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| RESEARCH ARTICLE

Nanoparticle-induced Ferroptosis for Cancer Therapy

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| ABSTRACT
Ferroptosis is a recently identified form of non-apoptotic regulated cell death (RCD). It is primarily characterized by the accumulation of lipid peroxide, which is iron-dependent. Ferroptosis is essential for the treatment of tumors, renal failure, and ischemia reperfusion exposure (IRI). Ferroptosis and nanomedicine are now the subjects of intense study and clinical attention. There is, however, a limited amount of data on the precise molecular pathways behind ferroptosis and the contribution of nanoparticles. This work provides a thorough overview of ferroptosis, its regulations, and the various mechanisms by which iron- and non-iron-based nanoparticles potentially trigger ferroptosis in the context of cancer therapy. We investigated the most recent developments in ferroptosis research and nanoparticles as ferrotosis-inducing agents by performing extensive literature studies based on the notion of ferroptosis and cancer therapy and a thorough examination of various publications regarding nanoparticles. Our results suggest that tumor suppression and treatment efficacy can both be enhanced by ferroptosis triggered via nanoparticles. New ideas and viewpoints have also been put out for the treatment of ferroptosis-induced cancer, which will make a significant contribution to cancer therapy.

| KEYWORDS

Nanoparticles, cancer therapy, ferroptosis, cell death

| ARTICLE INFORMATION

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1. Introduction

Cancer starts just as the cells grow out of control and the healthy cells crowd out. This makes it difficult for the body to function in the manner it should. This uninhibited proliferative capacity follows oncogenic expression dysregulation, which results in tumor formation. It describes the disease that results when alterations in cells lead to unregulated growth and cell division. Most cancer types lead to the rapid growth of the cells, while others trigger cells to grow and divide at a slower rate. Some forms of cancer lead to conspicuous growths called tumors, whereas others, such as leukemia, do not. Cancer is usually caused by (1) biological factors such as age, gender, and genetic defects, (2) Environmental exposure to UV radiation, (3) Occupational hazards such as chemicals, asbestos, and radioactive materials; (4) Factors relevant to lifestyle (Rathore R. et al., 2017) (Bansode S., 2019). Cancer is commonly treated by surgery, chemotherapy, radiation therapy, bone marrow transplant, immunotherapy, cryoablation, and targeted drug therapy. All these treatments are used to kill or eliminate cancer cells (cell death).

Recently, the traditional understanding of the cell death process has been challenged by the discovery of several novel cell death processes with unique regulatory pathways. Emerging evidence lays the foundation for cancer therapy to trigger ferroptosis, notably to eliminate aggressive malignancies resistant to traditional therapies (Liang C. et al., 2019). Ferroptosis is a newly discovered type of controlled necrosis that is free of caspase interaction and receptor-interacting protein 1 (RIPK1) kinase interaction as opposed to apoptosis or necroptosis (Bebber C. M. et al., 2020). Ferroptosis has attracted considerable attention since it was first detected in 2012 as a new type of cell death caused by lipid peroxidation. As a target for cancer therapy, many

steps have been taken to unfold its pathways and therapeutic potential. Currently, the mitochondrial tumor suppressor fumarase has been discovered and proven necessary for ferroptosis caused by cysteine-deprivation (Gao M. et al., 2019). Ferroptosis has been discovered by ferroptosis-inducing agents (FIN), which are made up of a cluster of small compounds. Despite the important role of ferroptosis in maintaining the survival of normal cells and tissues, it has been increasingly recognized that certain oncogenic pathways are linked to ferroptosis, making cancer cells extremely vulnerable to ferroptotic death (Angeli J. P. F. et al., 2019). Further studies confirmed the relationship between Ras oncoprotein and ferroptosis was becoming uncertain. An undeniable fact is that the ferroptosis inducer, artesunate / erastin, can enhance Ras-reliant ferroptosis in pancreatic cancer or transformed fibroblastic cells, while the leukemia cells are Ras-independent (Xie Y. et al., 2016; Ye J. et al., 2018). Ferroptosis is mainly associated with lipid peroxidation and iron metabolism. One way by which ferroptosis can occur is by inhibiting system Xc^- activity. This will lead to down regulation of glutathione synthesis as the uptake of cysteine will be hindered, resulting in GSH depletion in cancer cells. Ferroptotic cell death is induced when system Xc^- inhibitors inactivate the cystine/cysteine redox cycle to terminate the cysteine supply within the cells, thereby inhibiting the new synthesis of GSH (Liu M. et al., 2019).GPX 4, when inactivated, can prevent the degradation of lipid peroxide and ROS. This buildup of excess ROS can result in wide-range destruction of molecular substances such as proteins, lipids, and nucleic acids of cells (Ray P. D. et al., 2012; Yu H. et al., 2017). The second key factor involved in inducing ferroptosis is iron metabolism. Some studies have confirmed that when iron (Fe) is overfilled in cells, it can produce ROS. These reactive species can lead to the oxidation of proteins, DNA and lipids through a chemical reaction called Fenton reaction or Fenton chemistry. This reaction mainly involves the oxidation of organic substrates by iron (II) (Fe^{2+}) together with hydrogen peroxide (H_2O_2) (Bystrom L. M. et al., 2014; Doll S. & Conrad M., 2017). Recent studies show that nanoparticular trapping (nanocarrier) is a newly developed strategy to improve the delivery of anticancer drugs. By increasing solubility and enabling an increased effect on permeability and retention, the system allows penetration across leaky vasculature and increases accumulation of drugs in the tumor (Zhao Y. et al., 2019). Due to the unique physicochemical properties, nanomaterials can not only compensate for conventional medicinal deficiencies (e.g. low targeting efficiency, poor water solubility, severe side effects, etc.) but also bring in new features (e.g. magnetic properties, photothermal effects, electrochemical properties, etc.) (Wang Y. et al., 2018). In order to attain cancer-specific therapies, nanomaterials have been synthesized in a such a way as to increase accumulation of ROS after cellular uptake, which eventually leads to death of the cell. Most importantly, the nanoscale nature of manufactured nanomaterials has rendered them suitable to passively target tumor tissues via enhanced permeability and retention (EPR) effect. There have been reviews focusing on the mechanisms or inducers and ferroptosis inhibitions. This review emphasizes nanoparticles as a type of nanomaterial and how these nanoparticles induce ferroptosis, which is intended for cancer therapies.

