THE RELATIONSHIP BETWEEN DRUG RESISTANCE AND FERROPTOSIS IN BREAST CANCER CELLS FERROPTOTIC PROCESS IN BREAST CANCER

MEME KANSER HÜCRELERİNDE KANSER KAYNAKLI İLAÇ DİRENCİ VE BAĞIŞIKLIKTAN KAÇINMANIN KAVŞAĞINDA FERROPTOZ

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ABSTRACT

Because of their iron-dependent nature, cancer cells are more prone to ferroptosis, an iron-catalyzed necrosis. Accumulating evidence suggests that ferroptotic cell death leads to suppression of tumor growth. Targeting ferroptosis could be a promising anticancer strategy. Recent discoveries of ferroptosis-inducing agents and further identification of the regulatory mechanisms and genes involved in ferroptosis provide a basis for developing strategies to target ferroptosis in cancer therapy. Therefore, a better understanding of the processes that regulate ferroptosis sensitivity should ultimately aid the discovery of new therapeutic strategies to improve cancer therapy. In line with the studies, they found that triple-negative breast cancer is more sensitive to ferroptosis than ER-positive breast cancer. The most essential problem in breast cancer treatment is death due to metastasis and drug resistance. Doxorubicin (Dox) is one of the most commonly used chemotherapeutic agents in treatment, and a significant portion of patients die due to treatment-related resistance. Targeting agents that will trigger different types of cell death in overcoming Dox resistance is an important issue, and targeting cancer cells via the ferroptotic pathway has recently become the focus of attention. In conclusion, triggering the ferroptotic cell death mechanism is considered a promising new approach in overcoming resistance in terms of the potential to drive cancer cells to death in treatment-resistant cancers. In this review, possible molecular mechanisms of action in terms of ferrroptotic cell death and breast cancer treatment resistance and reviewed.

Keywords: Ferroptosis, Breast cancer, Drug resistance, Cancer

ÖZET

Demire olan bağımlılıkları, kanser hücrelerini ferroptoz olarak bilinen demir katalizli nekroza daha duyarlı hale getirir. Günümüze kadar elde edilen veriler, ferroptotik hücre ölümünün tümör büyümesinin baskılanmasına yol açtığını göstermektedir. Ferroptozu hedeflemek umut verici bir antikanser stratejisi olabilir. Bu sebeple ferroptozu indükleyen ajanların keşfinin devamlılığı ve ferroptozda yer alan düzenleyici mekanizmaların ve ilgili genlerin daha fazla tanımlanması, kanser tedavisinde ferroptozu hedeflemek için stratejiler geliştirmeye bir temel oluşturabilir. Ferroptoz duyarlılığını düzenleyen bu süreçlerin daha iyi anlaşılması, nihayetinde kanser tedavisini geliştirmek için yeni terapötik stratejilerin keşfedilmesine yardımcı olmalıdır. Yapılan çalışmalar doğrultusunda üçlü negatif meme kanserinin ferroptoza karşı ER pozitif meme kanserinden daha duyarlı olduğu belirtilmiştir. Meme kanseri tedavisindeki en önemli sorun, metastaz ve ilaç direncine bağlı ortaya çıkan ölümdür. Tedavide en sık kullanılan kemoterapötik ajanlardan biri ise Doksorubisin (Dox) olup, tedaviye bağlı direnç nedeniyle hastaların önemli bir kısmı kaybedilmektedir. Dox direncinin yenilmesinde farklı hücre ölüm tiplerini tetikleyecek ajanların hedeflenmesi önemli bir konudur ve son zamanlarda ferroptotik yolak üzerinden kanser hücrelerinin hedeflenmesi ilgi odağı haline gelmektedir. Sonuç olarak, tedaviye dirençli kanserlerde kanser hücrelerini ölüme sürükleme potansiyeli açısından ferroptotik hücre ölüm mekanizmasının tetiklenmesi direnci yenme açısından umut verici yeni bir yaklaşım olarak değerlendirilmektedir. Bu derlemede ferroptotik hücre ölümü ve meme kanseri tedavi direnci açısından olası moleküler etki mekanizmaları gözden geçirilmiştir.

