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Ferroptosis: An emerging approach for targeting cancer stem cells and drug resistance

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ABSTRACT

Resistance to chemotherapeutic agents remains a major challenge in the fierce battle against cancer. Cancer stem cells (CSCs) are a small population of cells in tumors that possesses the ability to self-renew, initiate tumors, and cause resistance to conventional anticancer agents. Targeting this population of cells was proven as a promising approach to eliminate cancer recurrence and improve the clinical outcome. CSCs are less susceptible to death by classical anticancer agents inducing apoptosis. CSCs can be eradicated by ferroptosis, which is a non-apoptotic-regulated mechanism of cell death. The induction of ferroptosis is an attractive strategy to eliminate tumors due to its ability to selectively target aggressive CSCs. The current review critically explored the crosstalk and regulatory pathways controlling ferroptosis, which can selectively induce CSCs death. In addition, successful chemotherapeutic agents that achieve better therapeutic outcomes through the induction of ferroptosis in CSCs were discussed to highlight their promising clinical impact.

1. Introduction

The last few decades have witnessed exceptional breakthroughs in the field of cancer therapy. Many new therapeutic strategies have been developed to battle cancer, such as utilizing nanomedicine (Tran et al., 2017), targeted therapy (Padma, 2015), and immunotherapy (Zhang and Chen, 2018). Unfortunately, despite the multidirectional and the intense battle against cancer, drug resistance continues to be the main limiting factor for achieving cures in cancer patients (Vasan et al., 2019). It is indeed the principal reason for treatment failure and cancer-related deaths (Vasan et al., 2019).

One major cause of drug resistance in cancer is the presence of a small population of cells in the tumor called cancer stem cells (CSCs) (Mansoori et al., 2017). These cells were reported to exist in several types of cancer, including leukemia, melanoma, breast, colorectal, liver, and brain cancers (Phi et al., 2018; Batlle and Clevers, 2017). Accumulating data demonstrate that CSCs play a pivotal role in chemotherapy resistance, tumor recurrence and aggressiveness (Phi et al., 2018; Chang, 2016). Accordingly, several mechanisms have been revealed to describe their resistant phenotype. First, CSCs are present in a special microenvironment consisting of fibroblasts, endothelial cells, mesenchymal cells, immune cells, and many secreted growth factors and cytokines (Prieto-Vila et al., 2017). This microenvironment promotes the survival of CSCs through activating specific molecular signaling pathways and physically sheltering the CSCs from therapeutic agents (Prieto-Vila et al., 2017). Second, ATP-binding cassette (ABC) drug transporters are overexpressed in CSCs, leading to drug efflux and sub-optimal therapeutic drug concentrations (Dean et al., 2005). Third, CSCs

Abbreviations: ABC, ATP binding cassette; ACSL4, Acyl-CoA synthetase long-chain family member 4; ALDH, Aldehyde dehydrogenase; AML, Acute myeloid leukemia; BCSC, Breast cancer stem cells; CML, Chronic myeloid leukemia; CSCs, Cancer stem cells; DHA, Dihydroartemisinin; DMT1, Divalent metal transporter 1; EMT, Epithelial-mesenchymal transition; FPN, Ferroportin; FTH, Ferritin heavy chain; FTL, Ferritin light chain; GC, Gastric cancer; GPX, Glutathione peroxidase; GPX4, Glutathione peroxidase 4; GSH, Glutathione; HCC, Hepatocellular carcinoma; HMLER cells, Human mammary epithelial cells; HNSCC, Head and neck squamous cell carcinoma; LOXs, Lipoxygenases; MUFAs, Monounsaturated fatty acids; NRF2, Nuclear factor erythroid 2-related factor 2; PUFAs, Polyunsaturated fatty acids; ROS, Reactive oxygen species; RSL3, RAS-selective lethal molecule 3; TNBC, Triple-negative breast cancer; ZEB1, Zinc-finger E-box-binding factor 1.

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are characterized by a quiescent state, which makes them inherently resistant to drugs that target the cell cycle or rapidly dividing cells (Chen et al., 2016). Fourth, several signaling pathways promote chemoresistance in CSCs. These include Notch, Wnt, and Hedgehog pathways (Pattabiraman and Weinberg, 2014). Other mechanisms contributing to the resilience of CSCs include the formation of multicellular spheroids (Vinogradov and Wei, 2012), epigenetic alterations (Munoz et al., 2012), and increased activity of aldehyde dehydrogenase (Cho and Kim, 2020). Therefore, several approaches have been explored to target specifically CSCs by using molecules that target the microenvironment of CSCs, inhibit drug efflux pumps and aldehyde dehydrogenases, or modulate signaling pathways in CSCs (Yang et al., 2020a). Despite the promising research, there are still challenges as the pathways involved in CSCs are yet to be fully understood, and the treatments developed to target them are not yet optimum as they are not very specific to CSCs (Du et al., 2019). Hence it is crucial to explore other ways to target these cells.

Ferroptosis is a term that was created in 2012 to describe a form of non-apoptotic cell death that is dependent on intracellular iron and occurs through the accumulation of lipid reactive oxygen species (ROS) in the cell. It has characteristics that make it distinguishable from other types of cell death like apoptosis, necrosis, and autophagy (Dixon et al., 2012; Dixon and Stockwell, 2019). Ferroptosis was found to be an important cell death pathway in various diseases, including cancer and diseases of the cardiovascular and nervous system (Han et al., 2020; Yan and Zhang, 2019). Moreover, activation of ferroptosis is one approach that has been gaining a lot of attention recently as a tool to combat cancer (Xu et al., 2019).

Aberrant lipid metabolism, ROS production, and iron addiction are some of the physiological differences between cancer and normal cells (Wang et al., 2018; Manz et al., 2016a; Kirtonia et al., 2020). Since lipid and iron metabolism, along with ROS production, play essential roles in regulating ferroptosis, cancer cells could be more susceptible to modulations in this death pathway compared to normal cells (Stockwell et al., 2017). This offers a safe and selective therapeutic strategy. Moreover, it has been shown that different types of cancer exhibit varying susceptibility to ferroptosis (Mou et al., 2019). For example, renal cell carcinoma and diffuse large B cell lymphomas are more susceptible to ferroptosis than cancers of the breast, colon, and lung (Mou et al., 2019). These differences can be linked to the distinct metabolic state of each cancer (Stockwell et al., 2017).

More interestingly, recent data demonstrate that ferroptosis inducers could specifically target CSCs in a tumor, which means that ferroptosis could potentially be exploited to induce CSCs death (Taylor et al., 2019; Friedmann Angeli et al., 2019). In fact, the superior selectivity and efficacy of ferroptosis in inducing CSCs death plays an important role in attaining complete tumor eradication and overcoming resistance to chemotherapy (Taylor et al., 2019). CSCs are specifically susceptible to ferroptosis due to their characteristic metabolic and signaling pathway preferences (Kahroba et al., 2019; Begicevic et al., 2019). In this paper, we will explore some regulatory pathways that make CSCs attractive targets for ferroptosis-inducing agents and how they could be exploited to our favor to eliminate CSCs.