2. Ferroptosis and its regulations

2.1 Molecular mechanism

In the past years, there has been wide research specifically on the mechanisms involved in the initiation and inhibition of ferroptosis. Several molecular mechanisms, such as inhibition of Xc^- activity/GPX4, lipid peroxidation, and iron toxicity, are fundamental mechanisms of ferroptosis (Angeli J. P. F. et al., 2019).

2.1.1 System Xc^- mediated regulation

When we talk about ferroptosis, the first mechanism we take into consideration is the inhibition of systemic Xc^- which directly inhibits GPX4. System Xc^- can be defined as a cysteine/glutamate exchange transporter found on the cell membrane responsible for importing extracellular cysteine and swapping it for intracellular glutamate (Su Y. et al., 2020). System Xc^- is Na^+ dependent and is characterized by a hetero-dimer on its surface. It consists of a twelve-pass transmembrane transporter protein SLC7A11, combined with the SLC3A2 single-pass transmembrane regulatory protein. These two proteins are connected by a disulfide bond (Bridges R. J. et al., 2012). It serves as an intermediate and sustains the intracellular levels of GSH as well as extracellular cysteine. The reduced form of cystine is cysteine and serves as a prototype from which GSH is synthesized. Notably, GSH is one of the abundant antioxidants which shield the organism from ROS (Dang D.-K. et al., 2017; Toyokuni S. et al., 2017). Cysteine is produced by the liver in the course of methionine metabolism. Not all cells are capable of generating cysteine. In order for cancer cells to keep growing, they will require amino acids from their environment (Gout P. et al., 2001). The supply of cysteine comes from a nearby somatic cell when there are low concentrations of cysteine in circulation. Additionally, cancer cells that have system Xc^- transporter expression on their membranes can facilitate the uptake of cysteine from their neighboring surroundings. The livelihood of some cancer cells is reliant on amino acids, thus making the transporter a powerful target for cancer therapies (Edinger A. L. & Thompson C. B., 2002). Glutathione peroxidases (GPXs) are enzymes that catalyze the reduction of ROS. When system Xc^- is inhibited, there is a reduction in cysteine uptake. Furthermore, a decrease in cysteine uptake results in GSH depletion (Dixon S. J. et al., 2014). GSH, as we know, is a cofactor of GPX4, so whiles GSH is being depleted, GPX4 is also being inactivated. Inactivation of GPX4 will lead to the build-up of lipid peroxides and ROS, gradually causing ferroptosis to occur (Angeli J. P. F. et al., 2014; Dixon S. J. et al., 2012). This is where erastin, a ferroptosis inducer, comes in. Erastin mediates the inhibition of system Xc^- function, causing GSH reduction and inactivation of GPX4, thus triggering ferroptosis (Cao J. Y. & Dixon S. J., 2016; Yang W. S. et al., 2014). Recent studies have also found a tumor-suppressing gene, p53, to be linked with ferroptosis (Galluzzi L. et al., 2015). It was reported that p53 had the capability of inhibiting the absorption of cysteine as well as exposing the cells to non-apoptotic ferroptotic cell

death by subduing SLC7A11 (Jiang L. et al., 2015). In another study conducted, it was determined that mutations of p53 and K98 could not bind to the promoter of the SLC7A11 gene. Hence, tumor suppression could not be achieved. The reason was that there was an inadequacy in acetylation. Owing to this, there should be an abrupt check whenever a p53-mediated ferroptosis pathway is chosen (Li T. et al., 2016; Wang S.-J. et al., 2016).

2.1.2 GPX regulation

GPX4 can be described as an extraordinary component of the peroxidase family, with its main function as an inhibitor of lipid peroxides in the ferroptosis process (Yang W. S. et al., 2014). GPX4, as an antioxidant, can reduce lipid peroxides in the cell membrane and gradually prevent the death of cells caused by oxidative damage (Garry M. R. et al., 2008). Additionally, it can cause hydrogen peroxide degradation into water or alcohols with the help of GSH (Go Y.-M. & Jones D. P., 2010). RSL3, a standard inducer of ferroptosis, when bound to GPX4, can inactivate it, thereby causing ferroptosis (Yang W. S. et al., 2014). When this happens, ROS builds up in the cell leading to ferroptosis. With the aid of another strategy, RSL3 can attach to GPX4 active site and inhibit its enzymatic activity. It was also discovered that when GPX4 is overexpressed, the cells could be shielded from an induced death caused by RSL3. However, when the GPX4 gene is reduced, ferroptosis is likely to occur. This deduces that GPX4 is a crucial factor in the control of ferroptosis induced by RSL3 (Yang W. S. & Stockwell B. R., 2008). Another new inducer known as FIN56 was discovered by (Shimalda et al., 2016a). This compound had the ability to retain the RAS oncogenes selectivity. Moreover, it can reduce the quantity of GPX4 by degradation. FIN56 works by acting on acetyl-CoA carboxylase (Shimada K. et al., 2016b). Any cell death induced by FIN56 is followed by ROS accumulation. The reason why FIN56 doesn't fall under the category of system Xc- inhibitor is that cells were handled with it and did not show any depletion in GSH levels. The only effect they had on the cell was the loss of GPX4 (Dixon S. J. et al., 2015).