Anahtar kelimeler: Ferroptoz, Meme kanseri, İlaç direnci, Kanser

Received:10.07.2024
Accepted:17.08.2024
Published:31.08.2024

How to cite: Çiçekli Ç, Altun ZS, Çiçekli MN. The Relationship Between Drug Resistance And Ferroptosis In Breast Cancer Cells Ferroptotic Process In Breast Cancer. SMJ 2024; 2(2): 30-8.

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Introduction

Cell death is an irreversible mechanism associated with the metabolism of the internal environment to maintain cellular homeostasis and development in mammals. To date, cell death mechanisms such as apoptosis, ferroptosis and necroptosis and their relationships in cancer pathways have been reported. Ferroptosis is a newly investigated cell death pathway in this sense (1). Cancer is a lethal disease characterised by uncontrolled cell proliferation, invasiveness and metastasis (2). Breast cancer is the second most common and most lethal type of cancer in women (3). In the treatment of breast cancer, surgery is performed to remove the tumour, followed by chemotherapy and radiotherapy, depending on the stage of the disease (4). Resistance to chemotherapy and molecularly targeted therapies is significant problem facing current cancer research that severely limits the effectiveness of cancer treatments (5). The mechanisms underlying sensitivity and resistance to ferroptosis, particularly in the context of cancer, have become an area of intense research in the last few years. Although the necessity of polyunsaturated fatty acid (PUFA) oxidation as a step in the ferroptotic pathway is accepted, the mechanisms underlying the sensitisation of oncogenic mutations and other non-oncogenic cancer-related conditions to ferroptosis have only recently begun to emerge. It has also been reported that in breast cancer, Lapatinib induces ferroptosis by increasing iron-dependent ROS production and overexpression of CDO1 (Cysteine dioxygenase type 1) gene may exacerbate ferroptotic cell death by further accumulation of high-level reactive oxygen species (ROS) resulting from decreased glutathione (GSH) levels in breast cancer cells (6). Triple-negative breast cancer (TNBC) is a specific subtype of breast cancer with higher recurrence and mortality rates than other types of breast cancer (7). Ferroptosis is an iron-dependent and lipid peroxide-induced cell death resulting from inhibition of the cystine/glutamate transporter, which is important for the survival of TNBC cells. Erastin is a low molecular weight chemotherapy drug that induces ferroptosis; however, poor water solubility and renal toxicity have limited its application (8). Moreover, the efficacy of chemotherapy may be increased by concurrently administering the ferroptosis inducer Erastin with chemotherapeutic medications such as Temozolomide, Cisplatin, Cytarabine, and Doxorubicin (9). Application of specific GPX4 inhibitors, such as RSL3 and ML210, was found to reduce cancer cell growth in BT474 breast cancer cells that persisted following lapatinib treatment but did not affect nontransformed healthy MCF10A breast cells. In this sense, targeting GPX4 in reversing acquired drug resistance in breast cancer cells appears to be a promising therapeutic strategy (10,11,12).

