitochondrial fission factor (MFF); (Mitochondrial Fission Process 1 (MTFP1/MTP18); Mitochondrial fission protein 1 (Fis1); mitochondrial fission factor (Mff); mitochondrial dynamics proteins of 49 and 51 (MiD49 and MiD51, respectively); Optic atrophy 1 (OPA1); mammalian target of rapamycin (mTOR); Optineurin (OPTN); Oxidative phosphorylation (OXPHOS); Phosphoglycerate-mutase 5 (PGAM5); PTEN-induced kinase 1 (PINK1); sequestosome 1 (encoded p62/ SQSTM1); Reactive oxygen species (ROS); Sirtuin 3 (SIRT3); Unc-51-like kinase 1 (ULK1); TANK-binding kinase 1 (TBK1); Tet methylcytosine dioxygenase 2 (TET2); Mitochondrial import receptor subunit TOM20 (Tom20); Translocase Of Inner Mitochondrial Membrane 50 (Timm50) Transferrin receptor protein 1 (TFR1)

sensitivity in renal cancer cells. [314] In contrast, p53 inhibition restores GPX4 protein levels. Conversely, p53 inhibition restores GPX4 protein levels. A similar effect is observed with the overactivation of the JAK2/STAT3 axis, which represses p53, but this is counteracted by an increase in AMPK activity. However, during glucose starvation, AMPK can downregulate PUFA biosynthesis, thereby decreasing ferroptosis sensitivity. [315,316]

In addition to the factors discussed above, the role of NCOA4A in ferroptosis should also be considered. NCOA4 serves as a cargo receptor responsible for the degradation of ferritin. [317] This process known as ferritinophagy (autophagic ferroptosis). The basic mechanisms of ferroptosis are described in the chapter 2.2. A more detailed examination of both the canonical (GPX4-dependent) and noncanonical (GPX4-independent) ferroptosis pathways, with a focus on ferritinophagy is described by Sung et al. in a comprehensive review. [317] During ferritinophagy, iron ions are released into the cytosol, potentially initiating ferroptosis. [318,319] Elevated iron levels promote the complexation of

Fe^{2+} ions by NCOA4, leading to the degradation of NCOA4 through the ubiquitin pathway. Conversely, under conditions of low iron levels, NCOA4 remains stable and can participate in the trafficking of ferritin to the lysosome. [233,320] It is noteworthy that a decrease in FTMT levels and subsequent increase in the mitochondrial free iron pool are associated with oxidative stress and ferroptosis. [168]. Yuan et al. have reported that the repression of mitochondrial lipid peroxidation inhibits ferroptosis. [321]

However, cardiolipin, a mitochondrial phospholipid, can also act as a receptor for mitophagy. [322] In a normal state, cardiolipin, which is a phospholipid rich in unsaturated fatty acids, is localized in the IMM. [323] Upon mild mitochondrial damage, cardiolipin is translocated to the OMM, initiating mitophagy. However, the presence of oxidized forms of cardiolipin can trigger mitochondria-dependent apoptosis. This raises questions about the interplay between mitophagy and ferroptosis. Yamashita et al. reported that deficiencies in BNIP3 and NIX, or the expression of their mutant forms incapable of inducing mitophagy, are associated with increased sensitivity to ferroptosis. [324] Further studies are needed to deepen our understanding of this relationship and its implications.

4. Chelators as therapeutic/mitophagy agents

Although iron is an essential element for the systems, its overdose is associated with serious issues (such as cancer, neurological diseases, cardiac and metabolism dysfunctions. [325–328] An increase in the labile intracellular iron pool (Fe^{2+} ion) generated reactive oxygen species (ROS) through the Fenton reaction, leading to oxidative damage of cellular membranes (via the formation of lipid peroxides) and subsequently causing specific cell death called ferroptosis. [329] It should also be mentioned, that the mitochondrial inner membrane is very sensitive to oxidation due to the abundance of unsaturated fatty acids. [330,331]

Therefore, strategies for reducing iron levels can be of high therapeutic importance. For example, iron chelation therapy significantly participates in the improvement of patient prognosis with iron overload. [332] In the present time, three iron chelators (deferoxamine, deferiprone, and deferasirox) have been approved for clinical applications. Additionally, a novel generation of iron chelators is being intensively developed. [333–338] In this line, it should also be mentioned that the therapeutic effects of natural polyphenol compounds are often

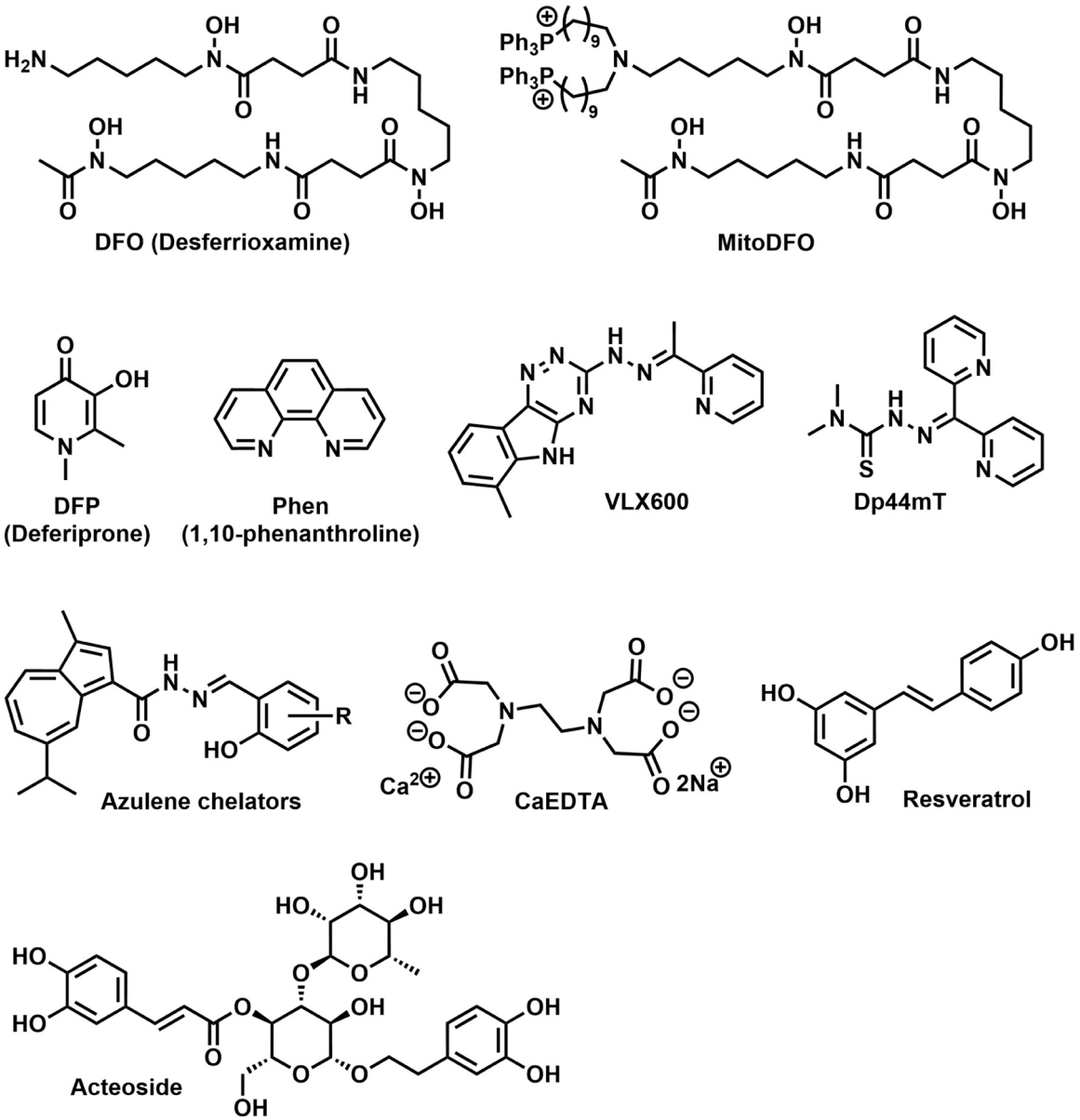

Fig. 5. Examples of iron chelators studied as mitophagy modulators.

associated with iron chelation. [339] Numerous high impact studies have implied, that reduction of iron levels through chelators could be promising therapeutic method for the treatment of oncological, neurological, cardiovascular and other serious diseases. [339] It has also been shown, that the biological effects of some iron chelation agents (Fig. 5) could be associated with modulation of mitophagy mechanisms as well.

Another significant point was made by Liu et al. [340], who deeply describes the connection between ferroptosis and mitophagy. The authors propose that the modulation of mitophagy and the inhibition of ferroptosis display high display synergy and recommend their combination targeting. In this line, it has been reported, that BNIP3 and NIX mediated mitophagy (in Hela cells) display protective effects against ferroptosis. [341] The suggestion above indicates, that mitophagy induction based on the iron chelators could be very promising therapeutic approach. Their applications for mitophagy induction are summarised in Table 2 and in the context of particular diseases will be detailed and discussed in subsequent chapters.

5. Mitophagy targeting in the cancer

Disruption in the regulation of mitophagy exerts a significant impact on severe pathologies, such as metastatic dissemination and reduced sensitivity to therapy, across various cancer subtypes. [357–359] Xiong et al. reported that specific mutations in PARK2, such as c.823 C>T, which are associated with lower Parkin activity, are not rare in lung cancer subjects. [360] ARK2 has been identified as a regulator of cyclin D and cyclin E stability, and the loss of Parkin functionality can lead to the accumulation of cyclin D, thereby promoting cell cycle progression. [361] Additionally, Parkin is involved in ubiquitin system, where it participates in the degradation of cyclin and D and E. Moreover, Parkin plays a role in the ubiquitin system, contributing to the degradation of cyclin D and E. Analysis of hepatocellular carcinoma patients revealed that genes associated with mitophagy (PGAM5, SQSTM1, ATG9A, and GABARAPL1) were linked to poor prognosis [362] Similarly, a majority of ferroptosis-related genes were highly expressed in the high-risk group in hepatocellular cancer patients.