2.1.3 Role of lipid peroxidation in ferroptosis

In relation to ferroptosis, another crucial event is lipid peroxidation. This is because it impairs the cell membrane structure and subjects the cell to suicide (Latunde-Dada G. O., 2017). Lipid plays a vital role in the phospholipid bilayer. The build-up of lipid ROS caused by too much iron can generate lipid peroxides. These peroxides will eventually trigger ferroptosis to occur in the cell (Reed T. T., 2011). From Fenton chemistry, we know that fatty acids are highly susceptible to undergoing oxidation. At this point, the antioxidant shield wall serves as an armor to fix the damaging free radicals in the inner cell membrane. Lipid radicals can react with other PUFA's in neighboring cells and form more peroxides needed for ferroptosis. Although repair and maintenance take place, if these mechanisms are overpowered, then the cell will be subjected to death (Doll S. et al., 2017; Skouta R. et al., 2014). Polyunsaturated fatty acids (PUFA) are those likely to undergo degradation, and this induces ferroptosis. At normal cell levels, the reduction of lipid peroxides to lipid alcohols by GPX4 can help to shield the cells from oxidative stress. However, this cannot take place when GPX4 is inactivated. PUFA's are very lethal to the cells and can damage them. Hence, the more lipids are oxidized, the increase the rate of ferroptosis (Stockwell B. R., 2018). Additionally, an abundance of PUFA's in the phospholipid membrane will determine whether ferroptosis will occur or not.

3. Mechanism through which nanomaterials can induce ferroptosis

Nanomedicine has been extensively explored for effective cancer imaging and targeted cancer therapy (Kim S. E. et al., 2016). By increasing the delivery of therapeutics, nanomaterials intended for targeting cancer may have therapeutic potential, but their relationships with cancer in clinical studies and their lengthy influence on cells remains unclear (Duncan R. & Richardson S. C., 2012). Several mechanisms are believed to be involved in the process of ferroptosis. The ferroptosis process is triggered by the inhibition of cysteine import, inactivation of GPX4 activity, glutathione depletion, lipid peroxidation, and excessive buildup of lipid-based ROS. Various studies have shown the effectiveness of cancer killing by triggering ferroptosis, which is achieved primarily by increasing the levels of intracellular ROS and inactivating the activity of GPX4 (Shimada K. et al., 2016a). Nanomaterials can release their own iron or loaded endogenous iron in the lysosome after endocytosis, which can be involved in the Fenton reaction to produce ROS and induce lipid peroxidation (Shen Z. et al., 2018b). Due to the need to enhance the tumor-sensitivity of ferroptosis-inducing agents, tumor-responsive nanomaterials are often used (Yue L. et al., 2017). In addition, nanomaterials are able to induce ferroptosis with the aid of other molecules such as proteins and genes. There are several mechanisms involved in ferroptosis in animal cells. The three main mechanisms involved in nanoparticle-induced ferroptosis include the following (Zheng H. et al., 2021):

1. Membrane impairment
2. Mitochondria damage
3. Lysosome dysfunction

The manner and mechanism via which nanoparticles are able to initiate ferroptosis in an animal cell are shown in **Figure 1**. Ferroptosis occurs via one or all of the pathways simultaneously.

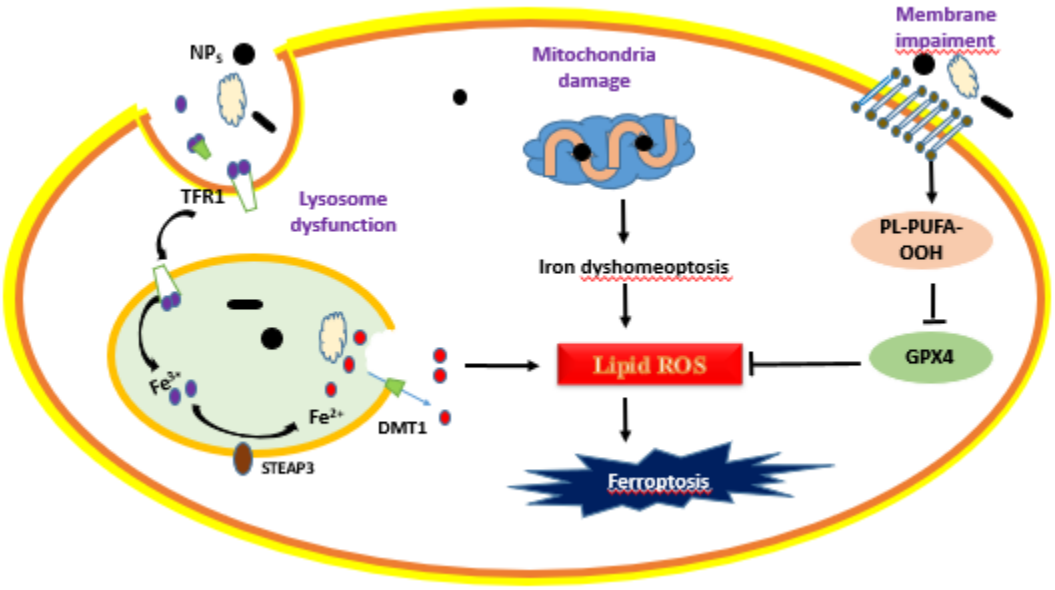

Figure 1. Nanoparticle-induced ferroptosis

Ferroptosis is initiated via various signal pathways, such as Fe^{2+} accumulation, glutathione depletion, and lipid peroxidation. (Zhang et al., 2010) conducted a study in order to find out how "Iron free" zinc oxide nanoparticles with ion-leaking properties disrupt intracellular ROS and iron homeostasis to induce ferroptosis. It was discovered that based on their size, shape, and zeta potential, the common mechanism that led to ferroptosis was excess ROS. This happens after they have been internalized and thus move to the mitochondria and dysregulate the mitochondrial antioxidant defense system leading to over-accumulation of lipid ROS (Shen Z. et al., 2018a; Zhou Z. et al., 2017). Alternatively, ferroptosis was also induced as the ZnO NPs are endocytosed into the lysosome, dissolve, and release zinc ions. The existing nanoparticles and zinc ions are able to trigger the p53 gene, which could suppress SLC7A11, a component of the cystine/glutamate antiporter causing glutathione depletion (Jiang L. et al., 2015; Ou Y. et al., 2016). GSH depletion also causes the excessive buildup of ROS, leading to ferroptosis (Murphy M. E., 2016). Another major deduction from their study was ZnO NPs-induced dysregulation of iron homeostasis. Mitochondria contain dynamic pools of these metal ions that are incorporated into corresponding metalloproteins (Slepchenko K. G. et al., 2017). Thus, Zn^{2+} overload-triggered mitochondrial injuries may induce the dysregulation of dynamic metal pools (including the labile iron pool), resulting in the elevation of intracellular iron. Iron overload causes mitochondrial oxidative stress leading to mitochondrial dysfunction and ultimately ferroptosis occurrence (Finney L. A. & O'Halloran T. V., 2003) as shown in **Figure 2**.

