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Exploring the miRNA-Ferroptosis Axis in Diabetic Retinopathy: Insights into Pathogenesis and Therapeutic Targets

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Abstract

Diabetic retinopathy (DR) is one of the most common complications of diabetes and a leading cause of vision loss among working-age individuals in industrialized countries, profoundly affecting the daily lives of millions. Despite stringent glycemic control, blood pressure management, and lipid-lowering therapies, the prevalence of DR continues to rise, and treatment options remain limited. Moreover, existing therapies are constrained by significant limitations and side effects, with suboptimal efficacy, partly due to the incomplete understanding of the underlying mechanisms of DR. Ferroptosis, a form of regulated cell death, not only exacerbates oxidative stress but also contributes to inflammatory responses, both of which are key drivers in the progression of DR. Furthermore, ferroptosis has been linked to the dysregulation of miRNA expression in the retina, offering potential novel therapeutic targets for DR. This article reviews the role of iron overload and ferroptosis in the pathogenesis of DR and provides evidence on the involvement of miRNAs as inducers or inhibitors of ferroptosis, aiming to uncover common molecular mechanisms and therapeutic targets for DR.

1. Introduction

According to the International Diabetes Federation (IDF Atlas, 4th Edition, 2009), diabetes currently affects approximately 285 million people worldwide, a figure projected to surge to 438 million by 2030. While diabetes manifests various complications, none proves more vision-threatening than diabetic retinopathy (DR), which maintains its status as the foremost preventable cause of adult blindness [1]. In individuals with type 1 diabetes, about one-quarter develop retinopathy within 5 years of diagnosis, increasing to approximately 60% after 10 years and nearly 97% after 25 years [2, 3]. For type 2 diabetes, retinopathy may already be present at diagnosis, with over 60% of patients developing some form of retinopathy after 20 years[4]. Data from Wisconsin, USA, estimate that DR results in an annual economic burden exceeding $500 million [5]. With lifestyle changes, increased life expectancy, and the rising global prevalence of diabetes, DR is expected to impose a growing and profound impact on public health worldwide. Clinically progressing from non-proliferative (NPDR) to proliferative (PDR) as per disease staging[6], this microvascular disorder exhibits hallmark ischemic changes in retinal tissue, which pathologically culminate in disorganized vasculogenesis[7, 8]. Despite the availability of various therapeutic approaches, including anti-VEGF therapies, laser photocoagulation, and corticosteroids, clinical outcomes remain suboptimal[8, 9]. This limited efficacy is partly attributable to an incomplete understanding of the underlying mechanisms of DR pathogenesis. A deeper investigation into the pathological mechanisms of DR is essential for identifying novel therapeutic targets and inhibitors that can effectively mitigate disease progression and its associated complications.

Preclinical studies now implicate ferroptotic pathways as key mediators of DR pathogenesis, with lipid peroxidation cascades exacerbating both microvascular dysfunction and ganglion cell degeneration in retinal tissues. Ferroptosis exacerbates oxidative stress and drives inflammatory responses, both of which are key contributors to DR development[10]. Furthermore, ferroptosis has been linked to the

dysregulation of microRNA (miRNA) expression in the retina, offering potential novel therapeutic targets for DR.

This review provides a comprehensive overview of the mechanisms underlying ferroptosis and its relationship with DR. Additionally, we present detailed evidence regarding the role of miRNAs as inducers or inhibitors of ferroptosis in the context of DR. By exploring shared molecular pathways and potential therapeutic targets, this study highlights promising strategies to advance the treatment of DR and address its significant clinical challenges.

2. Ferroptosis and DR

Iron, a trace element of critical importance, serves as an essential cofactor in numerous catalytic reactions and exerts profound effects on various metabolic pathways [11]. A prospective cohort study has established a link between total iron and non-heme iron intake with an increased risk of diabetes [12]. Within the pathophysiological axis of DR, iron dysregulation emerges as a critical mediator, principally through driving redox imbalance cascades that directly contribute to retinal vascular degeneration.

