

REVIEW ARTICLE

Research progress and insights on the role of ferroptosis in wound healing

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Abstract

Ferroptosis is a newly discovered cell death type which is different from apoptosis, autophagy, pyroptosis as well as necrosis in the following aspects: morphology, biochemistry, gene and regulatory mechanisms. Ferroptosis is regulated by multiples of mechanisms such as system Xc⁻ mechanism, glutathione peroxidase 4 (GPX4) mechanism, iron metabolism and lipid metabolism. Currently, ferroptosis has been revealed to be significant in wound healing such as diabetic wound, irradiated wound and ultraviolet (UV)-driven wound. Hence, how to intervene in the pathogenesis as well as the development of wounds and promote the wound healing by the regulation of ferroptosis have become a research hotspot. This review systematically summarises the latest scientific advances of ferroptosis and wound healing fields, with hoping to propose a new insight and advance in the wound treatment.

KEYWORDS

biomaterials, diabetic wound, ferroptosis, iron metabolism, lipid peroxidation, wound healing

Key Messages

- ferroptosis is a newly discovered cell death type which has been revealed to be significant in wound healing such as diabetic wound, irradiated wound and UV-driven wound
- we summarised the latest scientific advances of ferroptosis and wound healing fields, with hoping to propose a new insight and advance in the wound treatment

1 | INTRODUCTION

It has been widely accepted that wound is one of the most common and enduring clinical diseases or complications, which has burdened patients with huge economic costs and social interaction problems, especially chronic wounds. It has been estimated that the cost of chronic wounds care in

the medical system is more than US \$25 billion per year.¹ More importantly, with the growing number of patients who suffer with diabetes mellitus, the incidence of diabetic wound such as diabetic foot has experienced a great growth globally (>6.5 million yearly) and the cost of diabetic wound has been no less than US \$50 000 every year.² Although numerous methods have been applied to

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overcome this clinical issue, the outcomes of wound healing are still poor and the exact mechanisms underlying wound healing are still unclarified.³

In 2012, Dixon first coined the term ferroptosis, a unique iron-dependent form of regulated cell death, which was different from apoptosis, autophagy, pyroptosis as well as necrosis in the following aspects: morphology, biochemistry, gene and regulatory mechanisms^{4,5,6-21} (Table 1). Morphologically, unlike other four types of cell death, ferroptosis mainly shows as an apparent shrinkage and dwindled-sized of mitochondria with increased membrane density as well as the reduction or loss of mitochondrial crista and outer membrane. Biochemically, ferroptosis mainly involves iron accumulation, lipid peroxidation, Fenton reaction and cystine deprivation, which is different from other types of cell death.

Current studies have confirmed that the inhibition of ferroptosis can have an efficient therapeutical effectiveness on various diseases such as ischemia-reperfusion injury, cancer, stroke, neurodegenerative disorders, traumatic brain injury, lung fibrosis, liver fibrosis and acute kidney injury, etc.²² In addition, many studies have showed that ferroptosis plays a significant role in the occurrence, development, treatment and prognosis of many types of wounds and has become the research hot-spots in the field of burn and plastic surgery. Considering this, we reviewed and summarised the latest research progress on the relations between ferroptosis and wound to propose some new insights and advances for the improvement and promotion of wound healing.

2 | THE PROCESS OF WOUND HEALING

Wound healing is a complex process that contains the repair of tissue injury, the restoration of skin barrier and the maintenance of skin integrity, involving the dynamic interactions of multiples of cells, extracellular matrix and cytokine.²³ Currently, it has been confirmed that the process of wound healing can be divided into four stages: haemostasis, inflammation, proliferation, remodelling and maturation.²⁴

On the first stage of wound healing, platelets adhere to exposed fibrinogen underneath the broken blood vessel endothelium, and begin to be activated to release adenosine diphosphate (ADP), thromboxane A₂, prostaglandin 2- α , 5-hydroxytryptamine (5-HT) and platelet factor IV.²⁵ Subsequently, the coagulation system is activated and fibrinogen is transformed to an insoluble fibrin network, producing blood clots.²⁶ Thus, damaged blood vessels are sealed and bleeding is stopped.