Another instance of nanoparticle-induced ferroptosis is seen in superparamagnetic iron oxide nanoparticles (SPION). These nanoparticles were engineered with a magnetic photosensitizer and sofarenib(Srfn) (Liu T. et al., 2018). This complex, Fenton-Reaction-Accelerable magnetic NIR photosensitizer self-assemblies (CSO-SS-Cy7-Hex/SPION/Srfn) was constructed to overcome the therapy-resistant state of cancer, which is epithelial-to-mesenchymal transition (EMT) cells. Viswanathan et al. found that therapy-resistant cancer cells, which cross epithelial-mesenchymal transformation (EMT), were more susceptible to ferroptosis. In other words, ferroptosis could suppress EMT cancer (Viswanathan V. S. et al., 2017). This ferroptosis therapy involved lipid hydroperoxides (LPO) bursts. There are three ways to produce LPO leading to ferroptosis: Firstly, the oxidation/reduction response disulfide bond can consume GSH and release the drug, then Sorafenib expression of system xCT (cystine/glutamate antiporter) in conjunction with depression of GSH production produces LPO (Stockwell B. R. et al., 2017). Secondly, SPION(Fe^{2+}, Fe^{3+}) can release Fe^{2+} in late endosomes (acidic environment), which produces a high catalytic activity for the Fenton reaction to produce LPO (Bolobajev J. et al., 2016). Thirdly, the NIR nanophotosensitizer (Cy7-Hex) targets mitochondrial membranes and produces LPO under the illumination of NIR, which was accumulated ~18-fold in the treatment group in breast cancer cells (Yu Z. et al., 2015). Results of the in vivo pharmacodynamic tests revealed that this small particle-sized nanodevice with high cytotoxicity increased Srfn circulation and shortened the period of epithelial cancer treatment.

The mechanism via which nanoparticles are able to induce ferroptosis is demonstrated in a study conducted by (Sang et al.,2019). In their work, a Black Hole Quencher (BHQ)-based fluorescence "off−on" nanophotosensitizer complex assembly (CSO-BHQ-IR780-Hex/MIONPs/Sor) was developed. The complex assembly included CSO-connected BHQ-IR780-Hex, -loaded magnetic iron oxide nanoparticles (MIONPs), and sorafenib (Sor). The reason why they constructed a nanoparticle with the ability of photosensitizer-controlled, fluorescence "off−on" was to prevent lower tumor-specific and poor imaging of tumors (Sang M. et al., 2019). Since it

is deduced that the morphological alteration of the mitochondrial membrane plays a significant role in the ferroptosis process induced by LPO, hence it's of great importance to design a functional NIR photosensitizer to anchor the mitochondrial membrane. Interestingly, it proved to be an efficient LPO accumulation strategy for the successive occurrence of ferroptosis (Agostinis P. et al., 2011; Brown H., 2004). Two key pathway mechanisms for LPO accumulation and ferroptosis occurrence in their study were: one was xCT/GSH/GPX-4 system attenuated, and the other was ROS and iron concentration overload in cancer cells to promote a Fenton reaction (Liu T. et al., 2018). First of all, after the NP complex system was introduced into the animal cell, it disintegrated and the NIR photosensitizer anchored the mitochondrial membrane. As a near-infrared laser beam was shed on the animal, a large amount of ROS was produced. The ROS reacted with the phospholipids and caused a LPO burst. As the mitochondria collapsed, the cell was subjected to ferroptosis (Yu Z. et al., 2015). Simultaneously, MIONPs (Fe^{2+}, Fe^{3+}) can release Fe^{2+} under an acid environment in the lysosomal compartment, which is crucial for a Fenton reaction to take place (Bolobajev J. et al., 2016). Sorafenib inhibited the expression of xCT and GPX-4 as well, leading to GSH depletion. A decrease in GSH caused the buildup of more ROS and LPO in the cell (Hall M. D. et al., 2014; Stockwell B. R. et al., 2017). Their study conducted both *in vivo* and *in vitro* confirms the nanosystem processed extreme cytotoxicity to tumor cells, and showed an excellent long-circulating tumor accumulation ability and effectively inhibited tumor growth in tumor bearing mice.