While mitophagy inducers could be generally considered promising anticancer agents, the autophagy/mitophagy process in cancer presents a dual nature [357–359] However, PINK1-dependent mitophagy has been shown to promote therapeutic resistance. [363] Mu et al. reported that the brain-expressed X-linked gene 2 (BEX2), which is overexpressed in lung adenocarcinoma, encodes a protein that induces doxorubicin resistance in a mouse model of lung cancer through mitophagy induction (NDP52 dependent). [364] In hepatocellular cells, resistance to lenvatinib was linked to mitophagy induction (PINK1/Parkin dependent) and a reduction in ROS levels. [365] Li et al. demonstrated in MDA-MB-468 cells, a model of triple-negative breast cancer, that the oncoprotein mucin 1 (MUC1), a factor in chemoresistance, exerts a protective effect by inhibiting Pink1 degradation. [366] Conversely, suppression of mitophagy led to the inhibition of MUC1 activity. In pancreatic ductal adenocarcinoma, PINK1/Parkin deficiency and BNIP3L overexpression were found to drive disease progression. [367]

These findings suggest that the induction of mitophagy may not always result in anticancer effects. However, while iron chelators are not specific mitophagy agents, they can broadly target iron homeostasis. Iron chelators are recognized for selectively inhibiting cancer growth both in vitro and in vivo. [368] Iron ions are necessary elements for the survival, maintenance and proliferation of cancer cells, including cancer stem-like cells. [369,370] It has been reported, that higher iron levels can be associated with tumorigenicity and poor clinical outcomes. [369, 371] Therefore, strategies for targeting iron metabolism and homeostasis are being intensively developed. [371] Iron chelators display potent anticancer properties in many in vitro, vivo and in clinical trials. [370–373]

From a mitochondrial perspective, iron chelation can inhibit mitochondrial oxidative phosphorylation or trigger mitochondrial-

Table 2
Effect of iron chelators on the mitophagy.

Tested chelators	Used **Models**	**Obtained data**
Model studies		
DFO (200 μM) [342]	MEFs	*__Mitophagy__ (↑HIF−1α, ↓Atg7, ↓Atg12, ↓LC3-I, ↓mTOR, ↓**p-AMPK/AMPK ratio and ↑LC3-II/LC3-I ratio) ↑HSP1, ↑HSP70, ↑p53, ↑cleaved caspase 3 and ↑Apoptosis
Resistant mutations: $p53^{s/s}$ and $p53^{s/+}$ DFP (1000 μM) [343]	ARPE19 cells	↑**Mitophagy** (NIX/BNIP3 localization on the mitochondrial surface) and Lipid remodelling
Effective Targeting: DGAT1 DFP (1000 μM) [62]	HeLa cells	**Mitochondria** (↑Fis1), ↑**Mitophagy** (↑SENP3, **0**SENP5, ↓Fis1 SUMO−2/3-ylation, ↓CHIP, ↑LC3-I and ↑LC3-II), ↓SUMO−2/3-ylation and **0**SUMO−1-ylation
Effective Targeting: SENP3 and Fis1 knockdown DFO (100 μM) [230]	HeLa cells	↑**Mitophagy** (↓Tom20, ↓Tim23, ↑FUNDC1 dephosphorylation, and ↑LC3-II), ***__MF-Mitophagy__ (↑FUNDC1 and LC3 co-localization) and ↓Bcl-xL
Effective Targeting: FUNDC1, PGAM5 and IRP1 **Mitophagy induction**: ISCU, FXN, NFS1 and ISD11 **Oncological diseases**		

(*continued on next page*)

Table 2 (*continued*)

Tested chelators	Used **Models**	**Obtained data**
Phen (10–70 μM) [344]	HeLa/mito-YFP	**Mitochondria** (↑fragmentation, ↑depolarization, ↓mitochondrial mass, ↑ROS, ↓ATP and ↓mtDNA), ↑**Mitophagy** (↑LC3-I, ↑LC3-II, ↓p62, ↓Tom20, ↓OPA, ↓Mfn1 and ↓COX4) and ↓Cyclin A
VLX600 (1–5 μM)) [156]	**Effective Targeting**: Drp1, ATG5 glioblastoma (GBM) cells	↓**Mitochondrial respiration** (↓COX4I1), ↑**Mitophagy** (↑HIF−1α and ↓TOMM20), **MF-Mitophagy** (↑BNIP3 and ↑NIX), ↑**Histone trimethylation** (H3K9, H3K27, and H4K20) and ↓Cell viability.
	Effective Targeting: ATG5 and ATG7 **No effective Targeting:** BNIP3 and NIX (only cell vitality) NCH644GFPţ and GS−5 GFP-Luc sphere cultures	↓Tumour area
DFO (100 μM) [231]	Brest cancer cells	**Iron Metabolism** (↓FTH ↑FPN, ↓FECH ↑HMOX2 and ↓heme content), and ↓lipoic acid
MitoDFO (5–10 μM)[231]		**Mitochondria phenotype** (↑radial, ↓perinuclear, ↑fission and ↓ΔΨm), ↑**Mitophagy** (↑LC3B, ↑PINK1, ↑BNIP3 and ↓p62), **Iron Metabolism** (↓ISCU, ↓FTH, ↑FPN ↓FECH ↑HMOX2, **0**CIAO1, **0**MMS19, ↓ACO1 and ↓heme content), ↓**Mitochondrial respiration** (↓NDUF9, ↓SDBH ↓UQCRS1, ↓COXVa ↓mtCO1), ↓lipoic acid, ↓ lipoylated proteins, ↓glycolysis, ↑ROS and ↓Cell viability
mitoDFO (8 mg/kg, i.p.)[231]	Mice with 4T1 carcinoma	**Mitophagy** (↓p62, ↑PINK1 and ↑BNIP3) **Iron metabolism** (↑TFR1), ↓Tumour volume and ↓metastatic activity.
Azulene chelators (5 μM) [345]	Pancreatic cancer cells	**Mitophagy** (↑HIF−1α and ↑NDRG1), **Iron metabolism** (

(*continued on next page*)

Table 2 (*continued*)

Tested chelators	Used **Models**	**Obtained data**
		↑TFR1) and
		↓Cell viability
Dp44mT (0.1–5 μM)[346]	PANC1	↑**Mitophagy** (
		↑LC3-II),
		↑p-eIF2α and
		↑p-PERK
Effective Targeting: NDRG1 overexpression, PERK siRNA and N-acetylcysteine application		
No effective Targeting: Scr siRNA		
Dp44mT (5 μM) [346]	HCT166	**Mitophagy** (
		↑LC3-II),
		↑p-eIF2α and
		↑p-PERK
Effective Targeting: NDRG1 overexpression		
DFP (100–100μM) [232]	Huh7 and HepG2 cells	**Mitochondrial phenotype** (**0**HSP60 and very slow decrease in ΔΨm) **Mitophagy** (
		↑LC3-I,
		↑LC3-II,
		↑mitophagosome,
		↑p-p62 and
		↓p62), **MF-Mitophagy** (
		↑p-p62 and **0**Pink1), **Iron metabolism** (
		↑TfR and
		↓FTH1), **MF-Iron metabolisms** (
		↑FTMT and
		↑Frataxin),
		↓ROS and
		↓oxygen consumption rate
Effective Targeting: HiF−1α, SP1 and FTMT siRNA		
DFP (0.0375 and 0.0075 mg/kg) [232]	Mice with hepatocellular carcinoma	**Mitophagy** (
		↑mitophagosome,
		↑LC3-II and
		↑p-p62), **Iron metabolisms** (
		↑FTMT,
		↑TfR and
		↓FTH1)
		↓tumour size and
		↓number of liver tumour
DFP (1000 μM) [347]	Human lung cancer cells (A549) with A46T Parkin mutation	**Mitochondria** (**0**mitochondrial dynamic and **0**ΔΨm) and
		↓Cell viability
Neurodegenerative diseases		
DFP [62] (1000 μM)	Mammalian cells	↑**Mitophagy** (
		↑SENP3 (protein)
		↓SENP3 (mRNA), **0**SENP5
		↑LC3-II,
		↑P62 and
		↓CHIP),
		↓ΔΨm
		↓SUMO−2/3-ylation
		0SUMO−1-lyation
Effective Targeting: SENP3 (reactivation by non-SUMOylatable Fis1 K149) and Fis1		
DFP(1000 μM) [145]	SH-SY5Y	↑**Mitophagy** (
		↑LC3 and COXIV colocalization and
		↑p62), **OMM-Mitophagy** (
		↑MFN2 and
		↑BNIP) **IMS-Mitophagy** (
		↓Omi), **IMM** (
		↓Timm50 and
		↓HSP60), **Iron metabolism** (
		↑**TFR**),
		↓Citrate synthase activity and
		↓Oxygen consumption rate,
Effective Targeting: mTOR inhibition, AMP activation, Galactose glucose substitution, AT5 and Beclin1 siRNA		
No effective Targeting: Pink1 siRNA, BNIP3 siRNA		
CaEDTA (2.5 mM) [257]	*C.elegans catp−6* mutant *exposed rotenone*	↓Rotenone toxicity
Acteoside (100–500 μM) [348]	D. melanogaster (L3 larvae) *exposed rotenone*	↓Rotenone toxicity and
		↑Autophagy
Acteoside (25–100 μM)	*PC−12 cells exposed rotenone*	**Mitochondria** (
		↓mitochondrial injury and
		↑ΔΨm), **Mitophagy** (
		↑p-AMPK),
		↓ROS and
		↓Caspase−3,
		↑Survival
Effective inhibitor: 3-MA		
Acteoside (50 μM) [348]	SH-SY5Y *exposed rotenone*	**Mitochondria** (
		↓injury and