On the second stage of wound healing, attracted by such chemoattractive agents as tumour necrosis factor

(TNF), interleukin-1 (IL-1), C3a, C5a and LTB₄, inflammatory cells such as neutrophils, macrophages and lymphocytes begin to gather and accumulate in the wound sites,²⁷ which triggers a strong inflammatory reaction. Various inflammatory mediators such as vasoactive amines, arachidonic acid and its byproducts, platelet-activating factor, cytokines, active oxygen, NO, neuropeptide and bradykinin, etc, are key materials that participate and mediate inflammatory reactions. The important roles of this stage of wound healing include combating infection, removing harmful and necrotic substances and laying proper foundations for proliferation process.

On the third stage of wound healing, bleeding is stopped as well as immune and inflammatory responses are in balance, continual injury is transformed to repair phase. Epithelialization occurs initially in repair phase, which depends on the integrity of the basement membrane.²⁸ Subsequently, regulated by vascular endothelial growth factor (VEGF), angiopoietin and fibroblast growth factor (FGF), endothelial cells start to proliferate and migrate to the capillary formation, inducing angiogenesis, which is significant for the proper wound healing.²⁹ At the same time, neogenetic myofibroblasts on the edge of the wound begin to migrate to the centre of the wound and secrete a huge amount of collagen as well as extracellular matrix (ECM),³⁰ with the purpose to diminish the size of the wounds. Hence, signalled by platelet-derived growth factor (PDGF), epidermal growth factor (EGF), tissue growth factor (TGF)- β , FGF, IL-1 and TNF, capillary as well as fibroblasts proliferate quickly and more and more fibroblasts start to transform into myofibroblasts. Thus, granulation tissue are formed, which fill in the defects of injured tissue, indicating the completion of the repair process.

On the final stage of wound healing, granulation tissue start to transform to scar, which involves the processes of synthesis and degradation of collagen and ECM,³¹ of which the key enzymes are matrix metalloproteinase (MMP) family.³² MMP family can be divided into four types: interstitial collagenase, gelatinase or type IV collagenase, stromelysin and membrane type I matrix metalloproteinase (MT1-MMP). Induced by PDGF, FGF, IL-1, TNF- α and phagocytosis, MMP can be secreted by fibroblasts, macrophages, neutrophils and epithelial cells to degrade collagen and ECM. However, this biological process is regulated strictly. All types of MMP are secreted in a non-active form of zymogen and only can be activated by such chemical stimuli as HOCL and fibrinolysin.³³ Otherwise, activated MMP can be suppressed by tissue inhibitor of metalloproteinase (TIMP), which can be secreted by the majority of mesenchymal cells.⁴ Clinically, the imbalance of this phase can cause improper wound healing. For example, patients with

TABLE 1 Characteristics of ferroptosis, apoptosis, autophagy, pyroptosis and necroptosis