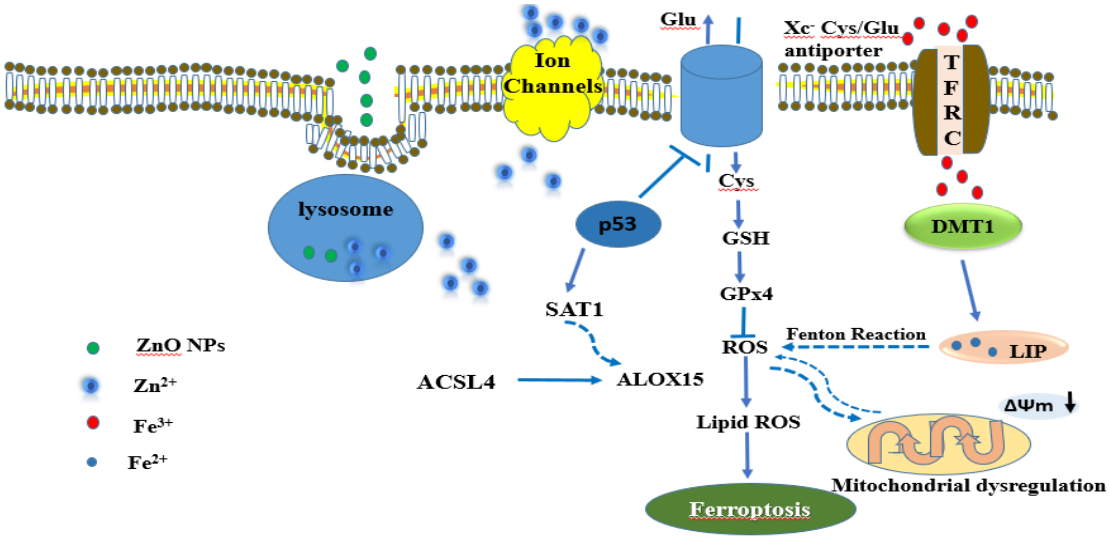

Figure 2. A proposed mechanism of ZnO NPs-induced ferroptosis

4. Nanoparticles

Cancer-specific and targeted therapies are able to differentiate between normal and cancer cells. Research has found and proven that targeted therapies are much more effective than the prevailing methods. The standard method, which involves non-specific and systemic drug delivery, proved to have certain effects such as rapid drug elimination, risk of higher dosage as well as increased toxicity. Nanoparticles can be defined as forms of nanomaterials that have a three-dimensional nano-scale dimension (Galluzzi L. et al., 2015; Jeevanandam J. et al., 2018). In recent years, there has been a great interest in technological advancements due to their suitable physical, chemical, and biological properties. They also have improved efficiency as compared to bulky materials. Recently, nanoparticles have been applied in emerging fields such as tumor targeting, diagnostic imaging, and therapy (Farokhzad O. C. & Langer R., 2009). They are nano-sized materials that serve as embedded drugs, imaging agents, and genes (Petros R. A. & DeSimone J. M., 2010). Nanoparticles have been able to overcome the challenge of conventional chemotherapy. Mostly, their aim is to surmount the resistance mechanism of cells and have minimal toxicity to healthy tissues (Zhang J. et al., 2010). Nanoparticles have desirable features which can be tuned and thus makes them powerful cancer therapy vectors. The sizes of nanoparticles play a crucial role in determining the fate of particles (Choi H. S. et al., 2007; Najafi-Hajivar S. et al., 2016). Those with sizes smaller than 7nm in hydrodynamic diameter when used, fall into renal filtration and excretion in urine, whiles nanomaterials larger than 100nm are more often removed from the circulation by phagocytic cells (Davis M. E. et al., 2010; Decuzzi P. et al., 2009). The surface of nanoparticles can be functionalized with positive charges to enhance cancer cell internalization. Polymers such as polyethylene glycol can be added to the nanoparticles to improve their circulation half-life and also the accumulation of the particles in the tumor areas (Qi H. et al., 2014). Although the surface functionalization of nanoparticles is good, however, it can affect their internalization in cancerous cells (Perrault S. D. et al., 2009). Scientists have sought to overcome this challenge by creating tumor-specific ligands and attaching them to the surface of nanoparticles. This phenomenon is referred to as active targeting. With this, there is the provision of adequate nanoparticle internalization (Kim C. et al., 2010).

4.1 Types of nanoparticles

The two main types of nanoparticles used for ferroptosis-based cancer therapy are:

- Iron-based nanoparticles
- Non-iron based nanoparticles

4.2 Iron-based nanoparticles

Iron-based nanoparticles are specifically designed to target the tumor areas passively. After this, they are able to give out the exogenous iron in the lysosome containing acid. Hereafter, the Fenton reaction efficacy is increased, and through the accumulation of ROS, the cancer cells could be killed effectively. Iron plays a key role in inducing ferroptosis. Iron-based nanoparticles, being a part of emerging nanomaterials, are considered for ferroptosis applications. Several nanoparticles, in recent years, have sought to trigger ferroptosis. Some of these include iron oxide nanoparticles, amorphous iron nanoparticles, iron-doped nanoparticles, iron-based upconversion nanoparticles, and many others.

4.2.1 Iron oxide nanoparticles

Iron oxide nanoparticle is a promising nano-biomaterial for treating iron deficiency or as drug carriers and contrast agents as well as a stimulator to elicit ROS generation. However, because of their intrinsic structure, therapeutic agents are hard to be loaded by them alone.

They are one of the important types of inorganic nanoparticles, with their sizes ranging from 1-100nm in diameter. They are also good for magnetic resonance imaging (MRI) purposes because they can be visualized. One other characteristic of this class of nanoparticles is that they are biodegradable. After undergoing degradation, the iron can readily be absorbed in the body (Peng X.-H. et al., 2008; Sun C. et al., 2010).

They are types of iron-based nanoparticles that have been asserted and confirmed by the FDA for iron-deficiency treatment, as contrasting agents, and as drug agents in cancer therapy. Ferumoxytol is a formulation of iron-oxide nanoparticles prepared intravenously and authorized by the FDA. The medicinal effects of ferumoxytol were determined, and the inhibition of mammary tumor growth and lung cancers through the ferroptotic pathway was discovered (Zanganeh S. et al., 2016). In-vitro studies where adenocarcinoma cells were cultivated with ferumoxytol, as well as macrophages, were conducted. There was a heightened display of caspase-3 activity. The macrophages showed an elevated inflammatory, Th1-type feedback. Popularly, the feedback given by the M1 macrophages was able to produce excess H_2O_2 and also merge with Fe^{3+} or Fe^{2+} in the cells to produce lethal OH by the Fenton chemistry reaction pathway (Sindrilaru A. et al., 2011). Ferumoxytol, used 'in-vivo' in tumor-bearing mice, suppressed the adenocarcinoma tumors greatly. Pretreating the mice models with ferumoxytol can serve as an inhibiting factor for liver metastases (Zanganeh S. et al., 2016).

4.2.2 Assembled Iron oxide nanoparticles

Li et al. (Li W.-P. et al., 2016) synthesized a form of assembled iron oxide nanoparticles, namely; H_2O_2/Fe_3O_4-PLGA (poly-lactic-glycolic acid) polymersomes. These kinds of Fe_3O_4 nanoparticles are capable of triggering ferroptotic cell death by accelerating the Fenton reaction and accumulation of ROS. Upon the divulgence of the ultrasound diagnostic system, these polymersomes are able to exhibit imitations of reflections and ROS-regulated cancer therapy. In their study, they found out that the aqueous H_2O_2 wrapped up in the pith of the polymersome, which was hydrophilic with Fe_3O_4 nanoparticles arranged in the sheath. When the ultrasound was exposed to the polymersome, the entrapped H_2O_2 inside was unbound and departed through the PLGA polymersome interruption. As a result of this, it reacts with Fe_3O_4 in the membrane to generate OH via the Fenton chemistry pathway. Their results signify an effective cell death and inhibition of tumor growth in the absence of heat.