2. Cancer stem cells

2.1. Overview of cancer stem cells

CSCs were first introduced in the nineteenth century when pathologist Conheim theorized that tumors emerge from embryonic stem cells that remain dormant in adult tissue until a certain stimulus triggers these cells to proliferate uncontrollably and produce large masses of cells (Capp, 2019). This hypothesis was one of the first to propose a role for stem cells in tumor formation; however, it was later invalidated and forgotten. It was not until 1994 that the talk about CSCs re-emerged when Lapidot et al. provided conclusive evidence of their existence as they managed to isolate CSCs from the peripheral blood of acute myeloid leukemia (AML) patients (Lapidot et al., 1994). When these cells were implanted in severe combined immunodeficient (SCID) mice, they were able to reproduce human AML in these mice, hence demonstrating the ability of this subset of CSCs in the cancer cell population to initiate tumors. The year 2003 witnessed the first identification of CSCs in breast tumors (Al-Hajj et al., 2003), and following that CSCs were successfully isolated from solid tumors in several other types of cancer, such as brain cancer (Singh et al., 2004), colorectal cancer (Ricci-Vitiani et al., 2007), and liver cancer (Ma et al., 2007).

The discovery of CSCs has revolutionized the field of cancer research and has steered researchers towards a more sophisticated understanding of cancer. After the emergence of the CSC theory, overwhelming findings have proved the heterogeneous nature of many tumors (Wang et al., 2013). Despite the CSC theory being widely accepted, there are still some controversies regarding the nomenclature of these subsets of cells, as there are conflicting views regarding the exact origin of these cells. Generally, these cells are named as 'cancer stem cells' due to the characteristics they possess that are similar to normal stem cells, such as expressing cell surface stemness markers and their ability to self-renew and produce differentiated cells (Zhao et al., 2017; Chen et al., 2013). The confusion brought about by this nomenclature is the assumption that these cells originated from normal stem cells that underwent genetic or environmental changes and became tumorigenic (Yu et al., 2012). Though this theory is a plausible one, it was also alternatively suggested that CSCs could also arise from differentiated cells that transform to cancer cells with stem-like characteristics (Yu et al., 2012). The latter concept became a topic of discussion more recently, as epigenetic plasticity has been implicated in the emergence of cancer stem cells (Nieto et al., 2016). Plasticity is embodied when the cells reversibly and dynamically assume different cellular phenotypes. It signifies a powerful cellular program that allows the selection of cancer cells with advantageous traits associated with the evasion of cancer therapy (Brabletz et al., 2018). Epigenetic plasticity often presents as epithelial-to-mesenchymal transition (EMT), where epithelial cells lose their epithelial traits such as cell-cell adhesion and gain mesenchymal features like increased motility and invasiveness (Brabletz et al., 2018). Importantly, the acquisition of mesenchymal features is reversible and dependent on epigenetic regulators (Nieto et al., 2016). Therefore, DNA methylation, histone modifications, and post-transcriptional control of gene expression are all implicated in this process. Furthermore, EMT is not just a biphasic process but involves several dynamic transitional states between epithelial and mesenchymal cells (Pastushenko et al., 2018). In fact, the intermediate states of EMT, manifesting as hybrid epithelial/mesenchymal states, have been linked to the resistance and CSCs phenotype (Pastushenko et al., 2018). Interestingly, several studies have demonstrated that EMT gives rise to cancer stem cells (Mani et al., 2008; Morel et al., 2008; McCoy et al., 2009; Giordano et al., 2012). For example, Mani et al. showed that when they force immortalized human mammary epithelial cells (HMLEs) to express EMT-inducing transcription factors such as Twist or Snail, the resulting mesenchymal cells express the characteristic stem cell $CD44^{high}/CD24^{low}$ antigenic pattern (Mani et al., 2008). Moreover, their induced cells were able to form mammospheres, further confirming the stem cell phenotype (Mani et al., 2008). An important observation is that CSCs themselves frequently exhibit EMT properties, which contribute to aggressiveness, metastasis, and tumor recurrence (Nieto et al., 2016). This reciprocal relationship between EMT and CSCs could be implicated in tumor progression and might be of interest in cancer therapy.

Because of the controversies surrounding the origin of CSCs, the use of the term' cancer stem cells' is controversial, and many researchers prefer using the term 'cancer stem-like cells' or 'tumor-initiating cells' to identify this group of cells. The authors would like to clarify that in this paper, the term ' cancer stem cells (CSCs)' refers to the group of cells that possess the ability to initiate tumors and have features similar to normal stem cells, as discussed earlier.

Despite the ongoing debate surrounding the CSC theory, it is evident that CSCs in the tumor are the cause of its initiation, growth, and resistance to treatment (Wang et al., 2013). In fact, a higher expression of CSC biomarkers in the tumor has been linked to poorer prognosis in patients with various types of cancer (Li et al., 2009; Wang et al., 2014; Lathia et al., 2020). Because of the significant role these cells play in tumor resistance to therapy, tumor metastasis, and tumor recurrence, it is crucial to understand the mechanisms through which CSCs maintain their stemness and tumor initiation capabilities, as well as how they drive metastasis and resist conventional treatment modalities, unlike other cancer cells.

2.2. CSC characteristics and key signaling pathways

CSCs share several features with normal stem cells, such as their ability to self-renew and their pluripotency, which makes them capable of producing heterogeneous tumors consisting of cancer cells with distinct phenotypes (Chen et al., 2013). They also express similar cell surface and intracellular markers to stem cells such as CD44, CD133, CD24, CD26, and CD166. Among these, CD44 and CD133 are the major markers with the most application to differentiate CSCs (Zhao et al., 2017). Some of these surface markers are confined to specific cancer types. For instance, SSEA-1 was mostly associated with colon cancer and glioblastoma (Mao et al., 2009), whereas TRA-1−60 was found confined in prostate cancer stem cells (Giwercman et al., 1993). An additional characteristic feature to CSCs is that they are found to be allocated in a side population that has augmented aldehyde dehydrogenase (ALDH) activity (Visvader and Lindeman, 2008).

Similar to normal stem cells, the microenvironment surrounding CSCs regulates their stemness and the expression of CSC markers (Fábián et al., 2013). For example, hypoxic conditions within tumor induce CSC features in several cancer cell types. In ovarian cancer cells, hypoxia induces elevated expression of CD44 and CD133 markers (Liang et al., 2012). Low oxygen levels in glioblastoma cells also caused the upregulation of stemness genes and CD133 (McCord et al., 2009). Findings by Dirkse et al. also demonstrated the high plasticity of CSCs and their ability to undergo reversible phenotypic changes based on stimuli from the microenvironment, when the induced expression of CSC surface markers in glioblastoma cells in hypoxic conditions was reversible in normoxia (Dirkse et al., 2019)

Moreover, CSCs express many of the stemness transcription factors such as Sox2, c-Myc, Nanog, and Oct4, and share the same signaling pathways involved in cell stemness and survival (Ajani et al., 2015). The difference, however, is that in CSCs, these signaling pathways are not strictly regulated as in normal stem cells, which makes these pathways involved in tumor proliferation, metastasis, and resistance to conventional anticancer treatments (Ajani et al., 2015). Besides cell surface proteins and transcription factors as key markers for CSCs, other equally important factors need to be considered, such as many proteins and chemokines that are needed for stem cells renewal and migration such as Nestin, Musashi-1, TIM-3, BMI-1, and CXCR (Zhao et al., 2017).

The major pathways that are activated in CSCs include the Wnt/β-catenin, Hedgehog, Notch, Janus kinase-signal transducer and activator of transcription (JAK-STAT), Nuclear factor erythroid 2-related factor 2 (NRF2) and Hippo-YAP/TAZ signaling pathways. These signaling pathways play a major role in the production of target genes that promote the development and stemness of CSCs (Sneha et al., 2020, Kahroba et al., 2019; Bhavanasi and Klein, 2016; Nwabo Kamdje et al., 2017; Yang et al., 2019a; Basu-Roy et al., 2015; Cordenonsi et al., 2011). Many of these pathways are not linear, and thus mediators of one pathway could have roles in other pathways. Furthermore, these pathways play a more sophisticated role in CSCs and are also involved in activating resistance mechanisms in these cells. Among these resistance mechanisms observed in CSCs is the overexpression of ABC proteins (Begicevic and Falasca, 2017), the evasion of apoptosis through the activation of anti-apoptotic pathways (Fulda and Pervaiz, 2010), and avoidance of oxidative damage by maintaining a low level of intracellular ROS (Diehn et al., 2009).