	Ferroptosis	Apoptosis	Autophagy	Pyroptosis	Necroptosis
Discovery time	2012	1972	1992	2009	2005
Discoverer	Scott J. Dixon, USA	John F R Kerr, Andrew H Wyllie and Alastair R Currie, UK	Yoshinori Ohsumi, Japan	Tessa Bergsbaken, USA	Alexei Degterev, USA
Morphology	<ul style="list-style-type: none"> • Round, shrunken and dwindled-sized mitochondria • Increased mitochondrial membrane density • Reduction or loss of mitochondrial crista and outer membrane • Structural damage in mitochondria and nucleus 	<ul style="list-style-type: none"> • Cellular and nuclear pycnosis • Chromatin agglutination • No significant damage in the integrity of cellular membrane • Formation of apoptotic bodies 	<ul style="list-style-type: none"> • Formation of autophagosomes and autolysosomes • Swell of endoplasmic reticulum, Golgi body and mitochondria 	<ul style="list-style-type: none"> • Cellular swell • Chromatin condensation • Cell and organelle membrane disruption • Aqtocytolysis 	<ul style="list-style-type: none"> • Cellular swell • Chromatin condensation • Cell and organelle membrane disruption • Aqtocytolysis
Biochemistry	<ul style="list-style-type: none"> • Iron accumulation • Lipid peroxidation • Feton reaction • Cystine deprivation 	<ul style="list-style-type: none"> • ATP-dependent • Regular DNA fragmentation • Ca²⁺ overload • Endonuclease activation 	<ul style="list-style-type: none"> • Lysosomal activation • ATGs activation • mTOR inhibition 	<ul style="list-style-type: none"> • NLRP3 activation • ROS production • Lysosomal disruption • Potassium efflux 	<ul style="list-style-type: none"> • ATP-independent • Irregular DNA fragmentation
Key genes	GPX4, ACSL4, TFRC, SLC7A11, SLC3A2, FSP1, ATM, MTF1, FPN1, NRF2, NCOA4, HSPB1, LPCAT3, ALOX12/15, JNK, p38, p53, NOXs, ATGs	Caspase-3, Bcl-2, Bak, Bax, Fas, ASK1, JNK, p38, p53	ATGs, LC3, Beclin-1, p62/SQSTM1, mTOR, AMPK, PI3K, VPS34, DRAM3, TFEB	Inflammatory caspase family, NLR family, Gasdermin family, NLRP1/3, p10, IL-1 β , IL-18	RIPK1, RIPK3, MLKL, TNFR1, Fas, TRADD, NOXs, REK, HMOX-1, TLR4, JNK
Regulatory mechanisms	<ul style="list-style-type: none"> • System Xc⁻ • Mevalonate pathway • IRP1/IRP2 • ATG5/ATG7/NCOA4 • Mitochondrial GLS2/glutaminolysis • Sulfasalazine transferation • p62/Keap1/NRF2 • RSL3 mechanisms, • HSPB1-TRF1 • Peroxidation of PUFA-PLs • p53/SAT1/ALOX15 • Amino acid starvation • FSP1-COQ10-NAD(P)H 	<ul style="list-style-type: none"> • MAPK/ERK • IKK/IκB/NF-κB • IFN-mediated • JAK-STAT • PI3K/Akt/mTOR • Caspase-3 pathway • Bcl-2 pathway • Bak/Bax pathway • p38 pathway • Hippo pathway 	<ul style="list-style-type: none"> • PI3K/Akt/mTOR • AMPK/mTOR • A2AR/SIRT3/AMPK • JAK/STAT3/SIRT1 • Akt/Nrf2 • NF-κB pathway • Notch pathway • p53 pathway 	<ul style="list-style-type: none"> • Inflammatory caspase family pathway • NLRP1/3 pathway • Gasdermin family pathway • HMGB1/RAGE/cathepsin B pathway • BAK/BAX-caspase-3-GSDME pathway • p38/MAPK pathway • IL-1β/IL-18 pathway 	<ul style="list-style-type: none"> • JAK/STAT1/IRF1 • PKC/MAPK/AP-1 • RIP1/RIP3/MLKL • Ripk3/Pgam5 • ROS-related pathway • MYC-mediated pathway • JNK pathway

(Continues)

TABLE 1 (Continued)