2.1 Iron Overload and DR

Clinical studies have demonstrated that the vitreous iron levels in DR patients are 2.5 times higher than those in healthy individuals[13]. Several mechanisms may account for this abnormal iron overload in the eyes of DR patients. The interplay between diabetes and iron metabolism is complex and bidirectional. Systemic iron overload is a common finding in diabetic patients. Experimental data demonstrate significant iron homeostasis dysregulation across genotypic groups: $Lepr^{db/db}$ mice exhibit higher serum iron than wild-type controls while compound transgenic $Lepr^{db/db}$+$Fpn^{wt/C326S}$ models show exacerbated hyperferremia[14]. Systemic iron overload in diabetic patients induces upregulation of hepcidin in the retina, leading to reduced expression of the retinal iron exporter ferroportin (FPN). Under systemic iron overload conditions, retinal zinc transporters ZIP8 and ZIP14 undergo compensatory overexpression, establishing preferential divalent cation channels that mediate pathological Fe^{2+} translocation into retinal parenchyma. These processes ultimately result in pathological iron accumulation in the retina of DR patients[10]. Additionally, elevated glucose levels have been shown to increase intracellular iron concentrations in human retinal endothelial cells[15]. This effect is likely driven by the chronic hyperglycemic environment, which exacerbates inflammation. Aberrant secretion of inflammatory cytokines further amplifies hepcidin expression, creating a vicious cycle of iron dysregulation.

Understanding the mechanisms underlying iron overload in DR is essential for developing targeted interventions aimed at modulating iron homeostasis and mitigating its harmful effects in this debilitating disease. The ferrotoxic microenvironment in DR pathogenesis arises from iron-driven Fenton reactions, that concomitantly activate NF-κB-mediated inflammatory pathways and deplete retinal antioxidant reserves. The excessive accumulation of iron induces oxidative damage and promotes pathological neovascularization, with particularly pronounced effects on the aging retina. This increased vulnerability

to oxidative stress leads to a rise in reactive oxygen species (ROS) production[16]. These ROS then attack lipid structures in photoreceptors and reduce the expression of brain-derived neurotrophic factor (BDNF) [17]. Oxidative stress further exacerbates mitochondrial dysfunction and triggers the release of interleukins, leading to damage of retinal vascular endothelial cells. These mechanisms together lead to pericyte cell death and impair communication between pericytes and endothelial cells, resulting in damage to the structure of the blood-retinal barrier [18]. Retinal pigment epithelial cells (RPECs) are particularly vulnerable to oxidative damage induced by iron overload. This results in ultrastructural abnormalities, cellular hypertrophy, and potential atrophy of RPECs[19]. Progressive RPE cell dysfunction culminating in cellular demise is mechanistically associated with two concurrent events: microglial activation/chemotaxis and diminished Rpe65 biosynthesis[19]. The cumulative effects of these pathophysiological changes lead to vascular leakage and vitreous hemorrhage, further driving DR progression[20]. Understanding the mechanisms by which iron overload impacts the retina provides critical insights into potential therapeutic strategies for preventing or mitigating DR.

2.2 The Role of Ferroptosis in the Pathogenesis of DR (Fig. 1)

Ferroptosis, a severe consequence of iron overload, is characterized by lipid peroxidation and dysregulation of the antioxidant system—mechanisms closely linked to the pathophysiology of DR. A hallmark of ferroptosis is the peroxidation of polyunsaturated fatty acids (PUFAs) on cell membranes. This process is primarily catalyzed by lipoxygenases and regulated by glutathione peroxidase 4 (GPX4). Studies have shown that DR rat models exhibit reduced GPX4 expression in retinal tissues and peripheral blood, accompanied by a significant decrease in the GSH/GSSG ratio, indicating impaired antioxidant defense. Treatment with the ferroptosis inhibitor ferrostatin-1 (Ferr-1) was found to upregulate GPX4 expression, partially restore the GSH/GSSG ratio, and alleviate oxidative stress in the retinal tissues of DR rats [21, 22]. Another study highlighted that hyperglycemia-induced death of human retinal microvascular endothelial cells (HRMECs) is driven by the ubiquitination and subsequent degradation of GPX4 through proteasomal or lysosomal pathways. This degradation disrupts lipid homeostasis and triggers ferroptosis[23]. The identified ferroptosis-DR pathogenic axis establishes this cell death modality as a therapeutic priority, with pathway-specific modulation demonstrating preclinical efficacy in preserving retinal cytoarchitecture.