The Wnt/β-catenin and Notch pathways that regulate the expression of c-Myc, one of the main drivers of cell stemness (Yan et al., 2018), also contribute to CSCs chemoresistance through the upregulation of ABC transporters in CSCs (Kim et al., 2015). The activation of the Wnt pathway also promotes the expression of the transmembrane protein cluster of differentiation 44 (CD44), which is a marker for stemness and also has a role in the expression of anti-apoptotic proteins and ABC transporters (Martin-Orozco et al., 2019). On the other hand, Notch-1 signaling activates its downstream effector Nuclear Factor Kappa B (NF-κB), which in turn promotes CSC proliferation through regulating the transcription of B-cell lymphoma 2 (BCL-2) and other anti-apoptotic proteins such as survivin (Fulda and Pervaiz, 2010).

Another mediator with a vital role in stemness and chemoresistance of CSCs is the transcription factor NRF2, which upregulates the expression of efflux transporters, as well as anti-apoptotic proteins such as BCL-2 (Jia et al., 2015). NRF2 also plays a crucial role in the protection of CSCs from oxidative damage, and one way through which NRF2 signaling is activated is via the activation of transcription factors like c-Myc, possibly as a defense mechanism against elevated levels of ROS induced by oncogenic transcription factors (DeNicola et al., 2011). It performs its role through the expression of target genes that encode for antioxidant proteins such as NADPH quinone oxidoreductase (NQO-1), glutathione (GSH) and glutathione peroxidase (GPX) (Ryoo et al., 2015).

In addition to chemoresistance, metastasis driven by CSCs is one of the main reasons for tumor aggressiveness and poor prognosis in cancer patients. It is driven by the Wnt, Notch, Hedgehog, and YAP/TAZ pathways (Nwabo Kamdje et al., 2017; Janse van Rensburg and Yang, 2016). They promote EMT, which is the process through which cells acquire mesenchymal properties and assume a more motile shape, which allows them to detach from neighboring tissues and migrate to different locations (Kalluri and Weinberg, 2009). One way these signaling pathways achieve this is through the expression of zinc-finger E-box-binding factor 1 (ZEB1) (Nwabo Kamdje et al., 2017; Janse van Rensburg and Yang, 2016). Several other factors link CSCs with EMT. For example, BMI1 plays an important role in facilitating the transition between epithelial and mesenchymal cells (Tam and Weinberg, 2013). Additionally, Snail and Twist are two key transcription factors that induce EMT. Besides, they have been associated with epigenetic regulation and the development of CSC phenotype in the mesenchymal cells (Martin and Cano, 2010; Wang et al., 2015).

2.3. Current modalities for targeting CSCs

Many of the recent findings point to CSCs as the key drivers of anticancer therapy failure due to their aggressive nature and chemoresistant and metastatic properties. Thus the elimination of these cells is crucial for complete tumor eradication and a higher patient survival rate. Several modalities have been proposed and tested to specifically target and sensitize CSCs (Majeti, 2011; Song et al., 2018; Kuhlmann et al., 2016). These include targeting surface biomarkers associated with CSCs. Several agents have been developed for this purpose, such as H90, which efficiently targets CD44 expressed on leukemia stem cells (Majeti, 2011), and oxytetracycline that target CD133, a marker that is preferentially expressed on liver cancer stem cells (Song et al., 2018). Targeting signaling pathways associated with CSCs such as Wnt, Notch, and Hedgehog is another promising means for eradicating CSCs (Kuhlmann et al., 2016). For instance, small molecules such as evodiamine, IGC-001, and acridine derivatives were shown to target CSCs in gastric cancer, nasopharyngeal carcinoma, and human ovarian cancer cell line (OVCAR-3) through Wnt inhibition (Müller et al., 2017). Agents like honokiol inhibit Notch signaling in the colon and melanoma CSCs (Kaushik et al., 2015; Nakanishi et al., 2013). Another molecule is cyclopamine, a steroidal alkaloid, which inhibits CSCs formation in glioblastoma (GBM) cell lines by down-regulation of Hedgehog

signaling pathway (Eimer et al., 2012). Molecules such as EC-70124 and napabucasin target another promising pathway that is important in the proliferation and differentiation of CSCs, which is the JAK/STAT pathway and display anti-proliferative activity on CSCs population in pancreatic and prostate cancer, respectively (Müller et al., 2017). Additionally, studies showed that CSCs altered their metabolic states within tumors towards either glycolysis or mitochondrial respiration as a source of energy depending on the surrounding cellular environment (Müller et al., 2017; Hanahan and Weinberg, 2011; Peiris-Pagès et al., 2016). For this mean, drugs such as atovaquone and artesunate inhibit oxygen-consumption and promote mitochondrial dysfunction in CSCs (Fiorillo et al., 2016; Subedi et al., 2016). CSCs interaction with their microenvironment provides an additional means for CSCs maintenance and proliferation through immune evasion (Relation et al., 2017). Targeting the microenvironment components such as cancer-associated fibroblasts (CAF) showed promise in sensitizing CSCs (Sun et al., 2019). Researchers have also studied the resensitization of CSCs to chemotherapy through the inhibition of ABC transporters and the repairment of apoptosis pathways (Talukdar et al., 2016).

Though many of these modalities seem promising for tumor eradication when combined with classical anticancer therapy, there are still challenges that hinder the use of these agents. One major problem is the selectivity of these agents, as the markers and pathways associated with CSCs are also essential in the maintenance of normal stem cells (Ajani et al., 2015). The toxicity of these agents is, therefore, one major obstacle that needs to be tackled. Another issue is the heterogeneity of tumors, which means that a single agent would not be enough to target CSCs, as cells within the same tumor may express different markers and overregulate different pathways (Sun et al., 2019). Because of these limitations, it is important to determine other characteristics that are unique to CSCs that could be exploited.

One feature of CSCs that has not been extensively targeted yet is their evasion of oxidative death via the overexpression of antioxidant and detoxifying genes (Kahroba et al., 2019), as well as their aberrant iron and lipid metabolism (Begicevic et al., 2019; Schonberg et al., 2015). Recent reports have shown that the accumulation of lipid peroxides by ferroptosis could specifically induce cell death in CSCs (Taylor et al., 2019). Ferroptosis inducing agents could, therefore, have a promising role in complete tumor eradication.

3. Ferroptosis as a mechanism to target CSCs

3.1. Overview of ferroptosis

Ferroptosis was first reported in 2003 when a compound named erastin was observed to induce death in RAS mutant tumor cells. However, the cells did not exhibit the features of typical apoptosis (Dolma et al., 2003). The same mechanism of death was also observed in 2008 in cells treated by RAS-selective lethal molecule 3 and 5 (RSL3 and RSL5) (Yang and Stockwell, 2008). This mechanism of death was found to be distinct from other modes of cell death. Instead of displaying apoptosis characteristics such as caspase activation, chromatin condensation, and cell shrinkage, or the morphological traits of necrosis such as organelle swelling and cell membrane rupture, these cells exhibited unique features such as shrinkage in their mitochondria, fading of their mitochondrial cristae, and an accumulation of intracellular lipid ROS (Dixon et al., 2012; Li et al., 2020).