(*continued on next page*)

Table 2 (*continued*)

Tested chelators	Used **Models**	**Obtained data**
		↑Δψm) **Mitophagy** (
		↑LC3-II and
		↑p62/SQSTM1),
		↓Rotenone toxicity and
		↓ROS
DFP (300 μM) [349]	C2C12 myotubes	**Mitochondria** (
		↑EV mitochondrial secretion,
		↓mtDNA) **Mitophagy** (
		↑BNIP3,
		↓Mfn2,
		↑Mtpf1,
		↑BNIP3 and
		↑BNIP3L) and
		↓**Respiration** (
		↓NDUFB8 and
		↓SDBH)
No effective Targeting: HIF−1α knockout, BNIP3 knockout, BNIP3L knockout, 3-MA (III Phosphatidylinositol 3-kinases inhibitor) and BAFA1 (vacuolar type H^+-ATPase inhibitor)		
Acteoside (50 μM) [350]	SH-SY5Y	↓ONOO,
		↓Drp1 mitochondrial translocation and
		↓LC3 mitochondrial accumulation
Acteoside (30 mg/kg) [350]	EAE mice	↓clinical score,
		↓demyelination and
		↓**Inflammation** (
		↓Ly6G,
		↓CD11 b,
		↓CD3,
		↓CD4,
		↓IL−6,
		↓TLR4,
		↓IFN-γ,
		↓iNOS,
		↓IL−1β,
		↓CXCL−11,
		↓CXCL−12,
		↓CXCL−2,
		↓CCL−2,
		↓CCL−20 and
		↓CXCL−1) **Lumber spinal cord: Mitophagy** (
		↓LC3-II/LC3-I ratio and
		↓Drp1 mt translocation)
		↓M-CSF
		↓G-CSF,
		↓GM-CSF,
		↓VCAM−1,
		↓ICAM−1,
		↓p-p67 and
		↓p-p47
DFP (1 mM) [351]	SH-SY5Y	**Mitophagy** (
		↑HIF−1α,
		↑NIX and
		↑BNIP3,
		↓OPA1,
		↓Omi and
		↓Mitolysosome/cell and **0**Pink1) and
		↓HSP60,
Effective targeting: HIF−1α knockout and AZD8055 (c ATP-competitive inhibitor-mTOR)		
Cardiovascular		
DFP (600μM) [352]	H9c2 (ATCC® CRL-1446™)	↑Cell viability in iron overdosing,
		↓**Mitophagy** (
		↓p-DRP1 and
		↓Parkin),
		↓Bax and
		↓Cleaved caspase 3
resveratrol (10 μM) [353]	H9c2 cells	↓**Mitophagy** (
		↓P62,
		↓LC3,
		↓NIX,
		↓Tom20,
		↓PINK1, and
		↓Parkin)
Effective knockout: Mfn2		

(*continued on next page*)

Table 2 (*continued*)

Tested chelators	Used **Models**	**Obtained data**
Others		
DFP (0.25 mM) [354]	Primary RGCs	↓Cell apoptosis and ↑Mitophagy
	Retinal explant culture	↑Mitophagy
DFO (250 mg/kg) [355]	Rat with methylprednisolone	**Mitophagy** (↑HIF−1α), **Bone** (↓Osteonecrosis and ↓empty Lacunae), ↓Subchondral bone collapse and ↓deleterious effects), ↑BDM, ↑Angiogenesis and ↑VEGF
DFO (100 μM) [355]	dexamethasone exposed rBMSCs	**Mitophagy** (↑HIF−1α, Parkin, ↑ MFF and ↑FIS1) and ↑VEGF
DFO (25–200 μM) [356]	chondrocytes	**Mitochondria** (↑LC3B mitochondrial colocalization and ↑ ΔΨm), **Mitophagy** (↑HIF−1α, ↑BNIP3, ↑ATG5 and ↑LC3B/A), cleaved-caspase 3, ↓MMP3, ↓MMP13, ↑COL2, ↑SOX9 and ↑Bcl−2/Bax ratio.
Effective Targeting: HIF−1α		
DFO (250 mg/kg) [356]	FVIII-deficient male mice with needle puncture induction of HA.	**Mitophagy** (↑HIF−1α and ↑LC3B), ↓OARSI score, and ↓MMP13

*Due to the deep connection between mitophagy and mitochondrial dynamics, the relevant proteins are mentioned together.
**Prefix p is used in this case of phosphorylated variant of protein
***Mitochondrial fraction, in case the proteins were not determined in the whole cell lysate, but in the mitochondria or in a part of it (e.g., OMM and IMM), the appropriate prefix is used.
1,10-phenanthroline (Phen); 5′ AMP-activated protein kinase (AMPK); Aconitase 1 (ACO1); Autophagy related 5 (ATG5); Autophagy related 7 (ATG7); autophagy related 12 (ATG12); bcl-2-like protein 4 (BAX); b-cell lymphoma (2Bcl-2); B-cell lymphoma-extra large (Bcl-xL); Bcl-2 interacting protein (BNIP3 and NIXi); BCL2 Interacting Protein 3 Like (BNIP3L, BNIP3a and NIX); The chemokine (C-C motif) ligand 2 (CCL2); The chemokine (C-C motif) ligand 20 (CCL20); C-X-C Motif Chemokine Ligand 1 (CXCL1); C-X-C Motif Chemokine Ligand 2 (CXCL2); C-X-C Motif Chemokine Ligand 11 (CXCL11); C-X-C Motif Chemokine Ligand 12 (CXCL12); Collagen, Type II (COL2); Cytochrome c oxidase subunit 4, mitochondrial (COX4, COXIV and COX4l1); Cytosolic Iron-Sulfur Assembly Component (MMS19); Cytosolic Iron-Sulfur Assembly Component 1 (CIAO1); Diacylglycerol O-acyltransferase 1 (DGAT1); Eukaryotic initiation factor-2α (eIF2α); Ferrochelatase (FECH); Ferritin heavy chain (FTH); ferroportin (FPN); FUN14 Domain Containing 1 (FUNDC1); Ferritin Mitochondrial (FTMT); Frataxin (FXN); Granulocyte colony-stimulating factor (G-CSF); Granulocyte-macrophage colony-stimulating factor (GM-CSF); Heat shock protein 1 (HSP1); Heat shock protein 1 (HSP60); Heme Oxygenase 2 (HMOX2); chaperone-dependent E3 ubiquitin ligase (CHIP/STUB1); Intercellular adhesion molecule 1 (ICAM-1); Inducible nitric oxide synthase (iNOS); iron regulatory protein-1 (IRP1); Iron-sulfur cluster assembly enzyme (ISCU); Makrophage colony stimulating factor (M-CSF) Matrix Metallopeptidase 3 (MMP3); Matrix Metallopeptidase 13 (MMP13); Microtubule-associated protein 1 A/1B-light chain 3 (LC3I), LC3-phosphatidylethanolamine conjugate (LC3II, LC3-PE); Mitochondrial fission protein 1 (FIS1); Mitochondrial fission process 1 (MTFP1); Mitochondrial import inner membrane translocase subunit (Tim23); Mitochondrial import receptor subunit (TOM20); Mitofusin 1/2 (Mfn 1/2); N-Myc downstream-regulated gene 1 (NDRG1); cysteine desulfurase (NFS1); NADH:Ubiquinone Oxidoreductase Subunit (A9NDUFA9); high temperature requirement factor A2 (HtrA2 and Omi); Optic atrophy 1 (OPA1); Phosphoglycerate-mutase 5 (PGAM5); Reactive oxygen species (ROS); RNA-like endoplasmic reticulum kinase (PERK); SRY-box transcription factor 9 (SOX9); Succinate dehydrogenase [ubiquinone] iron-sulfur subunit, mitochondrial (SDHB); Toll-like receptor 4 (TLR4); Transferrin receptor protein 1 (TfR1); Translocase Of Inner Mitochondrial Membrane 50 (Timm50); SUMO specific peptidase 3 (SENP3); SUMO specific peptidase 5 (SENP5); 3 Ubiquinol Cytochrome C Reductase Core Protein I (UQCRC1) vascular cell adhesion molecule 1 (VCAM-1);

dependent apoptosis. [374,375] This raises the question of whether, and to what extent, the therapeutic effects of iron chelators are associated with mitophagy induction. Below is discussed the intricate link between iron deficiency and mitophagy in the context of tumour biology. The subsequent subchapter elucidates the therapeutic efficacy of the tested chelators in relation to mitochondrial homeostasis, with a specific focus on mitophagy (Fig. 6.). The results of the studies are summarized (Table 2).

Although, p53 and or HIF-1 (both induced iron deficiency) can stimulate Ndrg1 expression (metastasis suppressor gene). [346,376,377] The anticancer effect of NDRG1 is deeply associated with the suppression of the survival autophagic pathway via the PERK/eIF2α axis. [346] In Ndrg1 expressing cells, iron chelators can display higher cytotoxic effects, but the mitophagy effect is slower, nevertheless still significant. On the contrary, Jadhav et al. reported that in MDA-MB-231 cells, the expression of Ndrg1 was correlated with reduced sensitivity to iron chelators (deferoxamine and deferasirox). [378] Additionally, other impactful studies suggest, that therapeutic effects of iron chelators, at least partially, could be associated with mitophagy induction (see you in the Table 2).

In cells, autophagy/mitophagy protects against oxidative stress, or nutrient deficit. Nevertheless, too high activity of autophagy/mitophagy can also cause autophagy-depended cell death. (ADCD). [379–381] ADCD (caspase-independent programmed cell death) is associated with prominent self-digestion of cellular components in autolysosomes beyond the point of cell survival. Because, in some cancers (e.g., GBM) exhibit a high frequency of mutation in Parkin genes (PARK2), [382] activation of other mitophagy factors such as mitophagy receptors is very promising method in the anticancer treatments.