Ferroptosis Overview

Iron (Fe) is involved in oxygen transport and DNA biosynthesis. It is also an element involved in cell survival as a co-factor of various proteins in the tricarboxylic acid (TCA) cycle and electron transport chain in ATP synthesis. In addition, it is closely associated with tumor formation and progression (13). It has been reported that divalent iron (Fe+2) significantly accelerates lipid peroxidation of saturated fatty acids in humans (14). Ferroptosis is a regulated cell death mechanism that is activated depending on the concentration of lipid peroxides and iron ions and is associated with diseases such as ischaemia/reperfusion, acute renal impairment, cancer and neurodegeneration (15). It has been reported that divalent iron (Fe+2) significantly accelerates lipid peroxidation of saturated fatty acids in humans (14). In the ferroptotic process, selenoenzyme glutathione peroxidase 4 (GPX4) is present to prevent uncontrolled peroxidation of phospholipids (Figure 1) (16). RAS family member GTPases (HRAS, NRAS and KRAS) are mutated in approximately 30% of all cancers. The discovery of selectively lethal compounds for RAS-mutant tumour cells is therefore gaining importance. As a result, Erastin and RSL3 molecules, which are selectively lethal for oncogenic RAS-mutant cells and also called RAS-selective lethal (RSL) compounds, were discovered (17). In addition, the relationship of these molecules with ferroptosis, a cell death mechanism different from apoptosis, necrosis and other well-characterised types of regulated cell death, has been demonstrated. Studies are

ongoing for the interaction in this iron-dependent death pathway and approaches to treating cancer by killing cancerous cells through these molecules.

