A graphical journey through iron metabolism, microRNAs, and hypoxia in ferroptosis

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ABSTRACT

Ferroptosis is an iron-dependent form of cell death, which is triggered by disturbed membrane integrity due to an overproduction of lipid peroxides. Induction of ferroptosis comprises several alterations, i.e. altered iron metabolism, response to oxidative stress, or lipid peroxide production. At the physiological level transcription, translation, and microRNAs add to the appearance and/or activity of building blocks that negatively or positively balance ferroptosis. Ferroptosis contributes to tissue damage in the case of, e.g., brain and heart injury but may be desirable to overcome chemotherapy resistance. For a more complete picture, it is crucial to also consider the cellular microenvironment, which during inflammation and in the tumor context is dominated by hypoxia. This graphical review visualizes basic mechanisms of ferroptosis, categorizes general inducers and inhibitors of ferroptosis, and puts a focus on microRNAs, iron homeostasis, and hypoxia as regulatory components.

1. Introduction

“To the well-organized mind, death is but the next great adventure” [1]. Death occurs to all life on earth, from the largest tree to the smallest unit of life, the single cell. For scientists the great adventure is to explore mechanisms of death, or more precisely cell death in its various forms, since it opens up ways for therapy either by inducing or inhibiting cell death. Different forms of cell death have been described over the last years. While apoptosis and necrosis are well defined, additional distinct forms such as pyroptosis or ferroptosis were noticed. Experiments conducted in the 1950s showed that cells die upon amino acid deprivation, which likely was the first hint towards a novel, but evolutionarily conserved form of cell death [2]. The term ferroptosis referring to this particular form of cell demise was coined in 2012 by Dixon and co-workers and describes an iron- and oxidative stress-dependent form of cell death [3]. Meanwhile it is known that ferroptosis is characterized by increased lipid peroxidation causing cell death by disturbing membrane integrity. Peroxidation of polyunsaturated fatty acids occurs via lipooxygenase pathways and/or Fenton chemistry and takes place when the glutathione (GSH) or ubiquinone synthesis pathways are dysfunctional (Fig. 1). The Fenton reaction is strongly dependent on iron. Consequently, the cellular iron status determines the sensitivity of cells towards ferroptosis (Fig. 2). Lowering intracellular free iron by its export or storage appears to dampen ferroptosis. In contrast iron uptake increases the labile iron pool, enhances hydroxyl radical formation by Fenton chemistry, and increases the susceptibility to ferroptosis. Besides these fundamental regulatory processes, microRNAs add another layer of regulation (Fig. 3). Several microRNAs were characterized to possess either anti- or pro-ferroptotic properties, depending on their distinct targets. While the antioxidant capacity of a cell, the peroxide tone and iron availability (Figs. 1 and 2) are basic ferroptotic modulators, microRNAs appear as fine-tuning regulators. They have the potential to alter the ferroptotic sensitivity of a cell, mostly shown in experiments when overexpressed. The complex regulatory network of ferroptosis will only be complete if the cellular microenvironment is taken into consideration. Oxygen is an essential factor for most forms of life which allows cellular respiration. Consequently, its absence is life-threatening. Nevertheless, oxygen bears the risk of adding to oxidative stress.
Fig. 1. Basic mechanisms of ferroptosis.
Ferroptosis is triggered by generating PLOO•, which damages cellular membrane integrity and finally promotes cell death [4]. To that end, PUFAs are processed via the ACSL4-ALOX axis to PLOOH, which react with hydroxyl radicals to form PLOO• [5]. Hydroxyl radicals are generated by Fenton chemistry from H₂O₂ and Fe²⁺ in a non-enzymatic reaction [6]. Activation of the hippo pathway contributes to ferroptosis by increasing the TIR, which adds to iron uptake and by inducing ACSL4. To protect cells from ferroptosis GPX4 processes PLOOH to the inert PLOH. This reaction demands GSH, which is produced from cystine. Cystine uptake is facilitated by SLC7A11, a glutamate/cystine antiporter. In addition, AIFM2 (alias FSP1) attenuates lipid peroxidation by regenerating the reduced form of the radical-trapping antioxidant CoQ, using NADH and CoQ as substrates [7]. CoQ production in turn is strongly dependent on the mevalonate-PDSS pathway. Interfering with any of the protective systems has been shown to enhance ferroptosis.
Fig. 2. Iron metabolism adds to ferroptosis.