Discovery time	Ferroptosis	Apoptosis	Autophagy	Pyroptosis	Necroptosis
2012	Erasatin, Piperazine erastin, Imidazole ketone erastin, RSL3, Sorafenib, Sulfasalazine, Iron, Cyst(e)inase, DPI family, FIN56, FINO2, Artesunate, Cisplatin, Doxorubicin	Various drugs or compounds and diseases	1992	2009	2005
			Rapamycin, MG-132, SB 203580, Cisplatin, Sorafenib, Olaparib	Inflammatory caspase family, Gasdermin family, Cisplatin, Metformin, Anthocyanin, DHA, Paclitaxel	Sorafenib, Artesunate, Shikonin, 5-FU, Iron, Resibufogenin, Doxorubicin
			3-Methyladenine, Chloroquine, Cycloheximide, Bafilomycin A1, Resatorvid	Inflammatory caspase family inhibitors, Gasdermin family inhibitors	Necrostatin-1
	Ferrostatin-1, Deferoxamine, Deferiprone, Ciclopirox, β -mercaptoethanol, Cycloheximide, Liproxstatin-1, Vitamin E, SRS11-9, SRS16-86, U0126	Caspase family inhibitors			

Abbreviations: ACSL4, acyl-CoA synthetase long-chain family member 4; ALOX12/15, arachidonate lipoxygenase 15; ATGs, autophagy-related genes; COQ10, coenzyme Q10; ERK, extracellular signal-regulated kinase; FSP1, ferroptosis suppressor protein 1; GPX4, glutathione peroxidase 4; HSPB1, heat shock protein family B (small) member 1; IRP1 and IRP2, iron-regulatory proteins 1 and 2; Keap1, kelch-like ECH-associated protein 1; LPCAT3, lysophosphatidylcholine acyltransferase 3; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NCOA4, nuclear receptor coactivator; NRF2, nuclear factor erythroid 2-related factor4; PUFA-PLs, polyunsaturated-fatty-acid-containing phospholipids; RSL3, RAS synthetic lethal 3.

matrix deposition problems will suffer with the poor strength of the wound. And patients with excessive collagen synthesis are common with the problems of hypertrophic scar or keloid.²⁵

3 | OVERVIEW OF FERROPTOSIS

It has been widely that system Xc⁻ mechanism, GPX4 mechanism, iron mechanism and lipid mechanism are four main mechanisms of ferroptosis. In addition, there are other mechanisms such as transsulfuration mechanism, p62/Kelch-like ECH-associated protein 1 (Keap1)/nuclear factor erythroid 2-related factor (NRF2) pathway and ATG5/ATG7/nuclear receptor coactivator 4 (NCOA4) pathway also playing important roles in ferroptosis (Figure 1).

3.1 | System Xc⁻

System Xc⁻ is an amino acid antitransporter, also called cystine/glutamate exchange system, which is mostly distributed in membrane phospholipids. System Xc⁻ is a necessary antioxidant system and is consisted of two subunits (SLC7A11 and SLC3A2).³⁴ Normally, system Xc⁻ could exchange extracellular cystine and intracellular glutamate at a ratio of 1:1, which is essential for the synthesis of GSH.³⁵ Driven by glutathione peroxidases (GPXs), GSH is important for the reductions of ROS and reactive nitrogen, maintaining the intracellular redox balance. As ferroptosis inducers, erastin, sorafenib and sulfasalazine could induce ferroptosis via the suppression of system Xc⁻, which causes the impediment of the absorption of cystine, leading to the decrease of GPXs activity, the lethal accumulation of lipid ROS and ultimately the oxidative damage.²² Moreover, p53, one of the key genes regulating ferroptosis, can inhibit the functions of system Xc⁻ through the downregulation of the expression of SLC7A11, which affects the normal structure of system Xc⁻, leading to the cystine deprivation, cellular redox balance disruption and the accumulation of lipid ROS, thereby inducing ferroptosis.³⁶

3.2 | GPX4

As one of the members of GPX family, GPX4 is the key gene of the occurrence and development of ferroptosis, which mainly acts its guardian role by converting GSH into oxidised glutathione (GSSG), thus reducing the cytotoxic lipid peroxides (L-OOH) to the non-cytotoxic alcohols (L-OH).³⁷ Therefore, the inhibition of GPX4 activity