4.2.3 Fe-Pt nanoparticles

Yue et al. (2017) discovered another class of iron-based nanoparticles called the Fe-Pt nanoparticles, which appeared to be pH-sensitive and can be applied in both MRI and CT imaging during cancer therapy. The Fe-Pt NPs had the ability to give out reactive Fe ions due to the low pH concentration in the cancerous sites. With this effect, H_2O_2 degradation is catalyzed and converted into ROS intracellularly; thus, triggering ferroptotic cancer cell death. Further conjugation with folic acid (FA), iron-Pt-dimercaptosuccinnic acid, or PEGylated composite nano assemblies resulted in effective targeting and localization of nanoparticles into the tumor sites with minimal toxicity to healthy cells. Additionally, these nanoparticles can reduce the MRI signal and rather elevate the ROS signal. This is very useful in the original visualization of iron released in cancer cells (Yue L. et al., 2017).

4.3 Non-iron based nanoparticles

Currently, there is still an extensive range of non-iron based nanoparticles being discovered for biomedical applications. There are various nanoparticles without iron that are capable of triggering cell death by using endogenous iron (Lin H. et al., 2018; Ranji-Burachaloo H. et al., 2017; Wang S. et al., 2018). Iron is a crucial factor required for ferroptosis occurrence. However, for the ideal

Fenton reaction to incite ferroptosis, relatively low pH (2-4) and large Fe dose (75 mg Fe/kg) are required, making it extremely difficult for these agents to be used therapeutically as a standalone drug. Furthermore, non-ferrous metals with various oxidation states, such as manganese and copper, were also used to design ferroptosis-inducing agents, displaying the versatility of therapeutics based on ferroptosis. A study was conducted by Kim et al. to develop a form of ultrasmall silica nanoparticle without any iron. They synthesized ultrasmall αMSH-PEG-C′ dots (6 nm) with a fluorescent (Cy5-encapsulated) core, a poly (ethylene glycol) (PEG) coating, and an α-melanocytestimulating hormone (αMSH)-modified exterior. These nanoparticles were used on the cancer cells, which were deprived of amino-acid. They discovered that the cell death triggered by the nanoparticle treatment under deprived conditions of amino acids was confirmed to be ferroptosis and not any other. The 'in-vivo' studies performed in tumor-bearing mice reports showed that there was an effective inhibition of tumor growth and a fragmental regression of tumor as compared to the group of mice treated with only saline. This indicated that the silica nanoparticles were a remarkable ferroptosis-inducing factor for cancer-specific therapy. Other forms of nanoparticles were synthesized, such as low-density lipoprotein nanoparticles, and this was merged with raw omega-3 fatty acid and docosahexaenoic acid (LDL-DHA). This was intended to kill the cancer of the liver cells and reduce the growth of liver tumors in the rat. As per the results, it was observed that both the rat and human hepatocellular carcinoma (HCC) cells treated with these kinds of nanoparticles went through lipid peroxidation, GSH depletion, and GPX4 inactivation before the death of cells. The cell death could not have occurred without cellular iron partaking in it. GPX4 is regarded as the key mediator od LDL-DHA induced ferroptotic death. All these notable properties show that LDA-DHA induced cell death is ferroptosis. 'In-vivo' studies performed also demonstrated the obstruction of tumor growth in HCC prototypes in rats.

Lin et al. (2018) designed manganese dioxide (MnO_2)-coated mesoporous silica NPs (MS@MnO_2 NPs) intended for cancer therapy. As the nanoparticle is introduced into the cell, MnO_2 initiates the conversion of glutathione to disulfide (GSSG), followed by the release of Mn^{2+}. Eventually, in the presence of HCO_3^-/CO_2, Mn^{2+} activates HO production from H_2O_2, increasing intracellular oxidative stress to a tumoricidal degree. It is demonstrated that MS@MnO_2 NPs only catalyze the generation of ROS in the presence of $NaHCO_3/CO_2^-$ after incorporation with methylene blue (MB), which easily degrades upon HO trauma. This enhances tumor sensitivity since elevated $NaHCO_3/CO_2$ is prevalent in the acidic tumor microenvironment. Besides that, under increased GSH concentration, the ROS-generating capacity of MS@MnO_2 NPs is also increased, which is another tumor cell characteristic. Most importantly, the *in vivo* research suggests that MS@MnO_2 NPs have reliable and promising anticancer effects, promoting the concept of using nonferrous metal to kill cancer cells by ferroptosis in a Fenton-like reaction (Lin L. S. et al., 2018).

4.4 Iron-containing nanoparticles for ferroptosis-based cancer therapy

In recent years, iron-containing nanoparticles have been applied in the area of chemodynamic therapy. Chemodynamic therapy (CDT) has proven to be a promising strategy for the management of cancer because of its high specificity toward a tumor microenvironment. Nanoparticles containing iron are able to induce ferroptosis in melanoma cells (Tang Z. et al., 2019; Wang L. et al., 2018). A study was conducted by Wang et al. where redox- and light-responsive (RLR) nanoparticles that contained iron to target a tumor microenvironment (TME) were devised. They showed specificity in targeting the overexpressed tumor-affected cells in the animal model (Wang S. et al., 2019). Another important application of iron-based nanoparticles in cancer treatment is magnetic hyperthermia. This method involves delivering magnetic nanoparticles suspended in an aqueous solution (a ferrofluid) into a tumor cell. After accumulation in the tumor area, the NPs are exposed to an alternating magnetic field that causes heat to be released. Fe_3O_4-Pd Janus nanoparticles were used to inhibit tumor progression of breast cancer cells via increased magnetic photo-heating and ROS production (Ma X. et al., 2019b). α-Fe_2O_3 nanoparticles coated with ultrasmall gold (Au) nanoseeds displayed a good therapeutic potential in cancer cells. Superparamagnetic properties of iron oxide nanoparticles have shown effective results in the hyperthermia treatment of solid tumors such as prostate cancer (Curcio A. et al., 2019; Zhong D. et al., 2019) and glioblastoma (Rego G. N. et al., 2020; Rego G. N. d. A. et al., 2019). A nanosystem containing DOX, $FeCl_3$, and tannic acid was constructed. This nanosystemwas used in an animal study to induce ferroptosis. The mechanism of ferroptosis was via decreased intracellular GSH levels and lipid peroxidation in vivo (Xiong H. et al., 2019). Similarly, ultrasmall poly (ethylene glycol) (PEG)-modified polydopamine nanoparticles containing either Fe^{2+} or Fe^{3+} have shown to be effective in inducing ferroptosis in tumor-bearing mice via induction of ROS formation and lipid peroxidation and inhibition of GPX4 activity (Chen L. et al., 2019).