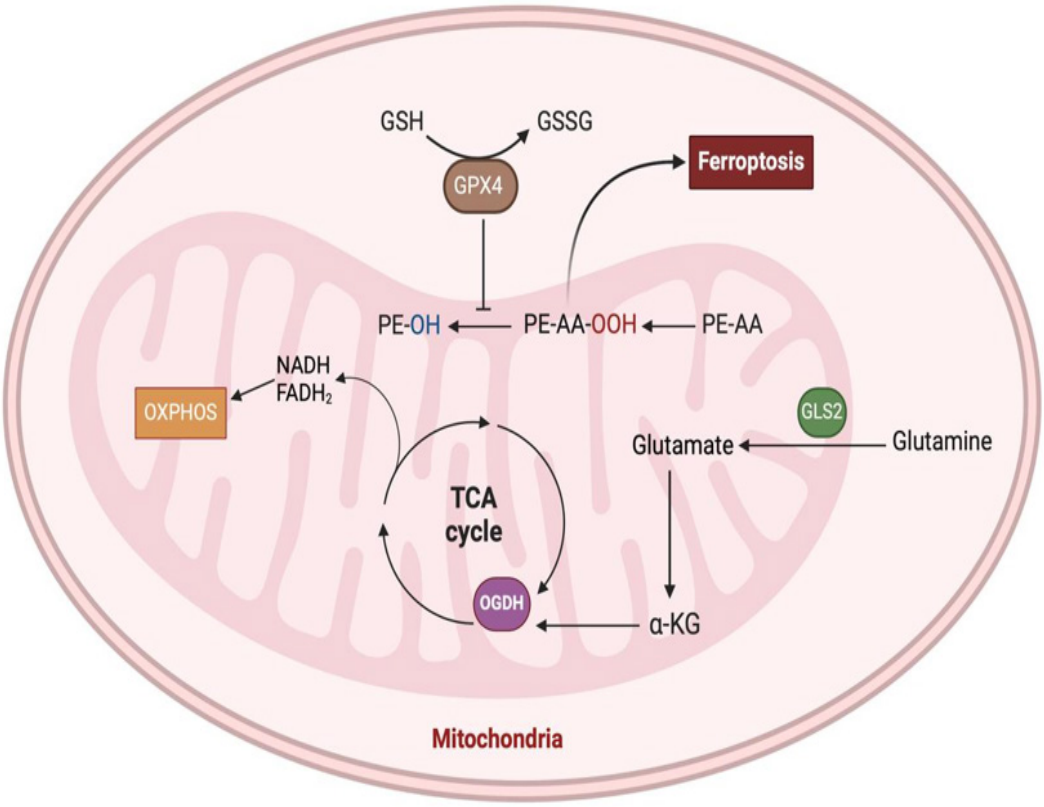

Figure 1. Ferroptosis formation via GPX4

In 2003, Erastin, a novel compound, was reported to kill selective oncogene Ras mutant tumour cell lines (18). Subsequently, it was realised that Erastin-induced cell death did not exhibit processes such as caspase-3 activation, cell shrinkage, chromatin fragmentation or formation of apoptotic bodies (19). It has been found that this type of cell death is associated with increased intracellular ROS levels and can be prevented by iron-chelating agents (20). Ferroptosis is the term Dixon et al. (2012) gave to this kind of cell death (15). The mechanism of ferroptosis involves factors such as intracellular uptake of iron ions via transferrin, cystine uptake, glutamate efflux, synthesis of the antioxidant tripeptide glutathione (GSH) and regular stimulation of GPX4 (21). Ferroptosis is programmed necrosis triggered by extra mitochondrial lipid peroxidation, mainly resulting from an iron-dependent accumulation of ROS (22). The recognition that some tumours are susceptible to ferroptosis suggests that ferroptosis inducers have high therapeutic indices for cancer. The tumour suppressor p53 gene, mutated in approximately 50% of all cancers, is the first protein associated with sensitivity to ferroptosis (23). A study showed that in the relationship between the p53 gene and ferroptosis, the metabolite change required to suppress tumour formation is by inhibiting the transcription of SLC7A11 (Solute Carrier Family 7 Member 11) (24). Suppression of SLC7A11 is sufficient to sensitise cancer cells to an oxidant action, making them prone to ferroptotic cell death (Figure 2) (22).