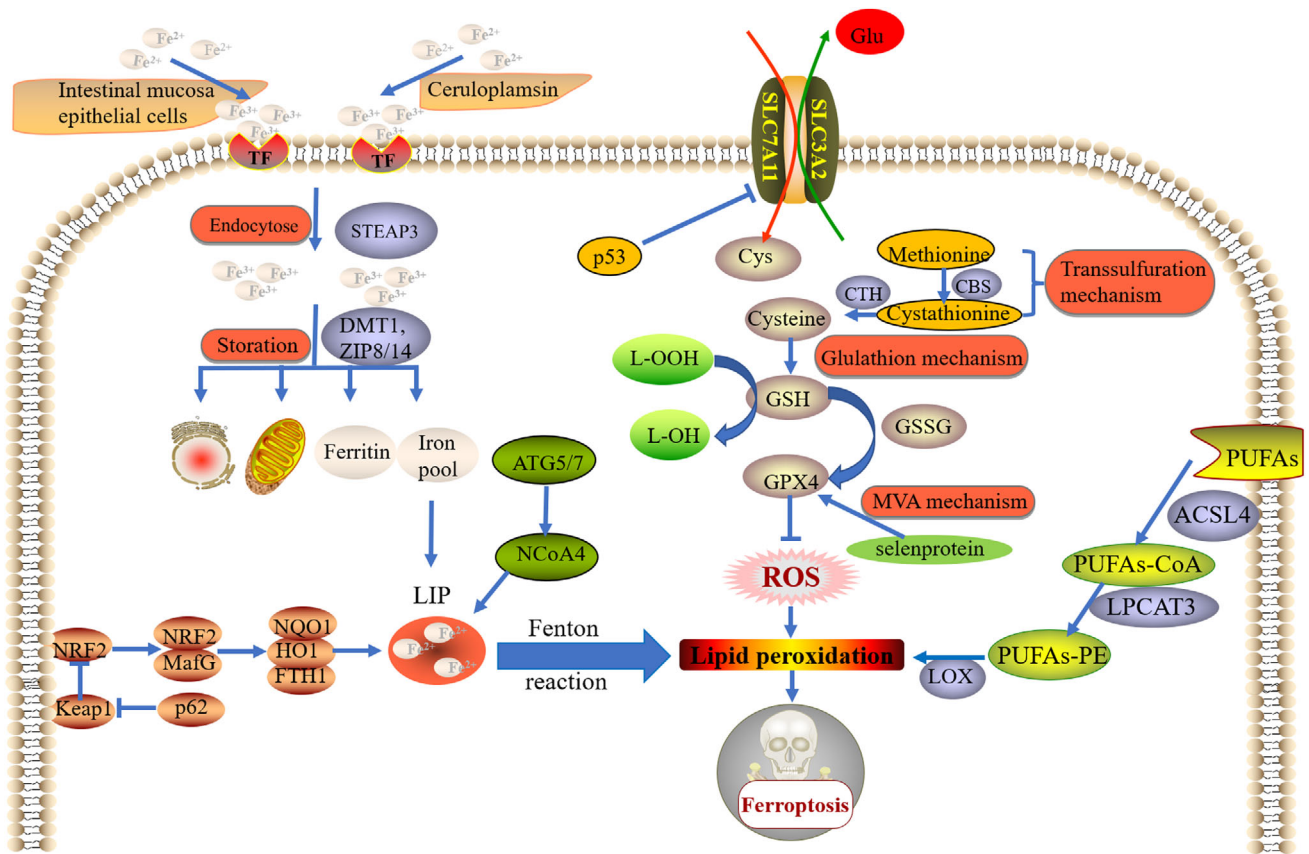


FIGURE 1 Mechanisms of ferroptosis. System Xc^- mechanism, GPX4 mechanism, iron mechanism and lipid mechanism are four main mechanisms of ferroptosis. In addition, there are other mechanisms such as transsulfuration mechanism, p62/Keap1/NRF2 pathway and ATG5/ATG7/NCOA4 pathway also playing important roles in ferroptosis