Several researchers have described the mechanisms by which ferroptosis is triggered in cells. Ferroptosis is a result of an imbalance between the levels of lipid hydroperoxides in the cell and the levels of lipid hydroperoxide detoxification enzymes (Dixon and Stockwell, 2019). In other words, ferroptosis occurs when there is either an overproduction of lipid ROS in the cell that the detoxification system cannot manage, or when there is a depletion of the detoxification system enzymes that cause an accumulation of lipid ROS levels as a result (Lei et al., 2019). We will discuss some mechanisms which lead to these phenomena.

3.2. Processes that trigger ferroptosis in cells

One of the ways through which ferroptosis is regulated is through lipid metabolism. Phospholipids that contain polyunsaturated fatty acids (PUFAs) were found to be key drivers of ferroptosis, as they are susceptible to oxidation into lipid peroxides (Stockwell et al., 2017). Enzymes that are responsible for the biosynthesis and remodeling of these PUFA-containing phospholipids such as Acyl-CoA synthetase long-chain family member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) were found to play a role in cell susceptibility to ferroptosis (Stockwell et al., 2017; Doll et al., 2017). Another group of enzymes that are involved in lipid metabolism is lipoxygenases (LOXs). LOXs catalyze the oxidation of both free PUFAs and phospholipids containing PUFAs and thus are believed to help modulate ferroptosis. This idea was supported when silencing of arachidonate lipoxygenase (ALOX) genes induced resistance to ferroptosis in imidazole ketone erastin (IKE) treated cells (Yang et al., 2016).

Abnormal iron metabolism is another triggering factor for ferroptosis. Increased levels of free iron in the cells are associated with high levels of ROS production through Fenton reaction, which could promote lipid peroxidation (Hassannia et al., 2019). Iron is also an essential component of the LOX enzymes (Yan and Zhang, 2019). Accordingly, several proteins that are involved in iron uptake and storage were suggested to contribute to ferroptosis (Hassannia et al., 2019). Transferrin receptor 1 is a membrane protein responsible for iron uptake into the cell. The upregulation of this protein was associated with sensitivity to ferroptosis (Yang and Stockwell, 2008). Another protein involved in iron transport is a metal ion transporter protein called divalent metal transporter 1 (DMT1), which transports iron from the lysosome to the cytoplasm. Inhibition of this protein was found to cause ferroptotic death through iron accumulation in the lysosome, which causes lysosomal damage and release of the iron content into the cytoplasm (Turcu et al., 2020). Proteins that are involved in iron storage are ferritin heavy chain (FTH) and ferritin light chain (FTL). Degradation of these proteins through nuclear receptor coactivator 4 (NCOA4)-mediated ferritinophagy was found to promote ferroptosis by increasing the levels of free iron in the cytoplasm (Hou et al. 2016, Lei et al., 2019).

Glutathione peroxidase 4 (GPX4) is the enzyme responsible for peroxide detoxification in the cell and is the main protector of cells from ferroptosis. Decreased activity and inhibition of this enzyme was observed to drive cells into death in a ferroptotic manner even before the term was recognized (Yang and Stockwell, 2008; Seiler et al., 2008). One study found that endothelial knockout of GPX4 in mice, along with depletion of vitamin E, a second antioxidant, resulted in the death of around 80 % of the mice, these findings indicating the crucial role of GPX4 for endothelial viability (Wortmann et al., 2013). Inhibition of GPX activity could happen through several mechanisms. One important way is through glutathione depletion. Glutathione is an antioxidant molecule that is an essential cofactor for GPX4, which is utilized by the enzyme to reduce lipid hydroperoxides to alcohols (Lei et al., 2019). Reduction in glutathione levels in the cell would result in decreased GPX4 activity. Glutathione depletion occurs through several mechanisms, one of them being the inhibition of System X_c^-. System X_c^- is an antiporter that is responsible for cystine entry into the cells in exchange for glutamate (Dixon et al., 2014). Cystine is reduced into cysteine inside the cell, which is an important molecule involved in glutathione synthesis (Yu and Long, 2016). One mechanism through which the ferroptotic agent erastin induces ferroptosis is through inhibition of the System X_c^- transporter (Dixon et al., 2012). Other than diminishing GPX4 activity through glutathione depletion, direct inhibition of the GPX4 enzyme is also possible through using the ferroptosis inducing molecule RSL3 (Yang and Stockwell, 2016). In a study targeting persister cells in several cancer cell lines by using GPX4 inhibitors such as RSL3 and ML210, results revealed that loss of GPX4 function results in ferroptotic cell death in those cells *in vitro*, in addition, prevents tumor relapse *in vivo* (Hangauer et al., 2017). In this study, a HER2-amplified

breast cancer cell line (BT474) was treated with cytotoxic concentrations of the anticancer lapatinib to acquire persister cells resistant to lapatinib. It was observed that the number of persister cells remaining after lapatinib treatment was decreased when pretreated for 24 h with RSL3 (Hangauer et al., 2017). Interestingly, the treatment of BT474 with RSL3 and ML210 had a cytotoxic effect on persister cells, with minimal effect on parental cells (Hangauer et al., 2017). These findings indicate that GPX4 dependence is specific to the drug-resistant persister cell state. Moreover, xenograft models using GPX4 knockout (KO) or GPX4 wild type (WT) melanoma A375 cells were developed in this study and treated with dabrafenib and trametinib along with ferrostatin-1, a ferroptosis inhibitor, to mask any effects of GPX4 deletion (Hangauer et al., 2017). When ferrostatin-1 was withdrawn, results showed that the GPX4 WT tumors relapsed while the GPX4 KO tumors did not (Hangauer et al., 2017). Taken together, results from this study concluded that inhibition of GPX4 results in ferroptotic death in cancer persister cells, which presents as a novel strategy to counteract tumor relapse (Hangauer et al., 2017).

3.3. Regulation of ferroptotic pathways in cancer stem cells

There are many pathways involved in modulating ferroptosis in cells. Interestingly, some of these pathways were also found to play an important role in the survival and maintenance of CSCs. By looking into these pathways and the processes they control, we could explain why CSCs exhibit sensitivity to ferroptosis inducing agents.

3.3.1. Lipid metabolism

Lipid metabolism is an essential process in CSCs. It has been established that lipid uptake in CSCs is upregulated and plays a crucial role in providing these cells with the energy needed for their survival (Visweswaran et al., 2020). Elevated lipid contents were reported in ovarian and colorectal CSCs (Stockwell et al., 2017; Tirinato et al., 2015). In addition to being an energy source for the cell, lipid metabolism in CSCs also provides protective mechanisms against peroxidation through the production of lipid droplets and lipid desaturation. Lipid droplets are organelles present in the cytoplasm that are responsible for the storage of lipids (Tirinato et al., 2017). These organelles are overexpressed in CSCs, and elevated levels were found to correlate to stemness in a subgroup of breast CSCs (Hershey et al., 2019). Through lipid droplets, cells could resist ferroptosis by the protection of lipids from peroxidation (Visweswaran et al., 2020). Another protective mechanism in CSCs against lipid peroxidation is lipid desaturation. This process is regulated by the enzyme stearoyl-CoA desaturase 1 (SCD1), which concurrently plays a role in the stemness of CSCs (Begicevic et al., 2019). Lipid desaturation involves the conversion of saturated fatty acids to monounsaturated fatty acids (MUFAs). MUFAs possess the ability to reduce the levels of ROS and PUFA-containing phospholipids, which in turn also protects cells from ferroptosis (Magtanong et al., 2019). The mevalonate pathway is also involved in lipid metabolism in CSCs. It is regulated by c-Myc (Wang et al., 2017), which is an important transcription factor that promotes stemness in CSCs. Activation of this pathway prompts the production of GPX4 and the antioxidant coenzyme Q10, which also serves a protective function against ferroptosis (Stockwell et al., 2017).