Alterations in iron metabolism determine the sensitivity of cells towards ferroptosis by regulating the cellular LIP. An increased LIP equals to higher amounts of Fe$^{2+}$ within the cell that is able to enhance Fenton chemistry and hydroxyl radical production. The LIP is subjected to various regulations. Iron is taken up through Tf, which binds to the TfR. The complex is then endocytosed followed by the release of Fe$^{2+}$, which is mediated by STEAP3 and DMT1 [8]. Additionally, the LIP can be enhanced by erythrophagocytosis [9]. Here, iron gets released from heme by HO-1, which accelerates ferroptosis [10]. Other major players in regulating the LIP are ferritins. Ferritins oxidize iron to Fe$^{3+}$ and store this less reactive form of iron in a 24 subunit complex, thereby preventing ferroptosis [11,12]. Of note, ferritins exist in the cytosol (FTH) and in mitochondria (FTMT). Ferritin-bound iron is released into the LIP by NCOA4-dependent autophagosomal degradation of ferritin (FTH and FTMT). Another way to reduce the LIP is iron export by FPN. Diminished levels of FPN are associated with increased intracellular iron and ferroptosis [13]. Besides these mechanisms, CP was shown to protect cells from ferroptosis by transforming iron to the less reactive Fe$^{3+}$ [14]. Within mitochondria Fe-S cluster synthesis is crucial for maintaining the ETC and the TCA cycle. The ETC, especially when damaged, is a generator of ROS, which may add to lipid peroxidation [15]. The TCA cycle in turn is crucial to keep the ETC running. Here α-KG is a central metabolite, which is synthesized either from citrate or glutamine. Apparently, central metabolic pathways can alter ferroptosis. Besides the ETC, CISD proteins need a Fe-S cluster to assure functionality of these proteins, which were shown to protect cells from lipid peroxidation and consequently ferroptosis [16–18]. Thus, CISD1 is assumed to transfers Fe-S clusters to ACO1, which suppresses FTH translation when no Fe-S cluster is bound and in turn contributes to regulate the LIP [19].
Fig. 3. Ferroptosis and microRNAs.

MicroRNAs regulate the cellular transcriptome by fine-tuning distinct mRNAs. This has not only profound effects on metabolism but also towards regulation of ferroptosis. MicroRNAs are categorized into anti- and pro-ferroptotic microRNAs. Anti-ferroptotic microRNAs target mRNAs that code for proteins which promote ferroptosis. This includes ALOX15 or ACSL4, which are involved in generating PLOOH [6, 20–23]. Iron uptake is decreased by miR-7-5p, which targets transferrin and indirectly reduces the labile iron pool and Fenton reactions [6]. Interference of microRNAs with glutamate metabolism was reported to decrease ferroptosis by reducing TCA cycle- and respiratory chain-mediated ROS production [24–28]. Nrf2, a major regulator of the antioxidative system, is inactive when bound to Keap1. Thus, microRNAs targeting Keap1 and activating Nrf2 can be considered as anti-ferroptotic [6]. Pro-ferroptotic microRNAs directly target the SLC7A11/GPX4 system and facilitate lipid peroxidation, which provokes ferroptosis [29–38]. Besides directly targeting GPX4, its expression was shown to be regulated by HSPA5, a target gene of ATF4. Additionally, ATF4 increased the expression of SLC7A11 and thus, appears to regulate two major anti-ferroptotic proteins. ATF4 in turn was reported to be a target of miR-214 [39]. Further, iron storage and release are altered by miRNAs which target FTH or FPN, respectively [6,40,41]. These changes likely enhance redox-reactive intracellular iron and Fenton chemistry. Ferroptosis was reported to be increased by mitochondrial ROS production, which was increased by a microRNA-dependent decrease in Mfn2 expression. Mfn2 is a regulator of mitochondrial fusion and fission and thus, likely alters ROS production [6]. Cellular oxidative stress is strictly regulated by the Nrf2 system, one of the main anti-oxidative systems in cells. A reduction of Nrf2 by miRNAs is associated with decreased target gene expression, increased oxidative stress, and ferroptosis.
The HIF- and Nrf2-pathways are known to interact with each other and thus, hypoxia facilitates HO-1 expression and thus, protects from ferroptosis [45, 46]. A major regulator of the anti-oxidative system. Increased Nrf2 activity under hypoxia elevates lipid accumulation, oxidative stress, and finally enhances ferroptosis.