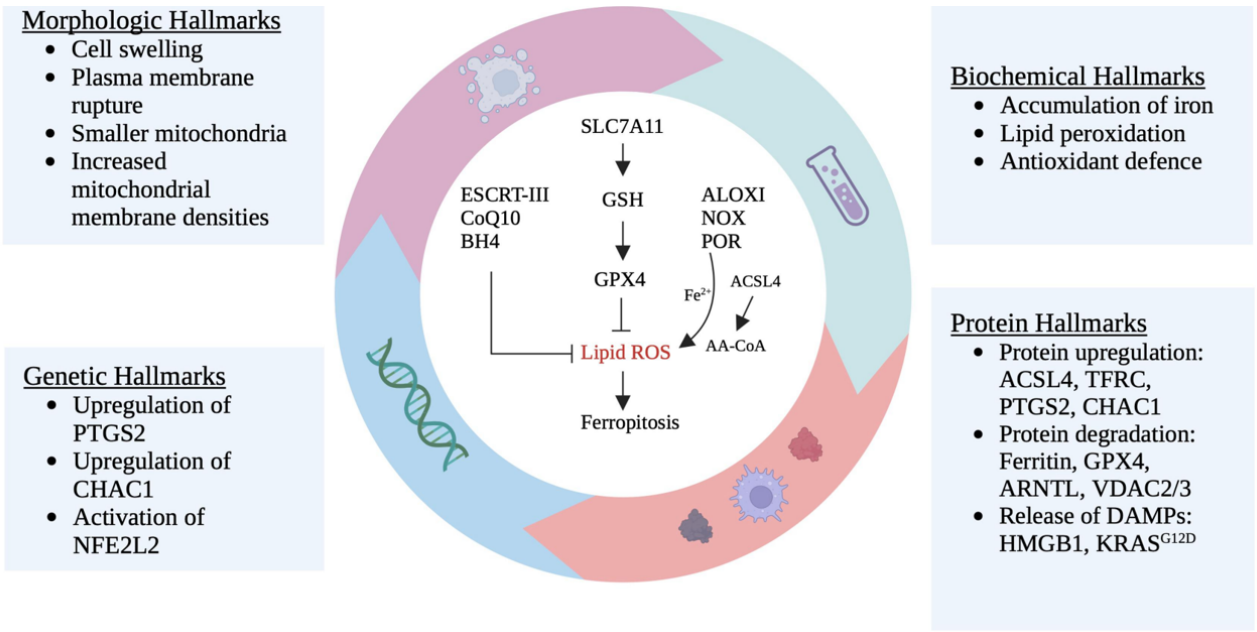

Figure 2. Morphological, genetic, biochemical and protein level characteristics of ferroptosis. (AA-CoA, Arachidonoyl-coenzyme A; ACSL4, Acyl-CoA synthetase long-chain family member 4; ALOX, lipoxygenases; ARNTL, Aryl hydrocarbon receptor nuclear translocator-like; BH4, tetrahydrobiopterin; CHAC1, ChaC glutstione-specific gamma-glutamylcyclotransferase 1; COQ10, Coenzyme Q10; ESCRT-III, endosomal sorting complex III; GPX4, glutathione peroxidase 4; GSH, glutathione; HMGB1, high mobility group box 1; NFE2L2, nuclear factor erythroid 2; NOX, NADPH oxidases; POR, cytochrome P450 oxireductase; PTGS2, prostaglandin-endoperoxide synthase 2; PUFA, polyunsaturated fatty acids; SLC7A11, solute carrier family 7 member 11; TFRC, transferrin receptor; VDAC2/3, voltage-dependent anion channel 2/3).