Based on these observations, it is clear that CSCs are highly dependent on antioxidant mechanisms for survival, which explains why interference with GPX4 pathways seems to render CSCs sensitive to ferroptosis. This is reinforced by a study done on CSCs that highly expressed ZEB1, which is a regulator of cell stemness and also involved in PUFA synthesis and utilization. ZEB1 expression in CSCs was shown to render the cells dependent on GPX4, so when GPX4 activity was inhibited in these cells, ferroptosis was induced (Viswanathan et al., 2017).

3.3.2. Iron metabolism

Aberrant iron metabolism is another prominent feature of CSCs. This is evident through the atypical expression of proteins modulating the import, efflux, and storage of iron in these cells. For example, transferrin receptor 1, which is a downstream transcriptional target of c-myc (O'Donnell et al., 2006), was reported to be overexpressed in ovarian, breast, and glioblastoma CSCs (Schonberg et al., 2015; Basuli et al., 2017; Mai et al., 2017) when compared to their respective non-CSCs. In addition, studies that were done on ovarian and cholangiocarcinoma CSCs also reported a downregulation in ferroportin (FPN), a membrane protein that exports iron from inside to outside of the cells (Basuli et al., 2017; Raggi et al., 2017). These characteristics make CSCs more efficient in driving more iron into their cells. This was clear in glioblastoma CSCs when iron-tracing experiments revealed a higher iron intake in these cells when compared to glioblastoma non-CSCs (Schonberg et al., 2015).

Mounting evidence points to the essential role of intracellular iron in the proliferation of CSCs and the maintenance of their stemness (Recalcati et al., 2019). In fact, in breast cancer cells, low iron levels induced by the upregulation of FPN were associated with a lower expression of EMT markers such as SNAIL1, TWIST1, and ZEB2 (Guo et al., 2015). Iron was also implicated in inducing the Wnt signaling pathway in cells with adenomatous polyposis coli (APC) mutations (Brookes et al., 2008). Moreover, iron also mediates the downregulation of E-cadherin expression, a hallmark of EMT (Brookes et al., 2008). In a recent paper by Müller et al., they report an interesting role for iron in inducing the expression of the CSC marker CD44 (Müller et al., 2020). They also reveal a novel mechanism of iron entry in cells under the mesenchymal state. Along with TFR1, CD44 can also act as an entry site for iron, when iron complexes with the free carboxylate end of hyaluronate, which is a CD44 ligand. CD44 mediates the endocytosis of this iron-hyaluronate complex, hence providing an alternative route of entry for iron when TFR1 is downregulated as a result of elevated intracellular levels of iron (Müller et al., 2020). This indicates the dependence of CSCs on high levels of intracellular iron. In fact, iron chelation was linked to the downregulation of stemness genes, CSC surface markers such as CD133, CD44, and CD24, as well as EMT-inducing transcription factors (Recalcati et al., 2019).

The iron storage ferritin was also observed to be overexpressed in CSCs like glioblastoma (Schonberg et al., 2015). As high levels of cytosolic Fe^{2+} makes the cell vulnerable to Fenton reaction and ROS accumulation, CSCs utilization of ferritin could possibly be a protective mechanism against this phenomenon (Manz et al., 2016b). This could suggest that targeting ferritin in cells with abundant levels of intracellular iron could make them susceptible to ferroptosis. Mai et al. successfully managed to eradicate breast CSCs using this method through salinomycin, a lysosomotropic agent that could induce the lysosomal degradation of ferritin through ferritinophagy and cause the accumulation of lysosomal ROS, leading to Fenton reaction and lipid peroxidation (Mai et al., 2017).

3.3.3. NRF2 signaling

Many of the present literature support the view that CSCs retain low levels of ROS inside their cells, which is one of the reasons that explains why they are able to resist death by chemo- and radiotherapeutics (Bystrom et al., 2014). One crucial transcription factor involved in the maintenance of ROS levels in CSCs is NRF2. The high expression of the CSC markers CD44 and ALDH is associated with high NRF2 levels in CSCs (Kim et al., 2018; Ryoo et al., 2018). NRF2 plays an important role in expressing detoxifying and antioxidative genes to protect cells from ROS-induced damage (Kahroba et al., 2019). Several studies have supported the association between NRF2 expression and cell protection against ferroptosis. NRF2 plays an important role in iron homeostasis. It controls the expression of FTL, FTH, and FPN, and thus their overexpression could limit the level of free intracellular iron in CSCs (Dodson et al., 2019). It is also crucial for the regulation of glutathione synthesis, as it controls the expression of solute carrier family 7 member (SLC7A11), which is a subunit of the system X_c^- transporter, and other enzymes such as glutathione synthase (Dodson et al., 2019; Sasaki et al.,

2002). NRF2 could also upregulate the transsulfuration pathway, which is an alternative pathway for the biosynthesis of cysteine when the system X_c^- transporters are compromised. This was found to be a resistance mechanism to ferroptosis in ovarian cells when treated with erastin (Liu et al., 2020). Together, these findings suggest that NRF2 is an attractive target for eliminating CSCs. Combining NRF2 inhibitors with ferroptosis inducers could be a sensible approach to overcome resistance to ferroptosis inducers.

3.3.4. CD44 expression

The CSC marker CD44 also plays an interesting role in regulating ferroptosis. In addition to its role in iron homeostasis and modulating iron entry into the cell (Müller et al., 2020) (refer to section 3.3.2), its isoforms CD44v have the ability to stabilize the protein xCT, which is one subunit of the system X_c^- transporter and hence promotes glutathione synthesis. In fact, increasing glutathione production is capable of impairing the ROS induced stress signaling, one of the ferroptosis hallmarks. This was reported to confer resistance to ferroptosis in gastric cancer (Hasegawa et al., 2016; Ishimoto et al., 2011). Therefore, targeting the X_c^- transporter in tumors of high CD44 expression is of potential therapeutic benefit to eradicate tumors by empowering ferroptosis. Indeed, administering an inhibitor of system X_c^- transporter-like sulfasalazine to CD44 expressing HCT116 cancer cells was shown to inhibit their growth (Ishimoto et al., 2011). In another study, they also reported that head and neck squamous cell carcinoma (HNSCC) CSCs that expressed CD44v showed sensitivity to sulfasalazine and that sulfasalazine did not exhibit the same efficacy on HNSCC that did not express CD44v (Yoshikawa et al., 2013). This could indicate that ferroptosis induction by inhibition of system X_c^- transporters could be more suitable for targeting specific types of CSCs, preferably ones that express CD44v. Moreover, oncoproteins such as MUC1-C was reported to promote tumorigenesis in breast cancer via the formation of a complex between CD44v and the overexpressed GSH, which in turn, halt ferroptosis (Hasegawa et al., 2016). This finding provides another promising window to target aggressive resistant breast cancer expressing CD44v by interfering with the MUC1-C/xCT interaction, as inhibiting xCT would allow induction of ferroptosis, and suppress the oncogene MUC1-C transcriptional activity (Hasegawa et al., 2016).