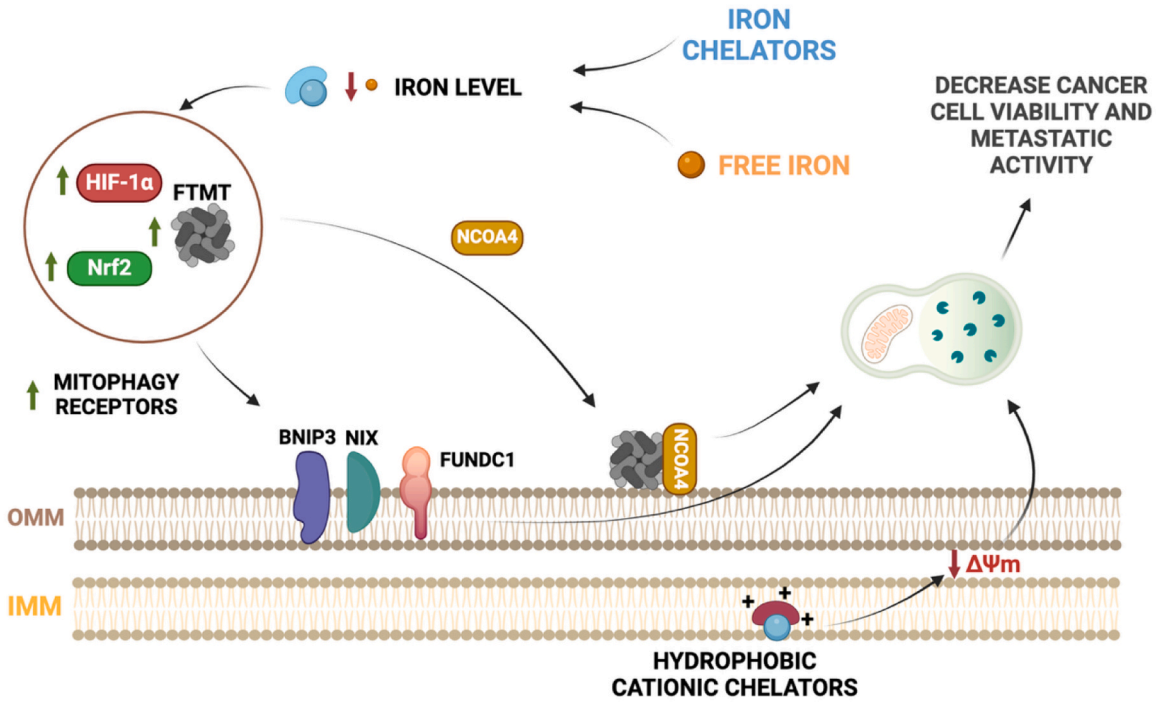

Fig. 6. Possible effects of mitophagy chelators in the cancer treatment: Cancer cell metabolism is closely linked to elevated iron levels and increased mitochondrial activity. Iron chelation by iron chelators leads to an increase in the protein levels of HIF-1α, Nrf2, and FTMT. The upregulation of HIF-1a activity subsequently induces the expression of mitophagy receptors, including NIX, BNIP3, and FUNDC1. It is pertinent to note that FTMT, or its precursor in cases of iron deficiency, can be localized to the OMM and trigger mitophagy through its interaction with NCOA4, a selective cargo receptor. Conversely, certain chelators or iron complexes containing a hydrophobic cation structure motif may localize to the IMM, leading to a reduction in ΔΨm and the consequent induction of PINK1/Parkin-dependent mitophagy. The restoration of mitochondrial function and the reduction of iron levels contribute to decreased cancer cell viability, inhibition of tumour growth, and suppression of metastatic activity (Created with Biorender.com).

On the other hand, the possible protective effect of autophagy/mitophagy on tumour cells should not be neglected. For example, chloroquine, a widely-used autophagy inhibitor, represses pancreatic tumour growth in vivo. [383] Nevertheless, in mice with oncogenic Kras and p53 depletion, the loss of autophagy (*Atg7*$^{-/-}$) no longer blocks tumour progression, but actually accelerates tumorigenesis. [384]

Similarly, KCP1 (pink1$^{-/-}$) and KCP2 (park2 $^{-/-}$) mice display shorter survival and increased metastatic activity in the liver and lung compared to the original KC mice strain (Pdx1-Cre; Kras$^{G12D/+}$; mouse models of spontaneous pancreatic cancer). [385] Applications of deferiprone (a mitochondrial iron chelator) display protective effects against pancreatic tumorigenesis associated with reduction of lactate serum level in KCP1 and KCP2 mice, but not in this case of KC mice. In PDAC cells (from KCP1 and KCP2 mice) decreased glycolysis and lower oxidative phosphorylation are observed. Nevertheless, depletion of Slc25a37/mitoferrin-1 and Slc25a28/mitoferrin-2 (in the KCP1 PDAC cells) reverses the Warburg effect and normalizes mitochondrial iron levels. HIF-1α protein levels and DNA binding were found to be significantly higher in the pancreate from KCP1 mice and knockdown of SLC5A37 represses HIF-1α expression induced by $CoCl_2$. This could imply, that higher levels of mitochondrial Fe^{2+} ion (unlike cytosol one) induce mytophagy via HIF-1α expression. In KC mice HIF-1α knockout slowly decreases survival, but for KCP1 and KCP2 mice, the opposite effect was observed.

On the other hand, it should be mentioned, that the opposite mechanism (ferroptosis) can also induce mitophagy. In KRAS-mutated cancer cells, Myoferlin targeting (by WJ460) induces mitochondrial energetic stress mitophagy culminating in ferroptosis. [386] Nevertheless, Mdivi1 (mitophagy inhibitor) and its combination with iron chelators (deferiprone and deferoxamine) repress the myoferlin-related ROS production and restore cell growth.

It was also reported, that nuclear accumulation of mutant p53 proteins (e.g., at codon 135) is associated with increased cell survival depending on autophagy control. [387] Nevertheless, some p53 mutants inhibit via the transcriptional suppression of p53 key downstream responsive autophagy related proteins (e.g., DRAM1, BECN1, ATG12, SESN1/2, P-AMPK, and TSC2), or indirectly via increased activity of growth factor receptors which stimulate the PI3K/Akt/mTOR pathway. [388,389] Unfortunately, oncogenic mutations in the TP53 are not rare (~ 50 % of human tumour cells), leading to loss-of-function and/or gain-of-function mutations in the p53 protein [21]. Additionally, p53 mutant protein commonly exhibits high accumulation and stability compared to wild-type p53, and some chaperone proteins, (e.g., Hsp90, Hsp70, and CHIP) can support their stability [23].

According to the proposed model, p53^{S} mutant cells exhibited resistance against DFO. [342] Unlike the wild type, levels of ATG7, ATG12 and proteins were increased, while mTOR and Akt levels were decreased and mitophagy activity was significantly higher. On the other hand, 3-MA (autophagy inhibitor) restored apoptosis activity in DFO-treated p53S MEFs. p53^{S} displays strongly protective effects on mitochondrial functionality. In the case of wild type cells, DFO only displays a slower effect on ΔΨm. Nevertheless, p53$^{s/s}$ mutants displayed lower ΔΨm compared to wild type, but ROS levels were also lower. Surprisingly, DFO application significantly increased ΔΨm in p53$^{s/s}$ mutants, while the increase in ROS levels was only mild.

5.1. *Application of mitophagy chelator in the anticancer treatment*

DFP is one of the most studied chelators for therapeutic applications. It should be mentioned, that the anticancer effect of DFP does not depend on the ΔΨm, or PINK1/Parkin induced mitophagy. A59 lung cancer cells with mutated Parkin display resistance against antimycin / oligomycin treatment (ADCD induction) associated with higher level HSP60. [347] Nevertheless the DFP application decreases the survival of

A46T Parkin-expressing cancer cells, most probably via the activation of the mitophagy receptor, hover mitochondrial potential was not affected. According to the proposed model, OPTN overexpression restores mitophagy induction.

Possible model of DFP induced mitophagy was proposed by Hara et al. [232] In hepatocellular cancer cells (Huh7), DFP sometimes displays a higher stimulation of expression of LC3-I and LC3-II than DFO, and DFX. A possible explanation could be difference in their effect on the concentration of mitochondrial free iron. In the case of DFX or DFO treatment, only the cytoplasmic level of Fe^{2+} ions was significantly decreased. However, after DFP application, the decrease in mitochondrial iron content was significantly higher, although the reduction of iron level was sometimes higher in the cytoplasm than in the mitochondria. Mitochondrial level PINK1, Parkin and HSP60 was not changed, but FTMT expression (most probably via HIF-1α/SP1 axis) was increased and its knockdown repressed DFP induced mitophagy. About the proposed model in this case of iron deficiency, the FTMT precursor did not uptake into mitochondria, but is localized on the OMM and can access to NCOA4 and thereby induce mitophagy, independently of the membrane potentials. In the mice model with hepatocellular carcinoma, DFP (0.075 mg/kg) repressed superoxide levels and strongly decreased tumour mass, most probably via mitophagy induction.