In recent years, nanozymes with iron containing nanoparticles have proven to be good anti-cancer agents. Nanozymes are nanomaterials which display innate enzyme-like characteristics. The peroxidase-like behavior of iron containing nanoparticles was first confirmed in 2007 (Gao L. et al., 2007). To date, iron containing nanozymes with multiple enzyme imitative characteristics have been confirmed, such as catalase, peroxidase, or SOD-like activities. (Huang et al., 2019) vividly explained how nanozymes are classified according to their catalytic properties and applications (Huang Y. et al., 2019). An example of a nanozyme used as an anticancer agent is a newly developed one which has been found to be biodegradable in an acidic environment with peroxidase-like catalytic activity along with microwave enhancing dynamic therapy (MEDT) and microwave thermal therapy (MTT) effects (Ma X. et al., 2019a). Microwave irradiation is capable of increasing the rate at which OH is produced in the tumor microenvironment. The newly developed nanozymes have the ability to increase the temperature as well as induce the formation of ROS, in particular

hydroxyl radicals resulting in inhibition of tumor development. The research establishment is constantly striving to enhance current or design more convenient nanosystems for cancer therapy. **Table 1** summarizes recent animal studies with iron nanodevices for cancer treatment by modifying oxidative damage metabolism.

Table 1. Recent animal studies with iron nanodevices for cancer treatment by modifying oxidative damage metabolism.

Tumor Type	Animal Tumor Model	Type of Nanoparticle	Reported Therapy	Mechanism	DOI NO
Breast Cancer	Breast tumor xenograft mouse model	RLR nanoparticle composed of Fe_3O_4 nanoparticles and a nanoflower-like MnO_2 shell	Chemodynamic therapy	overcoming ROS defensive mechanisms and sequential production of theranostic ion species	10.1016/j.biomaterials.2019.119498.
Breast Cancer	4T1 tumor-bearing mice	α-Fe_2O_3 nanoparticles coated with ultrasmall gold nanoseeds	Magnetic resonance imaging, photothermal therapy and radiosensitization	ROS generation and DNA damage	10.1016/j.biomaterials.2019.119369
Breast Cancer	4T1 tumor-bearing mice	Ultrasmall PEG-modified polydopamine nanoparticles containing $Fe^{2+}/^{3+}$	Chemotherapy, Ferroptosis therapy	Increase in ROS, lipid peroxide (LPO), and inhibition of GPX4 activity	10.1021/acsbiomaterials.9b00461
Breast Cancer	4T1 tumor-bearing mice	Fe_3O_4-Pd Janus nanoparticles (JNPs)	Simultaneous magneticphoto hyperthermia and chemodynamic therapy	amplified magnetic-photo heating, as well as elevated ROS production and ferroptosis of cancer cells.	10.1016/j.jphotobiol.2019.111648
Breast Cancer	4T1 tumor-bearing mice	Nanoparticles porphyrin-based metal–organic framework and $MnFe_2O_4$ nanoparticles as the nanoenzyme	Enhanced Photodynamic Therapy	H_2O_2 catalysis to produce O_2 and GSH consumption to decrease the depletion of ROS	10.1002/adfm.201901417
Breast Cancer	4T1 tumor-bearing mice	Nanosystem containing $Fe(OH)_3$ modified upconversion nanoparticles	Synergetic chemo- and photodynamic therapy	Conversion of near-infrared excitation to visible photon energy	10.1021/acsami.8b18427.
Breast Cancer	4T1 tumor-bearing mice	ROS nanoreactor based on coreshell-structured iron carbide nanoparticles	Magnetic Resonance Imaging Guided Cancer Therapy	Ionization of NPs in magnetic resonance imaging	10.1021/acsnano.9b01740
Breast Cancer	4T1 tumor-bearing mice	FeOOH nanoparticles coated with poly(norepinephrine) and loaded with artemisinin (Art)	Photothermal-chemical combination therapy	NPs release ART and iron as well as reaction with H_2O_2 to produce hydroxyl radicals for tumor-specific killing	10.1039/c9ra01289c.