3.3.5. Hippo-YAP/TAZ signaling

There is emerging evidence that indicates the role of YAP/TAZ signaling in maintaining CSCs. When activated, the YAP/TAZ signaling could drive the dedifferentiation of cancer cells and induce characteristics of CSCs such as self-renewal and chemoresistance (Park et al., 2018). It was recently reported that overexpression of TAZ conferred higher sensitivity to erastin-induced ferroptosis. This occurs through the induced expression of nicotinamide adenine dinucleotide phosphate oxidases (NOX), a group of enzymes that could promote ferroptosis through the production of superoxides. This process was reported to be regulated by TAZ-mediated expression of epithelial membrane protein 1 (EMP1) in renal cell carcinoma (Yang et al., 2019b), and TAZ-mediated expression of angiopoietin-like 4 (ANGPTL4) in ovarian cancer cells (Yang et al., 2020b). Another study also demonstrated the involvement of YAP with ferroptosis sensitivity as well (Wu et al., 2019). It is of note that the regulation by YAP/TAZ pathway is in direct correlation with the cellular confluency and density (Zhao et al., 2007). It is well established that a high cell density would usually activate the Hippo pathway by suppressing YAP/TAZ activity to halt cell proliferation. Therefore, controlling the seeding density and cell to cell contact would be a major player in mediating ferroptosis via the Hippo pathway (Pavel et al., 2018). Indeed, two studies demonstrated that renal and ovarian cancer cells were gaining enhanced sensitivity to ferroptosis when grown in cystine deprivation at low density and with minimal cellular communication and contact (Tang et al., 2015, 2017; Tang et al., 2016). Within the same context, high cellular density inhibited ferroptosis by suppressing yap activity in mesothelioma (Wu et al., 2019). Taking into account that increasing evidence is supporting the profound role of YAP/TAZ signaling in inducing chemotherapy resistance by virtue of cellular proliferation, metastasis, and recurrence gained by the Hippo pathway (Zanconato et al., 2016). Hence, the added role of this pathway in ferroptosis could provide another explanation as to why CSCs show sensitivity to ferroptosis inducers.

3.3.6. Autophagy

Among the many pathways and mechanisms exploited by cancer stem cells to provide the drive for their unique aggressive features, autophagy seems to be a pivotal player (Ojha et al., 2015). Autophagy is a particular biological process used by the cells as a sword of two edges, either to sustain the cells viability and survival or to induce cell death in a phagosome lysosome dependent features, all of which depend on the cellular context (McCarthy, 2014). Recent reports highlighted that autophagy is one of the major mediators in the establishment of cancer stem cells microenvironment, where it can maintain the balance between cancer stem cells and normal cells (Zhu et al., 2013). In fact, the role autophagy in cancer stemness could be reflected across various malignancies. For instance, a study demonstrated that beclin1 is highly needed for CSC maintenance in the athymic mice model of breast cancer (Gong et al., 2013). In addition, the role of autophagy is evident in chronic myeloid leukemia (CML) stemness, where the combination of autophagy inhibitor with tyrosine kinase inhibitor profoundly targeted CML stem cells (Kirkness et al., 1989). Interestingly, in a different context, autophagy can induce cell death by promoting the process of ferroptosis through the enhanced degradation of the iron storage complex ferritin (Hou et al., 2016; Ma et al., 2017; Park and Chung, 2019). The regulation of FTL1 and FTH1 levels contributes directly to ferroptosis, where increased levels counteract the process of ferroptosis. Autophagy can reduce the levels of ferritin and promote its degradation, which ultimately results in oxidative damage (Hou et al., 2016; Gao et al., 2016). The regulation of ferritin levels by autophagy is evident in multiple studies (Hou et al., 2016; Zhou et al., 2019a). For example, it was reported that the knockout or knockdown of both Atg5 and Atg7 would significantly increase the levels of FTH1, signifying the role of autophagy genes in ferritin regulation and, thereby ferroptosis induction (Hou et al., 2016). Moreover, it was noted that an increase in the autophagy flux in both cancer and fibroblast cells is directly associated with a parallel increase in the activation of ferroptosis (Zhou et al., 2019a). Furthermore, the relation between autophagy and ferroptosis was further elucidated by inhibiting the potential of ferroptosis inducing agents such as erastin from mediating its action in Atg5/Atg7 deficient cells (Hou et al., 2016).

4. Ferroptosis success in cancer therapy across different malignancies

Ferroptosis inducing agents have been studied extensively for their potential as anticancer therapeutic agents. Although the field of ferroptosis is relatively young, several agents were found to successfully promote cancer death and selectively target CSCs via ferroptosis induction (Fig. 1). Yet, it is noteworthy that the sensitivity of different types of cancer cells to ferroptosis induced cell death is significantly different (Xie et al., 2016). The possible reason behind this is the differences in the metabolic state among different cell lines (Yu et al., 2017). Further studies revealed that combining ferroptosis inducing agents such as erastin with chemotherapeutic agents like cisplatin, doxorubicin, and temozolomide; provided a notable synergistic anticancer activity (Yu et al., 2017). The coming sections summarize different *in vivo* and *in vitro* studies aimed at inducing ferroptosis in various types of cancer cells (Table 1), with special attention to CSCs studies (Table 2).

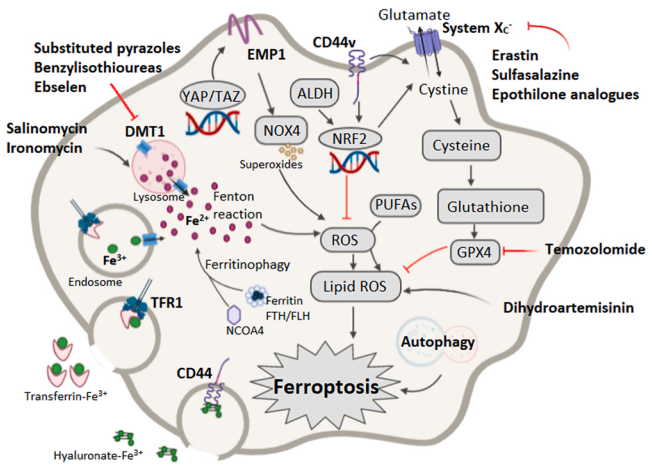

Fig. 1. Diagram depicting molecular targets of ferroptosis inducing agents in cancer stem cells CD44v, Cluster of Differentiation 44; EMP1, EPO (Erythropoietin)-Mimetic Peptide 1; DMT1, Divalent metal transporter 1; TFR1, Transferrin receptor 1; NRF2, Nuclear factor erythroid 2-related factor 2; ROS, Reactive oxygen species; PUFAs, polyunsaturated fatty acids; NOX4, Nicotinamide adenine dinucleotide phosphate oxidase 4; GPX4, glutathione peroxidase-4; FTH/FLH, ferritin heavy chain/ferritin light chain; NCOA4, nuclear receptor coactivator 4.