Molecular Mechanism of Ferroptosis

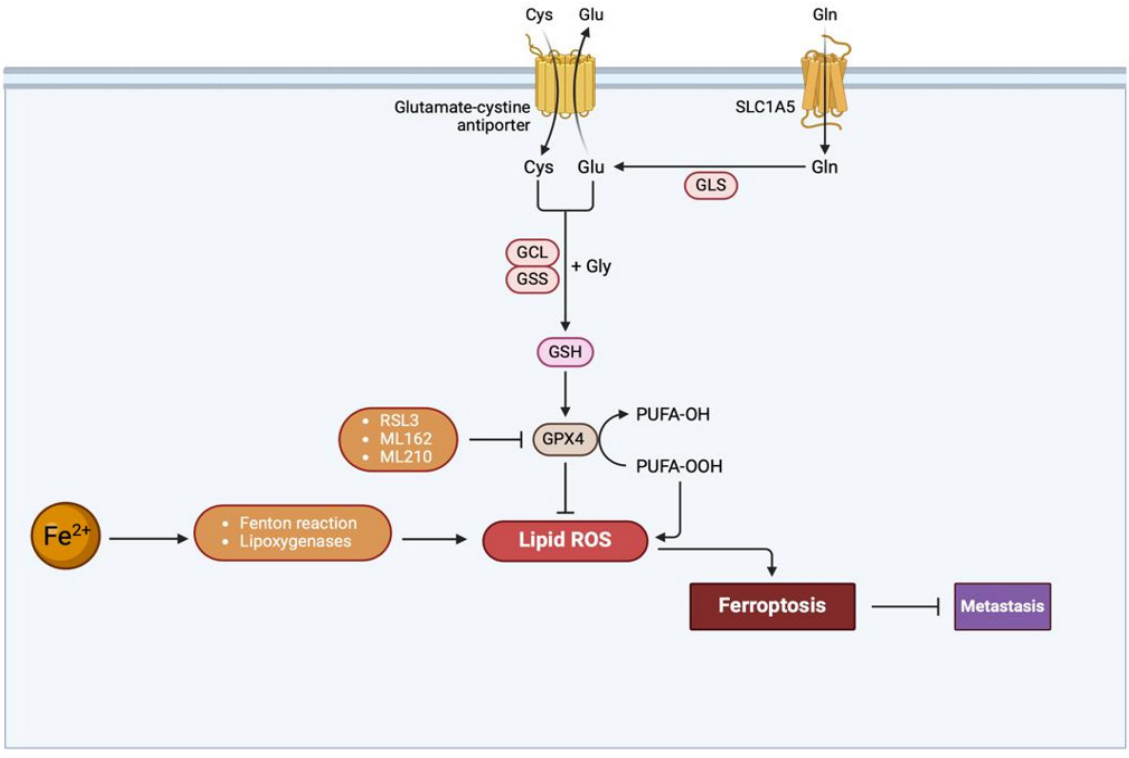

Figure 3. Ferroptosis mechanism

Xc- System

This system is a Na+2-dependent membrane cysteine-glutamate transporter with a heterodimer structure. While intracellular glutamate is transported to the extracellular space, system Xc transports extracellular cysteine into the cell, which is then converted to cysteine for glutathione (GSH) synthesis (25). Inhibition of system Xc leads to the upregulation of the SLC7A11 protein in cells (Figure 3). In light of these findings, it has been proved that system Xc plays a role in ferroptosis concerning GSH synthesis (26).

GPX4 inhibition leads to ferroptosis

Significant indicators of ferroptosis are the increase in lipid peroxidation and decreased expression or activity of the GPX4, a major component of the antioxidant system. Along these lines, ferroptosis induction is emerging as an effective strategy to eradicate therapy-resistant cancer cells (12).

The GPX family consists of several members, including the GPX1-8 (27). GPX4 is a unique gene encoding cytosolic, mitochondrial and nucleolar isoforms. The active site of GPX4 contains the rare amino acid selenocysteine (Sec) encoded by the UGA codon (28). The availability of reduced cysteine and glutathione (GSH) is central to ferroptosis by providing reducing equivalents for optimal function of GPX4 (29). The tumor suppressors p53 (28) and BRCA1-associated protein (BAP1) (30) have been identified as controlling this crucial checkpoint, which results in an innate sensitivity to ferroptosis. Since GPX4 is involved in the effective removal of phospholipid hydroperoxides, its appropriate activity seems to be essential for cell viability.

As part of the conventional process of ferroptosis, GPX4, a lipid peroxide scavenger that shields the membrane fluid from ferroptosis, is depleted or ceases to function via GSH (31). In the lipid metabolism of ferroptosis, compounds such as aldehydes, malondialdehyde and 4-HNE, which are by-products of lipid peroxidation, cause cell damage. Therefore, accumulation of lipid peroxides is considered a hallmark event of ferroptosis (31). Conversely, elevating the unstable iron pool initiates non-canonical ferroptosis (32). More specifically, ferritinophagy-induced cell death is caused by an increase in iron as a result of nuclear receptor coactivator 4 (NCOA4)-mediated degradation of ferritin heavy chain 1 (FTH1) (31, 32, 33).

Ferroptotic Pathway and Iron

High levels of iron in the cell contribute to ferroptosis by triggering the Fenton reaction by ROS (Figure 3) (31). By attaching to transferrin, circulating iron takes the form of ferric iron (Fe+3). Through the membrane protein transferrin receptor 1 (TFR1), Fe+3 enters cells and settles in endosomes. STEAP3's ferrireductase activity in the endosome converts Fe+3 to Fe+2. Ultimately, the release of iron from the endosome and the creation of an unstable iron pool in the cytoplasm are brought about by the divalent metal transporter (DMT1, also known as SLC11A2). Ferritin, an iron storage protein complex of ferritin heavy chain 1 (FTH1) and ferritin light chain (FTL), is where excess iron is kept. An iron efflux pump called ferroportin (SLC11A3), a membrane protein that can oxidize Fe+2 and Fe+3, mediates the iron's outflow (33). TFR1 expression rose, and ferritin expression decreased in a study comparing ferroptosis-sensitive cells with Ras mutations to ferroptosis-resistant cells (34, 35). Therefore, the presence of iron in the induction of ferroptosis is essential for cellular systems.