or the suppression of GPX4 expression can cause ROS accumulation and lipid peroxidation, thus inducing ferroptosis. Such ferroptosis inducers as RSL3, altretamine, DPIs, FIN56, JKE-1674, ML162 and ML210 have been confirmed to induce ferroptosis by inhibiting GPX4 activity. In addition, various studies have revealed that cells (BJ-fibroblast-derived cells, HT-1080 cells) with down-regulated GPX4 expression or GPX4 knockdown are more sensitive to ferroptosis compared with control cells.^{38,39} Moreover, it has been accepted that selenoprotein plays a pivotal role in the synthesis of GPX4 and protecting GPX4 from irreversible inactivation.⁴⁰ To ensure GPX4 can exert its proper functions, the metabolisms of selenoprotein are strictly regulated by mevalonate (MVA) pathway. Down-regulation of MVA pathway is responsible for the impediment of the synthesis of selenoprotein, thus inhibiting GPX4 activity and inducing ferroptosis.^{22,40}

3.3 | Iron metabolism

There are two forms of iron in the body include Fe^{2+} and Fe^{3+} . In the normal status, the content and

distribution of Fe^{2+} and Fe^{3+} are in homeostasis and some pathological conditions will be induced if this homeostasis is interrupted.⁴¹ Intestinal absorption and erythrocyte degradation are the two main sources of Fe^{2+} . On one side, Fe^{2+} absorbed from food can be oxidised by intestinal mucosa epithelial cells to Fe^{3+} and binds to transferrin (TF) to form $TF-Fe^{3+}$. On the other side, Fe^{2+} from erythrocyte degradation can be oxidised by ceruloplasmin to Fe^{3+} and binds to TF to form $TF-Fe^{3+}$. After the endocytose of $TF-Fe^{3+}$, Fe^{3+} is reduced to Fe^{2+} by six-transmembrane epithelial antigen of the prostate 3 (STEAP3), and Fe^{2+} can be stored in mitochondria, endoplasmic reticulum, ferritin and iron pool, of which the processes are strictly regulated by divalent metal transporter 1 (DMT1) and Zinc-Iron regulatory protein family 8/14 (ZIP8/14).⁴² Once the iron metabolism is disordered, Fe^{2+} stored in mitochondria, endoplasmic reticulum and ferritin will be released and iron pool will convert to unstable iron pool (LIP), which leads to the excessive content of Fe^{2+} in cytoplasm.⁴³ Then, iron accumulation induces Fenton peroxidation and lipid ROS accumulation, which triggers ferroptosis.

3.4 | Lipid metabolism

Lipid peroxidation is essential for ferroptosis and lipid peroxidation is closely related to lipid metabolism. Lipid metabolism participate in the process of lipid peroxidation and ferroptosis mainly by transforming free polyunsaturated fatty acids (PUFAs) to PUFAs-phosphatidylethanolamine (PUFAs-PE).⁴⁴ Free PUFAs is widely distributed phospholipid bilayers and functioned as an esterified form, which has nothing to do with ferroptosis. However, PUFAs-PE involves arachidonic acid (AA) and its derivative adrenaline, which are important substrates of lipid peroxidation.⁴⁵ Studies have revealed that acyl-CoA synthetase long-chain family member 4 (ACSL4) as well as lysophosphatidylcholine acyltransferase 3 (LPCAT3) are the key enzymes of lipid metabolism. First, ACSL4 combines PUFAs with CoA, thus producing PUFAs-CoA. Subsequently, LPCAT3 combines PUFAs-CoA with PE, thus producing PUFAs-PE. Finally, catalysed by lipoxygenase (LOX), PUFAs-PE can be oxidised, contributing to lipid peroxidation and thereby inducing ferroptosis.⁴⁶ Therefore, the expressions of ACSL4 in those ferroptosis-sensitive cells such as HepG2 and HL60 are higher than that in such ferroptosis-resistant cells as LNCaP as well as K562.⁴⁷ In addition, compared with control MLE cells, LPCAT3 knockdown MLE cells are resistant to RSL3-induced ferroptosis, showing lower rate of cell death.⁴⁸