4.1. Breast Cancer

Breast cancer is a heterogeneous disease composed of multiple subtypes, and this may largely explain the high occurrence of therapy failure in breast cancer, which leads to disease recurrence and reduction of overall survival (Polyak, 2011; Kansara et al., 2020). Despite the increasing number in treatment options, there is still an urgent necessity to find more optimum therapeutic alternatives that overcome chemoresistance and many side effects associated with the current treatments (Palomeras et al., 2018). Implementing ferroptosis targeting strategies in breast cancer disease attracted huge attention in current research due to the promising results obtained from several studies. Ma et al. showed that using lapatinib in combination with siramesine for the treatment of breast cancer cell lines (e.g. MDA MB-231, MCF-7, and SKBR3) induced ferroptosis and autophagic cell death via increasing intracellular iron level accompanied by an increase in ROS production. This new combination strategy has a therapeutic potential to overcome apoptotic resistance in breast cancer cells (Ma et al., 2017). Another study provided a novel formulation of erastin-loaded exosomes labeled with folate to target folate receptor-positive MDA-MB-231 (TNBC cell line). This formulation increased the uptake of erastin into the cells and significantly induced ferroptosis (Yang et al., 2019a). It is of note that the process of ferroptosis is regulated by different factors, especially in the case of triple negative breast cancer (TNBC), where it was reported that in MDA-MB-468, the transmembrane oncoprotein MUC1-C is aberrantly overexpressed (Siroy et al., 2013). This protein plays a crucial role in preventing the action of erastin by forming a complex with xCT. Hence, MUC1-C and xCT are involved in regulating ferroptosis and targeting those molecules is of great importance in future ferroptosis targeting studies (Hasegawa et al., 2016). Yu et al. showed that sulfasalazine induced ferroptosis in different breast cancer cells. However, the results revealed that estrogen receptors positive (ER+) breast cancer cell lines such as T47D and MCF7 are more resistant to sulfasalazine-induced ferroptosis in comparison with TNBC cell lines like MDA-MB-231 and BT549 (Yu et al., 2019).

Many ferroptosis studies have focused on targeting breast cancer stem cells (BCSC), as they play a central role in the acquisition of resistance to endocrine therapy and are the main cause of tumor relapse (Rodriguez et al., 2019; Li et al., 2008). In a study published in 2009, after screening of thousands of molecules, salinomycin was found to inhibit tumor growth selectively, and significantly reduced the proportion of breast CSCs both *in vitro* and *in vivo* (Li et al., 2008). Notably, ironomycin, which is a salinomycin derivative, specifically kills BCSC lines (HMLER $CD24^{low}$ and iCSCL-10A2) through the induction of ferroptosis. In particular, it was more potent and selective compared to salinomycin; it accumulates in lysosomes and increases iron sequestration in them, thereby induces the production of ROS and death of BCSCs with features of ferroptosis (Mai et al., 2017). A recent study published in Feb 2020 by Turcu et al.; investigated as well several agents that selectively target and induce ferroptosis in BCSCs (HMLER $CD44^{high}$ /$CD24^{low}$) through sequestering iron in the lysosome, which are the inhibitors of DMT1 such as ebselen and other pyrazole and benzylisothiourea containing derivatives (Turcu et al., 2020). Taylor et al. discovered new analogs derived from epothilone that exhibit antitumor activity against several cell lines through induction of ferroptosis by inhibition of system X_c^-, and highly selective toward BCSCs (transformed HMLER cells) (Taylor et al., 2019). Another interesting agent with an antitumor activity associated with ferroptosis is ferumoxytol, which is a superparamagnetic iron oxide nanoparticle (Cao et al., 2014; Auerbach et al., 2018; Bullivant et al., 2013). Magnetic hyperthermia is a new technique that selectively kills BCSCs (MDA-MB-231), and superparamagnetic iron oxide nanoparticles are found to be the key aspect of

Table 1
Compounds that induce ferroptosis in various types of cancer cells.

Ferroptosis inducing agent	Mechanism	Cancer type	Cells model	Outcome	Ref.
lapatinib and siramesine	Increase intracellular iron level causing oxidative damage.	Breast	MDA MB-231 MCF-7 SKBR3	Ferroptosis was detected in all cancer cell models; agents induced autophagic cell death as well.	(Ma et al., 2017)
Erastin	Erastin-loaded exosomes labeled with folate.	Breast	MDA-MB-231	Ferroptosis was detected, increased drug uptake into the cells.	(Yang et al., 2019a)
	Lipid peroxidation and oxidative damage.	Gastric	AGS, BGC823	Ferroptosis was detected in both cell lines.	(Hao et al., 2017)
Sulfasalazine	Increase in ROS, depletion of GPX4, and system X_c^-.	Breast	MDA-MB-231 BT549	Ferroptosis was detected; the agent showed selective efficacy in cells with low ER expression.	(Yu et al., 2019)
Artemisinin derivative					
Artesunate	Accumulation of ROS.	Ovarian	HEY1, HEY2	ROS detected in all cell lines.	(Greenshields et al., 2017)
	Generation of lipid peroxidation and iron accumulation.	Pancreatic	Panc-1, COLO357, AsPC-1, BxPC-3	Ferroptosis was detected in a ROS-dependent manner.	(Eling et al., 2015)
Dihydro-artemisinin	Altering cellular iron homeostasis.	Lung	H292	Ferroptosis was detected.	(Yang et al., 2019a; Chen et al., 2020)
Sorafenib	Increase intracellular iron level causing oxidative damage.	Hepatocellular carcinoma	Huh7	Ferroptosis was detected in HCC, and cell death was inhibited by ferroptosis inhibitors.	(Louandre et al., 2013)

Table 2
Compounds that induce ferroptosis in various types of CSCs.

Ferroptosis inducing agents	Mechanism	Cancer type	CSC model/related markers	Outcome	Ref.
Salinomycin, Ironomycin	Iron sequestration in lysosome	Breast	HMLER $CD24^{low}$ iCSCL-10A2	Ferroptosis was detected in both CSC models; agents showed selective efficacy in CSCs linked to the high iron content in CSCs.	(Mai et al., 2017)
Ebselen Substituted pyrazoles Benzyl-isothioureas	DMT1 inhibitors, Iron sequestration in lysosome	Breast	HMLER $CD44^{high}$ /$CD24^{low}$	Ferroptosis-induced cell death in breast CSCs. When compared to Salinomycin, they showed similar selectivity towards CSCs.	(Turcu et al., 2020)
Epothilone analogs	Inhibition of system X_c^-	Breast	Transformed HMLER cells	Ferroptosis-induced cell death in several cell lines, and high selectivity to breast CSCs.	(Taylor et al., 2019)
Erastin	Inhibition of system X_c^-	Ovarian	HGSOC	Ferroptosis was induced in ovarian CSCs and could be inhibited by ferroptosis inhibitors. CSCs exhibited more susceptibility to erastin than non-CSCs	(Basuli et al., 2017)
Sulfasalazine	Inhibition of system X_c^-	Gastric	Targeting marker highly expressed in gastric CSCs (CD44+)	Sulfasalazine impaired the ROS defense ability in GC cells and sensitized them to cisplatin and significantly inhibits their growth.	(Ishimoto et al., 2011)
Temozolomide & quinacrine	Accumulation of lipid peroxides	Glioblastoma	Glioblastoma stem cells (GSCs)	Ferroptosis was detected in GSCs, quinacrine increased GSC susceptibility to temozolomide.	(Buccarelli et al., 2018)

this technology (Sadhukha et al., 2013). Therefore, ferumoxytol may have potential activity against BCSCs through the induction of magnetic hyperthermia.

4.2. Ovarian Cancer

Ovarian cancer is one of the most common leading causes of cancer-related deaths; it is well characterized with high recurrence rates and therapy resistance (Sadhukha et al., 2013; Lengyel, 2010; Pal et al., 2020; Bindhya et al., 2019). Notably, Basuli et al. reported that ovarian CSCs are characterized by excessive iron uptake and retention and rely on it for self-renewal and metastasis (Basuli et al., 2017). This proposes that ovarian CSCs are more susceptible to ferroptosis inducing agents. In fact, erastin was successful in reducing ovarian CSCs viability by virtue of ferroptosis induction. Interestingly, CSCs were more sensitive to erastin compared to non-CSCs (Basuli et al., 2017). Artesunate is an anti-malarial agent that is known to induce ferroptosis and inhibit the growth of several ovarian cancer cell lines both *in vitro* and *in vivo*. It mediates its action by increasing ROS production in a dose-dependent manner. In contrast, ferrostatin-1, a ferroptosis inhibitor, significantly reversed artesunate-induced cell death (Greenshields et al., 2017).