Although incompletely understood so far, it appears logical that oxygen or its decrease, i.e. hypoxia modulates ferroptosis (Fig. 4). When the demand of oxygen exceeds its availability, hypoxia signaling affects canonical and non-canonical pathways to orchestrate the anti-oxidative machinery and/or iron homeostasis, which comprises among others the activity of hypoxia inducible factors (HIF) and nuclear factor erythroid 2-related factor 2 (Nrf2). Logically, the lack of oxygen will diminish Fenton chemistry and lipoxigenase activity, two critical systems involved in ferroptosis induction. Based on extensive research over the last years, we now can choose between a variety of ferroptosis inducers and inhibitors that target many of those systems described in Figs. 1-3 (Fig. 5). Each cell contains many building blocks that, when properly arranged, regulate ferroptosis. This knowledge will hopefully be useful to enhance or attenuate ferroptosis for therapeutic use (Fig. 6). During heart and brain injury or organ transplantation, conditions often linked to ischemic conditions, inhibition of ferroptosis could be beneficial, while induction of ferroptosis in tumor cells might be helpful to overcome chemotherapy resistance. This graphical review visualizes basal mechanisms of ferroptosis and integrates more specialized topics such as iron regulation, microRNAs and hypoxia.

ACS4: long-chain-fatty-CoA ligase 4, AIFM2: apoptosis inducing factor mitochondria associated 2 or ferroptosis suppressor protein 1 (FSP1), ALOX: polynsaturated fatty acid lipoxigenase, AMPK: 5′-AMP-activated protein kinase, CoQ: coenzyme Q, COQ2: 4-hydroxybenzoate polyprenyltransferase, cPLA2: cytosolic phospholipase A2, FA-CoA: fatty acyl-CoA, FA-PL: 1-acyl phospholipid, Fe^{2+}: reduced iron, yGCS: glutamate-cysteine ligase, GPX4: glutathione peroxidase 4, GRX: glutaredoxin, GSSG: glutathione disulfide/oxidized glutathione, GSH: glutathione, GS: glutathione synthetase, LPCAT3: lysophospholipid acyltransferase 3, Nf2: Merlin, *OH: hydroxyl radical, PDI: all-trans-polypropylene-diphosphate synthase, PUFA: poly unsaturated fatty acid, PLOH: hydroxy phospholipid, PLOO*: phospholipid hydroperoxyl radical, PLOOH: phospholipid hydroperoxide, SLC7A11: cystine/glutamate transporter, TFR: transferrin receptor, YAP: Yes1 associated transcriptional regulator.

**α-KG**: alpha-ketoglutarate, ACO1: aconitase1, CSD1: CDGS iron-sulfur domain-containing protein 1, CP: ceruloplasmin, DMT1: divergent metal transporter 1, ETC: electron transport chain, Fe^{2+}: reduced iron, Fe^{3+}: oxidized iron, Fe-S cluster: iron sulfur cluster, FPN: ferroportin, FTH: ferritin heavy chain, FTMT: mitochondrial ferritin, GLS: glutaminase, Glu: glutamine, Glut: glutamate, GLUD: glutamate dehydrogenase, HO-1: heme oxygenase-1, LIP: labile iron pool, MFRN: mitoferrin, NCOA4: nuclear receptor coactivator 4, *OH: hydroxyl radical, PLOO*: phospholipid hydroperoxyl radical, PLOOH: phospholipid hydroperoxide, ROS: reactive oxygen species, SLC1A5: neutral amino acid transporter B, STEAP3: metalloenductase STEAP3, TCA: tricarboxylic acid, Tf: transferrin, TFR: transferrin receptor.