3.5 | Other mechanisms

There are other mechanisms regulating the occurrence and development of ferroptosis. Apart from system Xc⁻ mechanism, transsulfuration mechanism is another important source of cysteine for GSH.⁴⁹ Cystathionine- β -synthase (CBS) and cystathionine- γ -lyase (CTH) are key enzymes of transsulfuration mechanism. Catalysed by CBS, methionine can be converted to cystathionine. Subsequently, CTH promotes the transformation from cystathionine to cysteine, thus providing the essential substrate for GSH generation.^{49,50} In addition, activating p62/Keap1/NRF2 pathway is demonstrated to fight against ferroptosis via the functions of various enzymes such as quinone oxidoreductase 1 (NQO1), heme oxygenase-1 (HO1) and ferritin heavy chain 1 (FTH1).⁵¹ Otherwise, investigations have found that autophagy can contribute to ferroptosis by degrading ferritin, increasing intercellular iron levels, and promoting Fenton reaction through ATG5/ATG7/NCOA4 pathway.⁵²⁻⁵⁴

4 | RELATIONSHIP BETWEEN FERROPTOSIS AND WOUND

4.1 | Diabetic wound

Diabetic wound always has some problems of iron metabolism such as reduced iron levels and dysregulated expression of iron genes, which may delay ECM deposition. Exogenous iron administration can promote ECM deposition of collagen type I and collagen type III. However, the knockdown of STEAP3 leads to impaired ECM deposition.⁵⁵ In addition, iron stored in FPN of skin macrophages is of significance for wound healing and FPN deletion in skin macrophages can impair wound healing by the compromises of angiogenesis and stromal cells proliferation.⁵⁶ Apart from abnormal iron metabolism, excessive oxidative and lipid peroxidation are also commonly observed in diabetic wound. For example, Li, et al.⁵⁷ has found that compared with control groups, the levels of ROS, malondialdehyde (MDA) and lipid peroxidation of fibroblasts as well as vascular endothelial cells that exposed to high glucose conditions are elevated obviously, and the cells display reduced survival rate and impaired migration. In addition, they also have revealed that ferroptosis is strongly induced in diabetic wound both in vitro and vivo aspects, which are confirmed by low level of GPX4, SLC7A11 expressions and high level of TFRC.

Moreover, various studies have demonstrated that ferroptosis inhibitors can promote diabetic wound by inhibiting ferroptosis. For example, the local application of ferrostatin-1 (ferroptosis inhibitor) can accelerate the rat diabetic wound healing by inhibiting ferroptosis through the upregulation of PI3K/Akt signalling pathway.⁵⁷ In addition, many investigations have showed that the administration of DFO, another type of ferroptosis inhibitors, can promote the diabetic wound healing. Gao, et al.⁵⁸ have found that the co-application of DFO and hydroxysafflor yellow A in hydrogel can accelerate rat diabetic wound healing via enhanced angiogenesis. Hopfner U, et al.⁵⁹ have found that DFO can promote the regenerative capacity of adipose-derived stem cells (ADSCs) in rat diabetic wound via the enhancement of hypoxia-inducible factor- α (HIF- α) and VEGF expressions. Furthermore, the combined applications of DFO and biomaterials also have been showed to have an efficient therapeutic effectiveness on diabetic wound. Kong, et al.⁶⁰ have showed that the application of injectable hydrogel combining with DFO and bioglass containing Si ions can promote the repair of diabetic wound by enhancing revascularization. In addition, Chen, et al.⁶¹ have found that the sustained release of DFO from

hydrogel nanofibrous scaffolds can enhance angiogenesis in diabetic wound by upregulating the expressions of HIF-1 α , VEGF and SDF-1 α . Dominik Duscher, et al.⁶² have revealed that the transdermal delivery of DFO can also significantly accelerate diabetic wound healing by promoting angiogenesis via the upregulation of HIF-1 α as well as VEGF expressions. Furthermore, this novel DFO delivery method can overcome such disadvantages of DFO as potential toxicity and short plasma half-life.