4.3. Gastric cancer

Hao et al. investigated the role of erastin in human gastric cancer (GC) cell lines (AGS and BGC823) and in mice models. The results revealed that erastin inhibited the growth of GC cells through the induction of ferroptosis. They confirmed that ferroptosis was the main cause of death by erastin through the silencing of cysteine dioxygenase 1 in GC cells, a non-heme iron metalloenzyme that plays a regulatory role in ferroptosis (Joseph and Maroney, 2007). The silencing of cysteine dioxygenase 1 was capable of blocking erastin-induced ferroptosis (Hao et al., 2017). Targeting gastric CSCs was reported by Li et al., where a combination of salinomycin and docetaxel-loaded nanoparticles effectively suppressed gastric CSCs population in nude mice bearing GC xenografts (Li et al., 2017). CD44, one of the important markers that are expressed in CSCs (Collins et al., 2005; Dalerba et al., 2007; Ishimoto et al., 2010), contributes to ROS mechanism of cellular defense by interacting with System X_c^-. CD44 is highly expressed in human gastrointestinal cancer cells. Ishimoto et al. investigated the role of sulfasalazine as an inhibitor of system X_c^- to impair the defense mechanism and induce ferroptosis by using a transgenic mouse model of GC. Results revealed that using sulfasalazine sensitizes tumor cells towards cisplatin and significantly inhibits their growth (Ishimoto et al., 2011). These findings suggest the critical role of CD44 as an important marker in determining tumors that would be successfully eradicated by ferroptosis manipulation.

4.4. Applications of ferroptosis in other malignancies

Ferroptosis induction in lung cancer cells has been achieved by several agents such as artemisinin (an anti-malarial agent) and its derivatives. Chen et al. investigated the activity of dihydroartemisinin (DHA) against human H292 (lung cancer cell line) and in a mouse xenograft model. The results revealed that alteration in cellular iron homeostasis makes the cells more vulnerable to ferroptosis (Chen et al., 2020). Interestingly, another study found that DHA targets CSC markers in glioma, such as (CD133, SOX2, and nestin) and impairs their formation (Cao et al., 2014). Hence, it is evident that DHA may have a dual role in CSC eradication through the inhibition of CSC stemness and the induction of ferroptosis. As mentioned earlier, artesunate induced ferroptosis in ovarian cancer cells; it can as well contribute to ferroptosis activation in pancreatic cancer through the induction of lipid peroxidation (Eling et al., 2015). Taken together, we can conclude that artemisinin derivatives target a wide range of cancers and CSCs through ferroptosis. On the other hand, Buccarelli et al. found that the combination of temozolomide with quinacrine (hydroxychloroquine derivatives) induced death in glioblastoma stem-like cells, through induction of ferroptosis in an iron-dependent form and by the accumulation of lipid peroxides. This combination weakened the invasion and made those cells more susceptible to chemotherapy and radiotherapy (Buccarelli et al., 2018). Ferroptosis was also found to be an effective mechanism to induce cell death in hepatocellular carcinoma (HCC). HCC accounts for 90 % of all primary liver cancer; it arises from the neoplastic transformation of hepatocytes (El-Serag, 2011). Sorafenib, a therapeutic agent, approved for advanced HCC, exerts its cytotoxic effect through the induction of oxidative stress in HCC cells by altering intracellular iron stores, which ultimately results in ferroptosis (Louandre et al., 2013). Another study using sorafenib in HCC showed that cells with a low level of retinoblastoma (RB) protein, which is closely related to liver tumors (Mayhew et al., 2007); were more susceptible to ferroptosis (Louandre et al., 2015). Therefore, iron and RB protein could be potential targets for effective ferroptosis targeting in HCC.

5. Conclusion

The field of cancer therapy has witnessed major advances, with numerous approaches to tackle a wide spectrum of malignancies. Despite the enormous efforts, optimal cancer eradication is challenged by the unique characteristics of tumors that can be utilized to evade therapy. Among the many features, cancer stem cells present the

greatest challenge in cancer therapy (Mansoori et al., 2017). Effective targeting of this population of cells would be sufficient to overcome chemotherapy resistance and tackle the most aggressive recurrent types of tumors (Phi et al., 2018). Hence, understanding and dissecting the mechanisms that supply and support CSCs is of essence. Of note, ferroptosis, a form of non-apoptotic cell death, was reported to be one of the successful means to combat CSCs across different malignancies. CSCs possess certain features that render them much more sensitive to ferroptosis activation as compared to their parental counterparts. For instance, CD44v expression has a direct role in regulating xCT system (Hasegawa et al., 2016), in addition to the dependence of CSCs on the hippo pathway, which has a tight role in controlling ferroptosis. Not to mention, the common axis that autophagy harbor between CSCs maintenance and ferroptosis induction (Ma et al., 2017). Therefore, it is of current interest to investigate the promising potential that ferroptosis inducers could bring to the forefront toward targeting and eliminating CSCs. Many ferroptosis inducing agents showed promising results in targeting CSCs such as salinomycin, ironomycin, ebselen, and other pyrazole and benzylisothiourea containing derivatives; especially in targeting BCSCs like HMLER $CD24^{low}$ (Dixon and Stockwell, 2019; Han et al., 2020). Artemisinin derivatives were also successful in targeting a wide range of cancers and CSCs through ferroptosis such as ovarian, lung, and glioma CSCs (Yang et al., 2016; Tirinato et al., 2017; Hershey et al., 2019). In addition, using ferroptosis activators, along with chemotherapeutic drugs, showed notable synergistic effects (Padma, 2015). Utilizing low dose of ferroptosis inducing agents such as erastin significantly restored the sensitivity of resistant cancer to standard chemotherapy such as doxorubicin and cytarabine in resistant AML cells (Yu et al., 2015). Another study highlighted the astonishing success of combining docetaxel with erastin in overcoming ABCB1 mediated resistance in ovarian cancer (Zhou et al., 2019b). Moreover, numerous approaches are under current investigation to empower the activation of ferroptosis in specific cancer types that are less sensitive to ferroptosis sensitizers such as NSCLC. For instance, a report by Gai et al. illustrated that combining erastin with acetaminophen successfully inhibited NSCLC growth and activated ferroptosis by regulating NRF2 signaling (Gai et al., 2020). These examples are a few of many reports that demonstrate that a broad variety of combinations can be used with ferroptosis inducing agents to maximize the benefit and empower cancer therapy (Gai et al., 2020).

Despite the encouraging potential of these agents, there are still several questions that need to be answered before researchers and clinicians could come up with conclusions regarding ferroptosis inducers. For example, many complex pathways are involved in the regulation and maintenance of CSCs that have not been fully understood. CSCs arising from different tumors and even from the same tumor possess distinct traits, so it is difficult to predict how each CSC type would respond to these agents. It is also important to note that a few studies have presented the capacity of certain agents that can be considered as ferroptosis inhibitors like iron chelators (Fiorillo et al., 2020) and vitamin E derivatives in specifically tackling CSCs (Marzagalli et al., 2018), hence, the role of ferroptosis inhibitors should not be disregarded in the context of anticancer treatments.

Nevertheless, ferroptosis induction remains a promising strategy for eliminating aggressive tumors. Thus, more research should be done to assess the safety of these agents and understand how they would affect normal stem cells that share similar regulating pathways with CSCs. Advances to fill these gaps in knowledge could potentially bring us many steps closer to eradicating CSCs.

Declaration of Competing Interest

The authors report no declarations of interest.

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