Drug Resistance and Ferroptosis in Breast Cancer

Breast cancer is a diverse illness with widely disparate molecular traits and clinical manifestations (36). In 2000, Perou et al. classified breast cancer subtypes based on the presence of the estrogen receptor (ER) for the first time in light of gene expression investigations (37). According to this still valid classification, Luminal A, Luminal B, Human epidermal growth factor receptor 2 (HER2) and triple-negative breast cancer (TNBC) subtypes exist. The Luminal A group includes tumours that are ER-positive and Progesterone (PR) positive but negative for HER2. Luminal B subtype includes ER positive, PR negative and HER2 positive tumours. The HER2 positive group includes tumours that are ER negative and PR negative but HER2 positive. Finally, TNBC includes tumours that are all three negative (37). These four types of breast cancer not only differ in their gene expression signatures.

They also lead to different prognoses in patients. Hormone receptors (HR), especially the estrogen receptor (ER), play essential roles in the development and progression of breast cancer (38). Although HR-negative breast cancer is sensitive to chemotherapy in initial treatment, tumour recurrence occurs frequently. Drug resistance is believed to be one of the most common causes of tumour recurrence and is associated with a poor outcome for HR-negative breast cancer patients (39). The development of multi-drug resistance (MDR) is a common phenomenon in many types of cancer. This development of resistance still leads to poor results in many chemotherapeutic treatments today. One of the critical factors limiting the effectiveness of anticancer drugs in the treatment is the resistance mechanisms of tumor cells against chemotherapeutic agents, which develop spontaneously in some cancer types and after chemotherapy in others (40). The resistance to these drugs shown by tumor cells results from the expression of membrane proteins that allow drugs to be excreted from the cell and cause a decrease in the concentration of drugs in the cell (41). An underlying mechanism of MDR is the cellular overexpression of P-glycoprotein (P-gp), which creates an efflux effect for various anticancer drugs (42). P-gp is encoded by the MDR1 gene,, and the overexpression of P-gp in cancer cells has been reported to be a therapeutic target for overcoming multidrug resistance (43). Therefore, in a subsequent study, MDA-MB-231 breast cancer cells were shown to have multidrug resistancethis, which was associated with upregulation of P-gp (44). Anthracyclines and taxanes are among the chemotherapeutic agents that lead to the development of MDR in breast cancer (45). In terms of the development of treatment resistance and metastatic potential in breast cancer, triple-negative breast cancers have an abysmal prognosis, and patients are lost in the early period due to these reasons. Fifty per cent of breast cancer patients are treated with regimen standard neoadjuvant chemotherapy regimens, including Doxorubicin (Adriamycin) (Dox), which belongs to the anthracycline family (46). Dox is used in patients in both early and late stages and has cardiotoxic side effects (47). Dox has more than one mechanism of action in cancer cells. Firstly, it causes DNA synthesis inhibition by inhibiting topoisomerase II via DNA polymerase (48). It is also reduced to form free radicals, generating ROS and causing oxidative damage to cellular DNA and mitochondria. This oxidative damage also increases lipid peroxidation in cells (49). Furthermore, overexpression of ABC transporter such as multiresistant protein 1 (MRP1/ABCC1), breast cancer resistant protein (BCRP/ABCG2) and P-glycoprotein (P-gp/ ABCB1/MDR1) have a significant impact on MDR (50,51).

Conclusion

In recent studies, it has become essential to understand ferroptosis and other cell death types, especially for cancer treatment, and to conduct detailed research on the effect of inhibition and activation of these pathways. Research into ferroptosis's potential to help breast cancer patients overcome their treatment resistance has also advanced as a result of studies. Thus, GPX4 is emerging as a critical ferroptotic target triggered by various ferroptosis inducers, including Erastin and RSL3 agents. These data suggest that ferroptotic cell death may play a key role in inhibiting breast cancer cell growth. Therefore, targeting ferroptosis may have great potential for anticancer therapy in breast cancer patients with drug resistance. In conclusion, further investigation of ferroptosis will shed light on the understanding and treatment of cell death-induced diseases.

Acknowledgements
None
Conflict of interest
None
Funding
None

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