Nevertheless, mitochondrial selectivity may not always be sufficient and therefore new chelators are being developed. One perspective strategy could be the modification of chelator structure motif by incorporating mitochondrial selective groups (e.g., triphenylphosphonium). For example, in the breast cancer model the conjugate of DFO and triphenylphosphonium (mitoDFO) displayed stronger anticancer activity than the original DFO. [231] In the MCF7 and MDA-MB-231 cells, mitoDFO repressed mitochondrial [Fe-S] cluster assembly and levels of [Fe-S] cluster-containing mitochondrial proteins (NDUFA9, SDHB, UQCRFS1, mtCO1 and FECH (last step of hem synthesis)). The effect of defeforoxamine was significantly slower. MitoDFO completely repressed mitochondrial respiration (reduction of [Fe-S] clusters) and ΔΨm, but ATP context was not changed. Nevertheless, mitoDFO decreased and N-acetyl cysteine (antioxidant) application increased cell viability in the presence of mitoDFO, respective. This implies, that mitoDFO can induce mitophagy via iron deficiency and or ΔΨm reduction. According to the proposed hypothesis, the protein levels of BNIP3 and PINK1 were significantly increased. In the mice model with 4T1 carcinoma, mitoDFO (8 mg/kg) strongly suppress tumour growth. This effect was associated with a decrease in p62 and an increase in PINK1 protein levels. The antitumour efficiency of DFO (80 mg/kg) was sometimes lower. More importantly mitoDFO strongly repressed metastatic activity in the lung, nevertheless, DFO application displays no significant antimetastatic effect. Mitochondrial depolarization and subsequent PINK1 activation were most probably caused by the triphenylphosphonium group of mitoDFO. Triphenylphosphonium is a hydrophobic cation and accumulation of hydrophobic cation in the negatively charged IMM can cause a decrease in ΔΨm and disturbance in mitochondrial respiration. [390–392]

Another chelator containing the structure of hydrophobic cation is 1,10-phenanthroline (Phen, pKa = 5.12)[393]. [394] In Hela cells, Phen causes mitochondrial fragmentation and mitochondrial dysfunctions (e.g., depolarization of mitochondrial potential, increase in ROS level and lover ATP level) in a Drp1 dependent manner. [344] At the molecular level a decreased protein level of Tom20, MFN1 and COX IV (dose dependently) was observed. In ATG5 deficient cells and LC3II expression was strongly repressed and the reduction of mitochondrial mass was significantly lower compared to wild type. Surprisingly, the basal level of OPA1 was higher in wild type cells than in ATG5 deficient cells, but after Phen application, a higher protein level was observed in ATG5 deficient cells.

A promising therapeutic strategy can be based on the application of mitochondria targeting agents with chelation ability such as VLX600 (iron chelator and OXPHOS inhibitors). In the U251 cells, VLX600 induced caspase-independent apoptosis, but ATG5 and ATG7 knockout repressed VLX600 cytotoxicity. [156] The chelator decreases oxygen levels, mitochondrial respiration and increases HiF-1α expression and mitochondrial localization of mitophagy receptors (BNIP3 and BNIP3L). Protein levels of COX4T1 and TOMM20 were strongly repressed, but in the autophagy-deficient cells this effect was significantly slower. VLX600 also displays a significant effect on the histone pattern, such as the induction of in H3 and H4 lysine trimethylation. It could be suggested, that VLX600 also induces gene repression via inhibition of histone demethylases. [155] In NCH644 tumour spheres, VLX600 completely blocks tumour proliferation, in the case of NCH644 ATTG5, or ATG7 KD a reduced response to the VLX600 treatment was observed. [156] Nevertheless, $FeCl_2$, or $FeCl_3$ supplementation protects NCH4644 cells against apoptosis and BNIP3L and COX4I1 protein level were restored.

Expert Opinion: Mitophagy chelators are potent anticancer agents. Their applications can strongly repress cancer cell viability, tumour growth and metastatic activity. However, to what extent is their anticancer effectiveness due to iron loss mitophagy is still an open question.

6. Mitophagy targeting in neurodegenerative diseases

Neurodevelopment and the long-term maintenance of neuronal health are impossible without cleaning aggregated proteins and defective organelles. [395] Because neuronal characteristic includes high mitochondrial activity and post-mitotic state, autophagic and mitochondrial dysfunction are critical for neuronal functionality and survival. [396–398] Serious neurodegenerative diseases are associated with defective mitophagy and modulation of mitophagy mechanism is very promising possibility in the treatment of neurodegenerative diseases. [399] Possible therapeutic effects of mitophagy chelators are shown on the Fig. 7.

Some chelators (e.g., DFP and DFO) are clinically available drugs, that are being studied in the treatment of neurodegenerative diseases. [400–403] Furthermore, iron accumulation is deeply associated with the pathogenesis of numerous serious neurodegenerative diseases including Friedreich's ataxia, Parkinson's and Alzheimer's disease. [163] Therefore, the application of iron chelators is intensively tested for treatment. Nevertheless, two significant obstacles can complicate the widely application of mitophagy chelators.

Firstly, our knowledge about mitophagy is too limited, and iron chelators (in tested dose) can have many effects on neurons. Therefore, explaining and predicting their effect can be in many causes too complicated. [398] In the case of acteoside, its therapeutic effects were associated with both induction and repression of mitophagy (in the dependence of the used model). [348,350] On the other hand, iron loss induced mitophagy could be no danger for neuronal cells. In the SH-SYSY cells, DFP, or DFO application led to the activation of mitophagy. [145] Oxygen consumption was practically abolished, but ATP levels and mitochondrial potentials were maintained. There was only a slight increase in ROS production. Iron chelation repressed CIII activity and decreased the protein levels of mitochondrial proteins(e.g., HSP60, OMI and OP1) [145,351] DFP induced decrease in citrate synthase activity by was prevented by depletion of ATG5, or Beclin1. [145] Unlike starvation induced autophagy with a similar number of autophagosomes, chelator application caused a significant increase in LC3-COXIV co-localization. Iron loss induced mitophagy was independent on the PINK1/Parkin pathway and BNIP3 depletion also did not influence mitophagy, although BNIP3 protein levels were increased in OMM. On the other hand, combined knockout, of NIX and BANIP3, or HIF-1α siRNA led to the restoration of mitochondrial protein levels. [351] According to the above, HIF-1α constitutive mutant display significantly higher mitophagy activity. Nevertheless, glycolysis inhibition (glucose substitution by galactose) repressed mitophagy. [145]

Secondly dysfunctional/overactive mitophagy can disrupt the

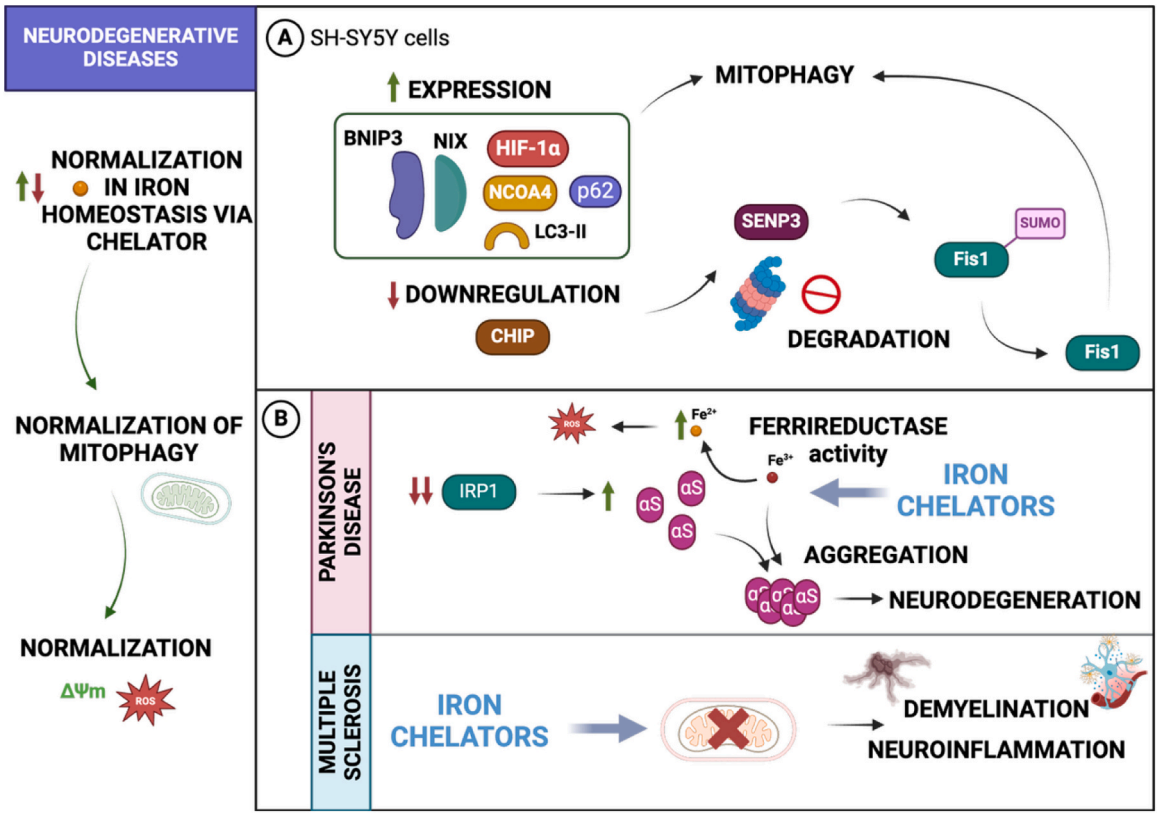

Fig. 7. Possible effects of mitophagy chelators in the treatment of neurodegenerative diseases: In the context of neurodegenerative diseases, the intricate interplay between dysregulated iron homeostasis and mitophagy assumes a pivotal role. The induction of mitophagy in response to iron loss provides cellular protection against various stressors, manifesting in the restoration of mitochondrial membrane potential (ΔΨm) and reduction in ROS production. This protective mechanism, observed in SH-SY5Y cells (A), correlates with an elevation in the expression levels of NCOA4, HIF-1α, NIX, BNIP3, p62, and LC3-II, alongside the downregulation of CHIP, a facilitator of SENP3 proteasomal degradation. This network suggests that mitophagy induction occurs through mitophagy receptors (NIX, BNIP3; hypoxia induced) and the interaction of FTMT with NCOA4. While the upregulation of p62 is associated with PINK1/Parkin-dependent mitophagy, the restoration of ΔΨm in this model does not depend on this pathway. Nonetheless, the significance of SENP3 in mediating deSUMOylation, thereby enabling the mitochondrial localization of Fis1 (a mitochondrial fission factor), and its loss in repressing mitophagy, should not be underestimated. On other hand, SENP3 knockdown did not inhibit CCCP-induced mitophagy (Parkin dependent) and an increase in SENP3 protein level was not associated with a decrease in p62 expression.
Conversely, the therapeutic efficacy of iron chelators may not be solely attributed to the induction of mitophagy (B). In the context of PD pathogenesis, the suppression of IRP1 leads to enhanced αS production. Conversely, αS influences cellular Fe^{2+} levels through its ferrireductase activity, with Fe^{3+} ions promoting αS aggregation. Iron chelators can mitigate αS aggregation and ROS production independently of mitophagy induction. Notably, MS model, a divergent outcome is observed. Despite the ameliorative effects of chelator application (acteoside) on demyelination and neuroinflammation, the therapeutic effect is strongly associated with the repression of mitophagy (Created with Biorender.com).