(In diabetic patients, retinal iron levels are significantly elevated, leading to iron accumulation through the upregulation of Zip8/Zip14 (iron transporters) and downregulation of the iron exporter FPN. Iron overload induces lipid peroxidation of polyunsaturated fatty acids (PUFAs) catalyzed by lipoxygenase (LOX) and ACSL4/LPCAT3, resulting in the production of lipid ROS. The antioxidant defense system against iron overload, such as GPX4 and GSH, becomes impaired and is unable to eliminate lipid ROS, ultimately causing cell membrane rupture and ferroptosis. Iron overload generates ROS via the Fenton reaction, triggering oxidative stress, mitochondrial dysfunction, and inflammatory responses, which

damage the blood-retinal barrier (BRB), leading to vascular leakage, pericyte apoptosis, and pathological neovascularization.)

3. The Link Between miRNAs, Ferroptosis, and DR

Functioning as conserved regulatory elements across eukaryotes, microRNAs (miRNAs) comprise 20–24 nucleotide non-coding RNAs ubiquitously expressed in metazoans, plants, and viral genomes[24]. By binding to the 3'-untranslated region (3'-UTR) of target mRNAs, miRNAs regulate post-transcriptional gene expression, playing pivotal roles in biological processes such as cell proliferation, differentiation, metabolism, and apoptosis. A single miRNA can target multiple genes, while multiple miRNAs can finely tune the expression of the same gene, creating a complex regulatory network[25]. In the context of disease, particularly DR, miRNAs have emerged as key regulators of pathological processes including inflammation, oxidative stress, angiogenesis, and cell death. Investigating their mechanisms and functions offers novel insights into the diagnosis and treatment of DR. Studies have demonstrated that miRNAs modulate DR-associated proteins by destabilizing their mRNA targets, thereby influencing protein translation. This regulatory capacity highlights the potential of miRNAs as therapeutic targets in mitigating DR progression and its associated complications[26].

3.1 miRNAs and DR

In DR, miRNA expression undergoes significant alterations in various retinal cells, including endothelial cells, Müller cells, microglia, retinal pigment epithelial (RPE) cells, and photoreceptor cells. These changes are closely associated with DR pathogenesis.

Lu et al. observed increased expression of miR-21 and PI3K/Akt/VEGF-related genes, along with reduced PTEN expression, in the retinal tissues of DR rats. Their findings suggest that miR-21 overexpression potentially stimulates retinal vascular endothelial cell (RVEC) viability and angiogenesis by activating the PI3K/Akt/VEGF signaling pathway through PTEN inhibition. This highlights miR-21's role in promoting endothelial proliferation and angiogenesis in DR[27]. Other studies have demonstrated the therapeutic potential of miRNAs in DR. For instance, administration of miR-124 to DR rats reduced the expression of inflammatory factors such as Tnf-α, Il-1β, Cd74, Ccl2, Ccl3, Vcam1, Tgf-β1, Arg1, and Il-10. Additionally, miR-124 mitigated activation of Müller glial cells and microglia, thereby improving neuroretinal function[28]. Similarly, miR-320 was shown to inhibit oxidative stress and inflammation via the TGF-β1/USP14 axis, preventing DR progression[29]. Other miRNAs play equally critical roles in DR:

miR-146: Acts as a negative regulator of NF-κB activation in Tr-iBRB endothelial cells, suggesting its potential as a therapeutic target to inhibit NF-κB activation in retinal endothelial cells (RECs)[30].

miR-27a: Protects RPE cells by reducing inflammation and apoptosis through the TLR4 pathway[31].

miR-346: Upregulated under hyperglycemic conditions, exacerbating oxidative stress and apoptosis in RPE cells [32].

miR-200b: Found in retinal neurons, glial cells, and vascular components, miR-200b prevents diabetes-induced increases in VEGF mRNA and protein levels when transfected into endothelial cells or administered via intravitreal injection. It also reduces glucose-induced permeability and angiogenesis. Downregulation of miR-200b leads to increased VEGF expression and worsened angiogenesis[33]. The following table supplements the functions of other miRNAs in different cells of DR patients' eyes.