4.2 | Irradiated wound

Irradiated wound is one of the common skin lesions in clinical, which mainly caused by irradiation therapies of tumours and unexpected irradiation accidents. Excessive irradiation can impair local vessels and cause angiogenesis by damaging the structures and activities of proteins and DNA, thus delaying the wound healing.⁶³ Gan, et al.⁶⁴ have demonstrated that the local injection of plasma-derived exosomes (RP-Exos) can promote the healing process of rat irradiated wounds by boosting the proliferation, migration, cycle progression as well as survival rate of fibroblasts. They also have found that RP-Exos can disrupt ferroptosis pathway, thus inhibiting ferroptosis in irradiated fibroblasts. In addition, various investigations have confirmed that irradiation can trigger cell death by inducing ferroptosis. For example, Stockwell, et al.⁶⁵ have found that applying Cs-137 gamma radiation to intervene in HT-1080 cells can trigger cell death by inducing ferroptosis, which can be reversed by ferroptosis inhibitors such as sorafenib and ferrostatin-1. Yuki Shibata, et al.⁶⁶ also have found that compared with normal cells, human cervical adenocarcinoma cells and lung adenocarcinoma cells that are irradiated by x-ray are more sensitive to ferroptosis, which can be reversed by erastin. Moreover, Khorsandi, et al.⁶⁷ have revealed that the laser irradiation can cause ROS accumulation in breast cancer cells and melanoma cells.

4.3 | UV-driven wound

Apart from irradiation treatments for tumour, excessive ultraviolet (UV) exposure, especially UVA and UVB, can also cause UV-driven cutaneous wound. Kavita Vats, et al.⁶⁸ have showed that excessive UVB exposure can initiate the inflammation and cell death of human keratinocytes by inducing ferroptosis, which can be inhibited by ferrostatin-1. Moreover, excessive UV exposure can cause GSH deprivation, thereby disrupting redox homeostasis. Feng, et al.⁶⁹ have showed that in

UV-driven wounds, the content of GSH is lower than normal so that GPX4 mechanism is comprised, thus ferroptosis is induced. However, this pathological process can be alleviated by GSH recruitment using nicotinamide mononucleotide.⁶⁹ Furthermore, excessive UV exposure can also lead to ROS accumulation in skin, thus inducing ferroptosis by lipid peroxidation mechanism.⁷⁰ Taken together, excessive UV exposure can induce ferroptosis by GSH deprivation mechanism, GPX4 mechanism and lipid peroxidation mechanism. Hence, in UV-driven wound, caused by frequent ferroptosis, weak capacity to keep redox homeostasis and high rate of cell death led to the impairment of DNA repair and dysregulation of wound healing-related genes (e.g. VEGF, FGF, PDGF and MMPs, etc), thus delaying the healing processes of UV-driven wound.

5 | CONCLUSIONS AND PROSPECTS

In summary, wound healing, especially chronic and refractory wounds healing, is an extremely complex process with the involvement of multitudes of mechanisms. As an emerging cell death mechanism, ferroptosis has been found to have strong relationships with wound healing. Taken together, abnormal contexts of iron, ROS and oxidative stress are the common features of both wound healing and ferroptosis, and ferroptosis inducing can be observed in different degrees in different types of wounds. Furthermore, inhibiting ferroptosis by ferroptosis inhibitors such as ferrostatin-1, DFO and sorafenib or dysregulating ferroptosis-related mechanisms has been confirmed to have an efficient acceleration and boost on wound healing. With the developments of engineering and biotechnology, biomaterials are regarded as a promising therapy for wound healing. Ferroptosis inhibitors-loaded biomaterials will potentially serve as a novel strategy for wound care and treatment.

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None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

Data is available.

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