physiological homeostasis of mitochondria and neurons and hyperactive mitochondrial clearance can induce mitophagy-mediated neuron death. [399]

6.1. *Application of mitophagy chelator in the treatment of neurodegenerative diseases*

In PD subjects were found mutations in genes associated with autophagy function such as PARK2, PINK1 (PARK6) and ATP13A2 (PARK9). [404–407] For example, in Kufor Rakeb Syndrome (a rare juvenile form of PD), were observed mutations in the ATP13A2. [407] ATP132 mutations repress clearance of the α-synuclein (αS) and cause its lysosomal accumulations thereby significantly contributing to disease progression. [253] It is well known, that αS in an aggregated form is an integral part of the pathology in Parkinson's disease and Dementia with Lewy Bodies.

Caenorhabditis elegans with catp-6 mutation (ortholog of the human ATP13A2 gene) display reduced motor function, defective autophagy, protein levels of autophagosome specific cleaved LC3-II were significantly lower compared to wild type. [257] Mitochondrial disturbances, such as lover mitochondrial potentials and oxygen consumption and dysregulation of iron metabolism (lover mRNA level of aco-1 and aco-2, Mfn1, dihydrolipoamide dehydrogenase and SMF3), were also observed. In the case of rotenone exposition, Calcium Disodium Ethylenediaminetetraacetic acid (CaEDTA) application displayed a significant protective effect. Similarly, a protective effect was observed for the urolithin A (mitophagy inductor)[258]. [257]

In the Drosophila model of PD disease, Acteoside (ACT) displayed strong protective effects against rotenone induced neuronal damage, most probably via the induction mitophagy pathway. [348] Exposed flies displayed alternation in synaptic vehicles (less visible with a slightly broken membrane) and mitochondria (smaller and less visible). Nevertheless, ACT application normalized the morphology of mitochondria and synaptic vesicles and induced autophagy. In neuronal cells, ACT stimulated autophagy an AMPK-dependent but mTOR-independent manner. In the PC-12 cells, ROT caused a significant reduction of ΔΨm and ROS production, but this effect was repressed by ACT application. In the SH-SY5Y cells, ACT caused the translocation of autophagy-related proteins LC3-II and Sequestosome 1 (p62/SQSTM1) to mitochondria, unlike rotenone.

In the PD, α-synuclein aggregation is deeply associated with dysregulation of iron homeostasis.[408] For example, αS synthesis (human αS) is regulated by IRP1/IRE. [409] IRP1 knockdown increases αS levels and thereby promotes the formation of αS aggregates. [410] In HEK293 cells, DFO application decreased human α-synuclein mRNA levels,

suggesting that αS levels could be regulated by iron at the post-transcriptional level. [411] On the other hand, αS (normal form) is a cellular ferrireductase, which can reduce Fe^{3+} to bio available Fe^{2+} ion. [412] αS overexpression significantly increases intracellular iron levels (in the Fe^{2+} form) in cells. Common disease mutations (E46K, A30P and A53T) associated with increased susceptibility to PD also show ferrireductase activity. Fe^{3+} ions in micromolar concentration stimulate αS aggregation formation of larger intermediates. [413] In the mice fibroblasts (wild and Pink1 deficiency type) chelator applications (22BP) cause strong overexpression of SNCB (antagonist of the ferriductase toxicity of α-synuclein). [414] Chelator (22BP and DFO) applications also induce an increase in NCOA4 expression, significantly more in the wild type.

Loss of SENP3 is deeply associated with ageing and age-related degenerative diseases. In the brain sample of AD, SENP3 expression was significantly decreased. [415] In the Hela cells, DFP application caused an increase in SENP3, p62 and LC3-II protein levels, but not in its mRNA levels. [62] In this case of Fis1 was observed decrease in protein level, but not in its mRNA. Depletion of Fis1, or SENP3 (Fis1 desumoylation) repressed mitophagy, but an expression of non-SUMOylatable K149R mutant (unlike K67, or K151) restored Fis1 mitochondrial accumulation and mitophagy induction. In this line DFP repressed expression of CHIP (inductor of SENP3 proteasome degradation). Although Fis1 should be involved in Parkin-dependent mitophagy, [63,416,417] and membrane potentials were decreased by DFP SENP3 knockdown did not repress LC3-II induction by CCCP in HEK293 cells. [62] In addition it was reported, that SENP3, can stimulate degradation of SQSTM1/p62 and thereby inhibit both basal and starvation-induced autophagy. [235]

Mitochondrial dysfunctions are a key aspect of multiple sclerosis (MS) pathology, [418,419] and overactivated autophagy/mitophagy has been observed in clinical MS patients. [420,421] For example, increased levels of ATG5 and Parkin were found in the cerebrospinal fluid (CSF) of MS patients.[421] Unlike basal autophagy/mitophagy, excessive autophagy/mitophagy cause demyelination and axonal destruction. [422,423] On the other hand, iron chelators, including those affective mitophagy, display therapeutic effects in the MS model. [349,350] Therefore it is critical to evaluate, that possible therapeutically applications of chelator with described mitophagy effects are truly related to mitophagy induction. For example, therapeutic effect of acetoside was associated with mitophagy repression. [350]

In the EAE mice (MS model), acteoside treatment resulted in a decrease in neurological deficit score and postponed disease onset. [350] This effect probably caused inhibition of inflammation, demyelination, and encephalitogenic CD4+ T and CD11b+ infiltration in spinal cords. The neuronal apoptosis and mitochondrial damage induced by oxidative stress were alleviated. On the molecular level, an increase LC3-I/LC3-II ratio and inhibition of Drp1 translocation to the mitochondria were observed. Acteoside decreased $ONOO^-$ production and thereby repressing excessive mitophagy activation. Similarly, effects were observed in SH-SY5Y cells.

However, it should be also mentioned that activation of mitophagy receptors by mitophagy chelators cannot always lead to mitophagy. In myotubes, DFP application increased expression of BNIP3 and BNIP3L gene and mitochondria were found in the lysosome-like vesicular structure. [349] Nevertheless, mitophagy was not observed, but mitochondria were secreted from the cells via extracellular vehicles. This secretion was not repressed by autophagy inhibition (PI3K inhibitor 3-MA and a vascular type H(+)-ATPase inhibitor BAFA1), or knockdown of mitophagy-related proteins (BNIP3 and BNIP3L, or HIF-1α). In the mitochondria decrease in mtDNA copy number was found, along with decreased protein levels of OXPHOS complex subunits NDUFB8 (complex I) and SDHB (complex II). However, proton leak, HADH activity, CS activity or protein levels of OXPHOS complex subunits CQCRC2 (complex III) and ATP5A (complex V) were not significantly affected. It is well known, that iron deficiency can decrease skeletal muscle mitochondrial quantity and function culminating in impaired oxidative substrate metabolism. [122,424,425]

In the context of neurodegenerative pathogenesis, the impact of inflammatory cytokines such as IL-1β and TNF-α is closely linked to mitochondrial dysfunction, characterized by a decrease in $\Delta\Psi m$ and an increase in ROS production. [426–429] Research has shown that in a co-culture environment of oligodendrocytes with astrocytes and neurons, exposure to IL-1β and TNF-α (in vitro MS model) leads to mitochondrial disturbances, triggering the activation of the AMPK-mTOR-ULK1 autophagy pathway [430] and the upregulation of high mobility group box 1 (inductor of macrophages inflammation) [431]. [432] Furthermore, studies by Patergnani et al. have demonstrated that inhibitors of autophagy/mitophagy can effectively restore myelin production in oligodendrocytes co-cultured with astrocytes and neurons exposed to IL-1β and TNF-α). [432] Similarly, remyelination was observed with the use of clozapine and haloperidol (used antipsychotic drugs and autophagy inhibitors)[433]. [432] It could also be suggested that the repression of the autophagy/mitophagy process may be a promising strategy in multiple sclerosis (MS) treatment. However, blocking autophagy through these drugs could potentially be toxic to neurons. Therefore, targeting autophagy/mitophagy in MS treatment should be carefully considered and thoroughly evaluated.

Expert Opinion: Mitophagy chelators display possible therapeutic efficiency in the PS and MS model. Nevertheless, a positive correlation between mitophagy and therapeutic effect was found only for PS model. In MS model this correlation was negative.

7. Mitophagy targeting in cardiovascular diseases

Hypertrophic cardiomyopathy is a complex heart disease, that causes the thickening of your heart muscle via an increase in the size of cardiomyocytes. Because mitochondria play an essential role in mediating the alteration of cardiac cells, mitochondrial disturbance, including defective mitophagy is demonstrated to play a critical role in the development of cardiac hypertrophy. [434–437] Possible role of mitophagy in the cardiovascular pathology and chelators therapeutic effects is showed on the Fig. 8.