**ACSL4**: long-chain-fatty-acoa ligase 4, AOX15: polyunsaturated fatty acid lipoxigenase 15, ATP4: activating transcription factor 4, α-KG: alpha-ketoglutarate, FA-PL: 1-acyl phospholipid, Fe^{2+}: reduced iron, Fe^{3+}: oxidized iron, FPN: ferroportin, FTH: ferritin heavy chain, GLS: glutaminase, Glu: glutamine, GOT1: aspartate aminotransferase, cytosolic, GPX4: glutathione peroxidase 4, Glu: glutamate, HSPA5: heat shock protein family A member 5, Keap1: Kelch-like ECH-associated protein 1, miR: microRNA, Mfn2: mitofusin 2, Nrf2: nuclear factor erythroid 2-related factor 2, *OH: hydroxyl radical, PLOO*: phospholipid hydroperoxyl radical, PLOOH: phospholipid hydroperoxide, PUFA: poly unsaturated fatty acid, ROS: reactive oxygen species, SLC1A5: neutral amino acid transporter B0, SLC7A11: cystine/glutamate transporter, TCA: tricarboxylic acid cycle, Tf: transferrin, TFR: transferrin receptor.

**CA9**: carbonic anhydrase 9, Fe^{2+}: reduced iron, Fe^{3+}: oxidized iron, FTMT: mitochondrial ferritin, HIF: hypoxia inducible factor, ILIPD: hypoxia-inducible lipid droplet-associated protein, HO-1: heme oxygenase-1, LIP: labile iron pool, MUFa: monounsaturated fatty acid, NCOA4: nuclear receptor coactivator 4, Nf2: nuclear factor erythroid 2-related factor 2, PLIN2: perilipin 2, PLOO*: phospholipid hydroperoxyl radical, SCD1: stearoyl-CoA desaturase 1, SLC7A11: cystine/glutamate transporter.

**Fig. 4.** Hypoxia and ferroptosis. Hypoxia is a hallmark of the tumor microenvironment and thereby a relevant factor when considering ferroptosis for tumor therapy. Major regulators of hypoxia are the HIF transcription factors. HIF-1 increases transcription of SLC7A11 and HO-1, which both protect from ferroptosis [42,43]. In contrast, HIF-2 was shown to increase the expression of PLIN2 and HILPDA, which elevate lipid accumulation, oxidative stress, and finally enhance ferroptosis [44]. Besides HIF, hypoxia is known to increase the activity of Nrf2, which is a major regulator of the anti-oxidative system. Increased Nrf2 activity under hypoxia facilitates HO-1 expression and thus, protects from ferroptosis [45,46]. The HIF- and Nrf2-pathways are known to interact with each other and thus, facilitate target gene expression [47]. Besides activation of these major regulatory mechanisms, expression of proteins such as SCD1 increases under hypoxia. This increase might compensate for the lack of O2, which is a substrate of SCD1. Nevertheless, SCD1 was shown to protect hypoxic cells from ferroptosis by generating MUFAs [48]. In addition, SCD1 has a ferrooxidase activity, which potentially attenuates ferroptosis by limiting intracellular Fe^{2+}. Another mechanism which reduces Fe^{2+} and, thus, the LIP is the storage of iron by ferritins. NCOA4-mediated degradation of ferritins and the release of iron into the LIP is facilitated by ferritinophagy. This process is inhibited by decreased NCOA4 expression under hypoxia, which increases iron storage and in turn protects cells from ferroptosis [12,49]. Furthermore, inhibition of CA9 blocked ferritin-mediated iron storage and increased transferrin receptor abundance, which sensitized cells towards ferroptosis. An induction of CA9 under hypoxia reduces oxidative stress and thus ferroptosis [50].
Fig. 5. Inhibitors and inducers of ferroptosis. A variety of inducers (red) and inhibitors (green) of ferroptosis and their targets have been identified [51]. These compounds are instrumental in interrogating several distinct pathways that either promote or protect from ferroptosis.
Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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