Breast Cancer	4T1 tumor-bearing mice	IONPs modified with glucose oxidase and polydopamine	Photothermal therapy	Conversion of NIR into heat and H_2O_2 into OH to induce cell death	10.1039/c8tb03320j
ER + Breast Cancer	MCF7 tumor xenograft model Balbc	Drug-organics-inorganics selfassembled (DFTA) nanosystem with DOX, $FeCl_3$, and tannic acid	Chemotherapy, Photothermal therapy and Ferroptosis therapy	Photothermal excitation causes drug to be released from DFTA, which combines with a laser group to decrease intracellular GSH	10.1016/j.jconrel.2019.07.029
Breast Cancer	4T1 tumor-bearing mice	Mitochondrial membrane Targeted nanophotosensitizer complex containing SPION and sorafenib	Ferroptosis as cancer therapy	Release of ferrous and ferric iron upon near-infrared radiation leading to LPO burst.	10.7150/thno.36283
Breast Cancer	4T1 tumor-bearing mice	Mitochondrial membrane targeted nanophotosensiti-zer complex containing magnetic IONPs and sorafenib	Ferroptosis as cancer therapy	Magnetic targeting of nano-device and release of Fe^{2+} and Fe^{3+} in tumor cell environment.	10.1021/acsami.9b12469.
Hepatocellular carcinoma	H22-tumor bearing mice and HepG2 tumor-bearing nude mice	PEG-modified nanoparticles loaded with photosensitizer and MnFe2O4 and silica upconversion nanoparticles	Photodynamic therapy	NIR activation, which activates PSs to generate ROS and O_2 needed for a Fenton reaction to take place	10.1039/c9nr04858h.
Glioma	Ectopic glioma tumor-bearing mice	Fe_3O_4-IR806 super particles	Photothermal-photodynamic therapy	Generation of reactive oxygen species (ROS) with the NIR light	10.1016/j.cej.2019.122693
Lung adenocarcima	A549 tumor-bearing nude mice	Modified IONPs with β-lapachone encapsulated in the nanostructure formed by H2O2-responsive polyprodrug and pH-responsive polymer (LaClONPs)	Chemo/chemodynamic combination therapy	Decomposition of NPs in tumor environment to release La and iron, which triggers peroxide formation needed to produce hydroxyl radicals	10.1002/advs.201801986
Prostatic cancer	PC3 tumor-bearing nude mice	γ-Fe2O3 with copper sulfide shell	Photothermal Therapy, Magnetic Hyperthermia and Photodynamic Therapy	Subjection of nanoparticles implanted in the animal model to magnetic hyperthermia	10.7150/thno.30238

Breast cancer	4T1 tumor-bearing mice	Silica nanoparticles with MnO_2 nanoparticles and FeCO	Synergistic Gas therapy (GT) and chemodynamic therapy (CDT)	Generation of ROS and hydroxyl radicals which trigger FeCO to release CO	10.1186/s12951-019-0507-x.
Breast cancer	MCF-7 tumor-bearing mice	Nanogel loaded with magnetic IONPs and 10-hydroxy camptothecin	Enhanced photothermal chemotherapy	MNPs/HCPT-nanogel generates ROS to inhibit tumor growth. The nanocarrier also initiates photothermal therapy in the NIR region.	10.1016/j.apmt.2018.11.008.

5. Conclusion and Future perspective

Cancer therapy still poses a great threat to human beings. To date, though varieties of treatment methodologies have been developed for effective cancer therapy, the main focus has been on the form of cell death known as apoptosis. However, apoptotic-induced cancer therapies which have been discovered so far have not proven to be effective enough. This is due to the problem of apoptosis evasion and anti-apoptosis, which are caused when some apoptotic protein inhibitors are overexpressed. Cancers that possess RAS mutations show some sort of endogenous inhibitory effects of this mutation. Ferroptosis, a new form of non-apoptotic programmed cell death that was discovered in 2012 and depicted by an iron-dependent build-up of lipid peroxides to toxic levels, have been able to provide a better technique and opportunity in overcoming the resistance of apoptosis in cancer cells. Numerous researchers have sought to have a closer look at this phenomenon. Ferroptosis is different from the other forms of cell death in terms of morphology, biochemistry, and genetics. Thus, more efforts have been put into discovering new agents which might be able to induce ferroptosis as well as those intended for cancer specific therapy. In order to meet the requirements of ferroptotic-induced therapy, a number of small molecule drugs and nanomaterials have been introduced as ferroptosis inducers. However, small molecule drugs have certain disadvantages, such as short half-life, rapid renal clearance, and poor selectivity, and this restricts their clinical and therapeutic applications. Nanoparticles have proven to overcome these shortcomings of small molecule drugs due to their unique and remarkable features. Nanoparticle-induced ferroptosis can improve the treatment efficacy, effective localization, and tumor suppression.

The review summarizes the recent advancement in developing some nanoparticles for cancer-specific therapy, which was based on two main things: lipid peroxidation and iron metabolism, illustrating both molecular and pathway mechanisms as well. Iron based nanoparticles were discovered in 2016 through the Fenton reaction and were reported to hinder the growth of tumors. Non-iron based nanoparticles have also been described, and how they are able to trigger ferroptotic cell death. The difference between iron-based and non-iron based nanoparticles lies in the fact that iron-based nanoparticles can provide Fe^{2+} or $Fe^{3+,}$ which is required to catalyze hydrogen peroxide (H_2O_2) and transform it into highly lethal reactive oxygen species via the Fenton reaction, whereas non-iron based nanoparticles make use of the endogenous iron within the cells to improve the ROS production which eventually results in cell death. Many non-ferrous elements with multiple oxidation states, such as the Mn^{x+}/Mn^{x+1}, $Cu/Cu^{2+,}$ Al^0/Al^{3+}, Co^{2+}/Co^{3+}, Ce^{3+}/Ce^{4+}, Ru^{y+}/Ru^{y+1}, and Cr^{3+}/Cr^{6+}, have been explored as highly effective Fenton reaction reagents that can operate under a biologically relevant pH. The concept of ferroptosis is therefore expected to be extended as a type of cell death induced by an abundance of different polyvalent metals beyond iron. Even though nanoparticles can produce a good ferroptotic effect, there are so many problems facing them that need to be taken into account before their clinical and therapeutic applications. Firstly, nanoparticles and ferroptotic-inducing agents should be developed more to improve the Fenton reaction performance. Secondly, more pathways and molecular mechanisms should be established and approved to focus on two or more regulators simultaneously. Thirdly, adverse reactions of nanoparticles and drugs need to be checked, as well as any new positive targeted strategies to induce ferroptosis. Fourthly, iron build-up and release should be enhanced to elevate the iron levels intracellularly. Last of all, the biocompatibility, biodistribution, and immunogenicity of nanoparticles should be improved to ensure drug safety. Most importantly, looking at the future of nanotechnologies, there is the need to integrate all other efforts from oncology, biochemistry, nanotechnology, medicine, and materials science fields in order to invent new initiatives and ideas on how to design nanoparticles for ferroptosis-induced cancer treatment.

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