Although cardiovascular diseases are associated with ascensive mitophagy, its physiological function cannot be neglected. For example, in a mouse model, it was observed, that double knockout mice (Bnip3 and Nix) exhibited massive cardiac enlargement with depressed left ventricular ejection performance but without wall thinning associated with dysregulation mitochondrial maintenance and functionality. [435] On the other hand, the suppression of Bnip3 can increase survival in cardiomyocytes under stress conditions. [435,438] However, overexpression of Parkin (induced by Drp1 deletion) and subsequently mitophagy was not associated with any pathology in young adult mouse hearts. However, Parkin ablation in cardiac Drp1 KO mice increased their survival. [439] On the other hand $PINK1^{-/-}$ mice display greater levels of oxidative stress, impaired mitochondrial function and higher risk cardiovascular pathology (ventricular dysfunction, pathological cardiac hypertrophy fibrosis, cardiomyocyte apoptosis, and a reciprocal reduction in capillary density) compared to normal mice. This strongly suggests a protective role of Pink1 in the heart and cardiomyocyte. On the mitochondrial level was observed decreasing in mtDNA copy number and expression, ATP context and CI activity. Protein levels of OPa1, Drp1 and Mfn1 were significantly lower compared to wild control. It is hard to predict how Drp1 and Mfn1 down expression can influence mitophagy in this case. [440] Generally, mitophagy and mitochondrial functionality are strongly dependent on the balance between mitochondrial fusion and fission. Nevertheless, Song et al. reported, that, in cardiomyocytes fusion repression (Mfn1/2 ablation) suppresses mitophagy and increases toxic mitochondria, whereas fission inhibition (Drp1 ablation) accelerates MPTP-dependent mitophagy and cell necrosis. [127] It was reported, that phosphorylated Mfn2 (via PINK1) acts as Parkin receptor and supports its recruitment. [60]

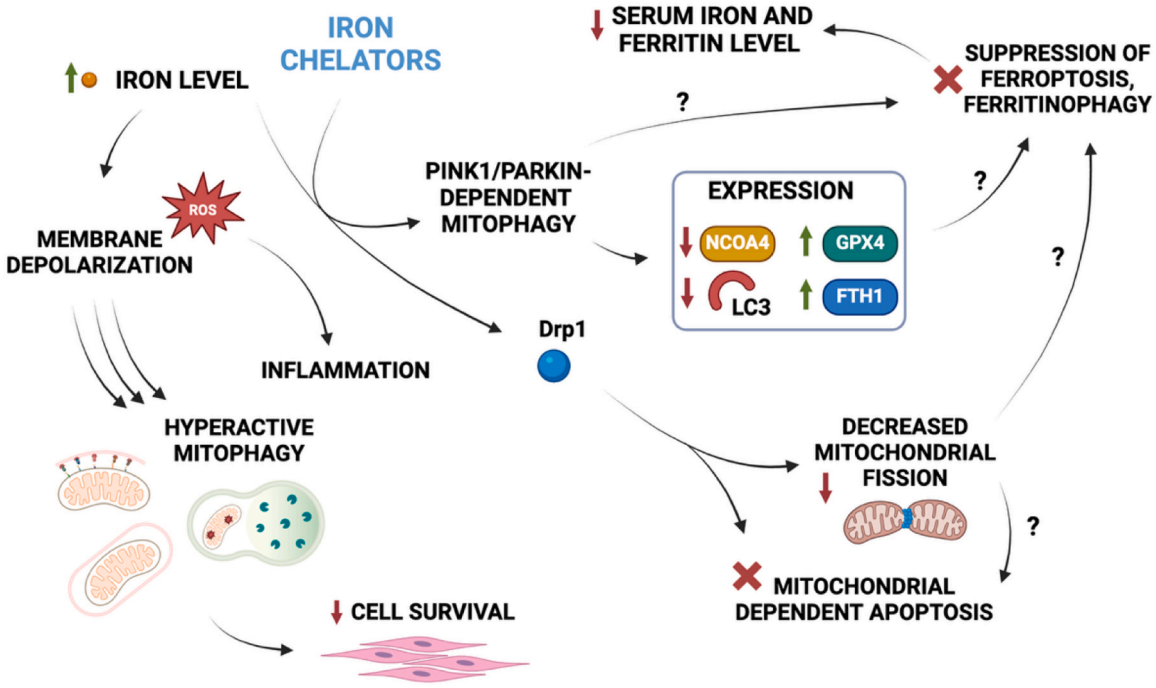

Fig. 8. Possible effects of mitophagy chelators in the treatment of the cardiovascular diseases: Elevated iron levels in cardiac tissue serve as a significant marker of cardiovascular diseases. Increased iron levels can trigger ROS production and IMM depolarization, leading to hyperactive mitophagy and reduced cell survival. The application of chelators can mitigate PINK1/Parkin-mediated mitophagy, decrease mitochondrial fission (via reduced phosphorylation of Drp1), and inhibit mitochondrial-dependent apoptosis. Moreover, a decrease in NCOA4 and LC3 levels, coupled with an increase in GPX4 and FTH1 expression, suggests that the therapeutic effects of chelators may be linked to the suppression of ferroptosis and ferritinophagy (Created with Biorender.com).

In the case of cardiomyocytes mitochondrial disturbance should also be considered the role of MST1 (serine/threonine-protein kinase). Its excessive activation significantly represses cardiomyocytes survival, and promotes left ventricular dysfunction after myocardial infarction. [441, 442] Phosphorylated Beclin1 (via Mst1) has a higher affinity for the Bcl-2, which represses its autophagy activity, and liberated Bax activates apoptosis. [94] In a mouse model, Mst1 suppresses cardiac proliferation and hypertrophy through inhibition of mitophagy and subsequently inducing dilatation of the heart.

According above cardiomyoblast differentiation (H9c2 cells) was associated with an increase in the protein levels of HIF-1α, HK and BNIP3. [351] In the case of NIX, its decrease was observed, followed by the restoration of its protein levels. Higher mitochondrial activity and co-localisation with LC3 and LAMP1 were also found. HIF-1α siRNA decreased beside mytolysosome area, oxygen consumption, and Troponin T protein levels. NIX knockout strongly repressed mitophagy but troponin expression and cardiomyoblast differentiation were unaffected. On the other hand, during differentiation higher mitochondrial activity and respiration were found, along with an increase in level protein of citrate synthase, myosin heavy chain, HSP60, PGC1a and Troponin.

Another factor that controls mitochondrial functionality in cardiomyocytes and heart tissue is p53. [241] p53 (at normal condition) controls embryonic and post-natal heart development. Nevertheless, abnormality in its expression and protein modification strongly stimulate development of cardiovascular diseases. For example, higher p53 levels correlate with cardiomyocytes apoptosis and hypertrophy in end-stage human. [443] Increased expression of p53 and BCL-2 has been observed in heart tissue samples from patients with dilated cardiomyopathy. [444] In a mouse model deletion of p53 was sufficient to trigger the development of spontaneous pathological hypertrophy in older mice. [445]

A higher iron level in the heart is associated with cardiac dysfunction and failure, also known as iron overload cardiomyopathy (IOC), which is leading cause of death in iron overload patients. [446–449] IOC displays strong connection with mitochondrial disturbances (increase mitochondrial ROS levels and depolarization of mitochondrial membrane). Studies conducted on isolated murine cardiac mitochondria (Wistar rats) demonstrated that an exposure to Fe^{2+} and Fe^{3+} ions results in higher ROS level and membrane depolarization. [450] When these same mitochondria were pre-treated by R360 (10 μM, inhibitor of mitochondrial calcium uniporter), the deleterious effects of iron overload were not observed, DFO efficiency was significantly lower. Nevertheless, in the iron-overloaded cardiomyocyte, deferiprone applications resulted in increased cell viability and decreased Fe^{2+}/Fe^{3+} uptake. [352] This effect was associated with decreased p-DRP1 protein levels, in this case Fe^{2+} exposition was observed decrease in Parkin and Bax protein levels and caspase 3 activation, suggesting that in cases of IOC, loss of membrane potentials did not induce mitophagy. The positive effect of chelator application was also observed in vivo. In the diabetic cardiomyopathy rats, DFP (100 mg/kg/per day) caused reduction serum iron and ferritin level (39 vs 23 μM/L and 165 vs 128 ug/L, respectively) associated with anti-inflammatory effect (decreases in NF-κB and COX2 protein levels) and suppression oxidative stress. [451] In the hearts of diabetic rats (compared to control) were found intracellular collagen accumulation and cardiomyocytes disarrangement. After DFP application, collagen levels were obviously decreased and cardiomyocytes were neatly arranged.

Also results obtained from other studies suggest that the reduction in iron level caused by chelator application did not lead to mitophagy induction. For example, in iron-overloaded rats, deferoxamine application strongly decreased plasma iron level. [452] However, the effect on cardiomyocyte iron level iron level was sometimes lower. On the other hand, deferoxamine restored the autonomic balance and cardiomyocyte cross-sectional area, protein level of IL-1, and TNF-α. On the mitochondrial level, DFO decreased mitochondrial ROS production but did not repress cardiac mitochondrial depolarization and swelling. DRP1 protein and the p-DRP1/DRP1 ratio were significantly increased in

iron-overloaded rats, but DFO decreased their original protein value. Expression of mitochondrial proteins (Mfn1, Mfn2, OPA1) and Bax/Bcl-2 ratio was not decreased by DFO application.

Resveratrol inhibited ferroptosis (in H9c2 cells), mainly by increasing the protein expression of GPX4 and FTH1. [453] However, protein expression of autophagy markers such as Beclin1, NCOA4 and LC3 was significantly decreased upon resveratrol treatment. Also, its protective effect against myocardial ischemia-reperfusion injury (mice model) was associated with the downregulation of USP19 and Becklin-1.

Similarly, in the H9c2 cells resveratrol repress zinc deficiency induced mitophagy (PINK1/Parkin pathway) and thereby displayed cardiac cytoprotective effects. [353] On the protein level, resveratrol decreased the expression of mitophagy related proteins (e.g., P62, LC3, NIX, TOM20, PINK1 and Parkin). Resveratrol most probably repressed the opening of the mitochondrial permeability transition pore via activation of AMPK-Mfn2 axis.

Furthermore, it was reported, that histone trimethyllysine demethylase JMJD2A (Fe^{2+} dependent enzyme) participates in cardiac hypertrophy in response to hypertrophic stimuli. [454] Treatment with VLX600 (in GBM cells) resulted in increased histone trimethylation. [156] It cannot be excluded that the therapeutic effect of iron chelation could also be associated with JMJD2A inhibition.

Expert Opinion: Iron chelators, including mitophagy ones, display promising potential for treating cardiac dysfunctions. However, their possible therapeutic effect was not associated with mitophagy induction but its repression.

8. Mitophagy targeting in other diseases

Glaucoma is the leading cause of global irreversible blindness. [455] Mitochondrial damage is a widely discussed phenomenon in glaucoma pathogenesis. Mitophagy/autophagy is a well discussed protective mechanism for eye functionality and maintenance. [456] In the Primary RGCs, DFP repressed apoptosis induced by oxidative stressors (tert-butylhydroxide and paraquat). [354] This effect was associated with the induction of mitophagy activity. In the case of staurosporine, DFP antiapoptotic efficiency was sometimes lover, but still significant. Similarly, the effect was observed for DFP application in retinal culture. In the mouse model, mitophagy activation decreases glaucoma relevant stress factors.

One of the most serious side effects of corticosteroid administration is glucocorticoid induced osteonecrosis of the femoral head. [457] On the other hand, in the rat model (methylprednisolone and LPS), DFO application induced and promoted angiogenesis and decreased apoptotic rate via HIF-1α/VEGF axis in the femoral heads. [355] The incidence of osteonecrosis incidence was 93 % (14/15) in the exposed group, and only 20 % (3/15) in the treated group. Micro-CT showed normalization in bone structure and density in chelators treated groups. In rat BMSCs a decrease in mitochondrial number and change in morphology (shortened and granulated shape) were observed, along with an increase in mitochondrial potential. On the protein level, it was found overexpression in HIF-1α/VEGF, axis and Parkin.

Hemophilic arthropathy is one of the most common serious complications in patients with hemophilia and is characterized by cartilage damage and synovitis. [458] Excess iron deposition significantly supports haemophilia progression, for example participate in haemophilic arthropathy. [459] In mice chondrocytes, ferric ammonium citrate causes down expression of SOX9 and COL2, MMP3 and MMP13 and mitochondrial apoptotic pathway (cytochrome C overexpression, decrease mitochondrial membrane potential and caspase 3 induction). [356] Nevertheless, DFO co-application repressed iron effects. DFO also stimulated expression of HIF-1α and mitophagy markers (BNIP3, ATG5 and LC3) and LC3 mitochondrial colocalization. In the mice model of haemophilic arthritis, DFO application led to decreased ORSI score and MMP13 expression and overexpression of HIF-1α and LC3B.

Expert Opinion: Mitophagy chelators represent promising potential agents for the treatment of glaucoma, femoral head and hemophilic arthropathy. However, this conclusion should be verified by further studies.

9. Future directions

In the present time, a deep connection between iron metabolism and mitophagy is becoming increasingly apparent. It is already confirmed, that iron loss-induced by chelators can induce Pink1/Parkin independent mitophagy via HIF signalling. Role other factors such as FTMT in the mitophagy induction is intensively discussed. Nevertheless, iron induced mitophagy also displays significantly effect on the cellular metabolic pattern cells such as cell lipidome. Increased lipid droplets biogenesis (DGAT1-dependent) enables the transport of damaged mitochondria into acidic endolysosomes. [343] DGAT1 knockout increases intracellular level free acid and represses mitophagy. On the other hand, some mitochondrial lipids such as cardiolipin can serve as mitophagy receptor. [322] Dysregulation of mitophagy is associated with numerous oncological, neurodegenerative, cardiovascular and other serious diseases. Mitophagy modulation is an intensively studied treatment modality. Mitophagy agents such as iron chelators are very promising therapeutic agents. Currently they are mostly studied as anticancer agents, but positive results have been obtained for the treatment of neurodegenerative treatment (e.g., Parkinson disease), or some model of glaucoma and haemophilic arthropathy as well. Positive results could be expected in this case of other diseases such as Friedreich ataxia. Friedreich ataxia is caused by polymorphic expansion of the GAA triplet in the frataxin gene and subsequently mitochondrial iron overload and oxidative stress. [460,461] Nevertheless, FTMT overexpression (in FRDA fibroblasts) decreased ROS formation and restored the activity of ISC-enzymes. [462] It was also reported, that in frataxin-deficient HEK-293 cells (induced by tetracycline) DFP (50 μM) restored impaired mitochondrial membrane and redox potentials, increased ATP production and oxygen consumption and decreased mtDNA damage. [463] On the other hand, possible limits of mitophagy induction by iron chelators should be also mentioned.

Firstly, while iron chelators are generally considered as safety agents, possible side effects cannot be excluded. For example, a cytotoxic effect associated with mitophagy was *observed for bacterial* siderophores. [464,465] Their application (*P. aeruginosa* siderophores) increased the ROS level in platelets and subsequently apoptosis via mitophagy induction (PINK1/Parkin and BNIP3 pathways). [465] In zebrafish liver cells, hypoxia decreased Fe^{2+}, ROS and lipid perodoxidation level. [466] Nevertheless, cell survival was strongly reduced. But, iron supplement displays protective effect on the cell viability associated with restoration of membrane potentials and mitophagy repression. However, DFO application displayed rather opposite effects on the cell vitality. Besides, even if iron loss induced mitophagy is associated with therapeutic effects, it may not always be therapeutically desirable. Candida glabrata (haploid budding yeast) can cause severe systemic infections in immunocompromised patients. In such cases, free serum iron level (~0.2 μM for healthy volunteers)[467] can be limited by transferrin, or chelation therapy. It was reported, that iron deficiency could enhanced Candida survival in the patient's body via mitophagy induction. [468]

Secondly, it should not be assumed, that decreasing iron levels by chelators would not display any other biological effect besides including mitophagy. In this case of DFO and DFP (most tested chelators), inhibition of other iron dependent enzymes (e.g., Tet proteins and JmJC demethylases) cannot be excluded due to test concentrations (0.1–1 mM; you can see in the Table 2). [469–472] Chelators with selective mitochondrial distribution (structure motive of hydrophobic cations) exhibit mitophagy activity at microsomal concentrations, but can they also disturb mitochondrial functionality by decreasing ΔΨm [231,344]. In the case of polyphenolic compounds such as acteoside, or CBD, the effective autophagy/mitophagy concentration (in tens

micromole) was significantly lower with compared to iron chelators mentioned previously. [348,473] At this concentration, polyphenols display numerous biological/therapeutic effects, [474,475] likely mostly independent of mitophagy induction.

Thirdly, the presumed link between iron chelator application and iron loss mitophagy may not always be filled. Fe^{2+}/Fe^{3+} ions are not the only transition metal ions that can control mitophagy. In this case of Cu^{2+}-induced oxidative stress, (in HEK293 cells) ULK1 phosphorylate Sestrin2 (Ser73 and Ser254), which interacts with ATP5A in OMM (repressed by Cu^{2+} chelator) and subsequently recruiting LC3-II. [476] In addition, phosphorylated Sestrin2 activates ULK1 activity toward p62 phosphorylation as an autophagy induction signal. [476,477] Some iron chelators (DFO, PFP, DTPA, bipyridyl and phenanthroline) also display significant affinity for the other metal ions such as Zn^{2+} and Cu^{2+}. [478] Although Fe^{2+} is the most abundant intracellular and intra-mitochondrial transition metal ion, chelation of other ions cannot be excluded.

Fourth, mitophagy induction by iron chelators cannot be caused by the chelation of iron ions. For instance, in Huh-7 cells, curcumin induces cell death via autophagy/ mitophagy induction and higher iron levels repress this effect. [479] However, the effect of curcumin is associated with a decrease in $\Delta\Psi m$ and the inhibition effect of iron ions is associated with their formation of curcumin metal-complexes. A decrease in $\Delta\Psi m$ was observed for the bipyridyl and phenanthroline chelators (Table 2). CBD is a potent iron chelator [480] and its applications restore MFMT level (repressed by iron). [481] Nevertheless, CBD also induces Pink1/Parkin dependent mitophagy via activation TRPV4 (Ca^{2+} channel). [473] In addition, positive therapeutic effects of iron chelators in models of cardiovascular diseases, and multiple sclerosis, were not associated with mitophagy induction, but rather with mitophagy inhibition. For example, resveratrol cardioprotective effect was caused by repression (PINK1/Parkin dependent mitophagy. [353] In this line, it should be mentioned, that polyphenols such as resveratrol can control expression of the mitochondrial protein (e.g., COX1 and Tfam) via NRF1. [482]

The above strongly suggests that the possible therapeutic application of mitophagy should be thoroughly considered and other research is necessary for more valid recommendation. We hope that the presented and discussed model of interconnection between iron metabolism and mitophagy could contribute to a better understanding and predictability of mitophagy chelators.

10. Conclusion

Iron homeostasis significantly participates in the control of mitophagy. Conversely, mitochondria play an important role in the control of iron homeostasis. Currently, it is established that a decrease in the labile intracellular iron pool can activate mitophagy. Some high impact works, have shown promising potential of iron chelators as mitophagy agents. This review discusses various applications of mitophagy chelators and shows their usefulness and limitations, especially in the treatment of oncological, neurodegenerative and cardiovascular diseases. Nevertheless, the obtained results are strongly dependent on the experimental condition and cell types. For the construction of a more precise model our knowledge is still too limited, future studies are highly requested.

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Declaration of Competing Interest

did not any conflict of interest.

Data Availability

No data was used for the research described in the article.

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