Table 1
Functions of miRNAs in different cell types of DR patients' eyes.

Cell Type	miRNA	Function
endothelial cells	miR-590-3p[34]	Reduces pyroptotic death by targeting NLRP1 in an HG-induced EC injury model
	miR-126[35]	Inhibits EC proliferation and migration in DR rats.
	miR-301a-3p[36]	Stimulates inflammatory factor expression and apoptosis in ECs in DR rats.
	miR-124-3p[37]	Overexpression of miR-124-3p suppresses HG-induced EC injury.
Pericytes	miR-138-5p [38]	Regulates and promotes cell proliferation to prevent early DR.
	miR-199a-3p[39]	Accelerates cell proliferation and migration, thereby promoting DR progression.
	miR-15b[40]	Facilitates cell proliferation and migration to advance DR progression.
Retinal Ganglion Cells	miR-145-5p [41]	High expression induces damage to retinal ganglion cells.
Glial Cells	miR-9-3p[42]	Transfers to retinal endothelial cells and activates VEGFR2 phosphorylation to promote angiogenesis in DR.
	miR-125a-5p[43]	Targets and regulates Ninjurin1 to prevent macrophage-induced vascular leakage.
	miR-29a/b[44]	Impairs Müller cell function via Forkhead box protein O4 (FOXO4), improving DR pathology.
RPE Cells	miR-5195-3p[45]	Protects RPE cells from HG-induced damage.
	miR-126[46]	Counters the pro-angiogenic effects of HG in RPE cells.
	miR-122[47]	Regulates TIMP3 to promote apoptosis in HG-induced human RPE cells.
	miR-139-5p[48]	Reduces apoptosis, oxidative stress, and inflammation caused by HG levels.

3.2 miRNAs and Ferroptosis

Based on their regulatory roles in ferroptosis, miRNAs can be categorized into ferroptosis-suppressing miRNAs and ferroptosis-promoting miRNAs. Ferroptosis-suppressing miRNAs target specific mRNAs, such as ACSL4 or LPCAT3, to inhibit ferroptosis. For example, miR-424-5p suppresses ferroptosis by

targeting ACSL4 without altering intracellular Fe^{2+} levels[49]. Similarly, miR-124-3p and miR-7-5p inhibit ferroptosis by downregulating STEAP3, reducing reactive oxygen species (ROS) levels, and stabilizing mitochondrial membrane potential [50–52].. Conversely, certain miRNAs exacerbate ferroptosis. Under high-glucose conditions, increased expression of miR-338-3p has been observed [53], which promotes ferroptosis by inhibiting SLC1A5, a key ferroptosis regulatory gene involved in redox balance, thereby increasing lipid ROS and Fe^{2+} levels.

3.3 miRNAs in DR and Ferroptosis

Emerging evidence underscores the intricate interplay between miRNAs, DR, and ferroptosis. Tang et al. demonstrated that miR-138-5p overexpression suppresses the Sirt1/Nrf2 pathway, reducing antioxidant enzyme expression and promoting ferroptosis in ARPE-19 cells cultured under high-glucose conditions[54]. Similarly, in high-glucose-cultured HRMECs, miR-93 upregulation was closely linked to ferroptosis induction, characterized by elevated intracellular iron levels and decreased expression of ferroptosis-associated proteins GPX4 and SLC7A11. Administration of $25(OH)D_3$ suppressed high-glucose-mediated oxidative damage and iron-dependent cell death through miR-93 inhibition, whereas miR-93 mimic transfection abolished these therapeutic benefits. This mechanistic reciprocity confirms miR-93's regulatory dominance in ferroptotic pathways, proposing targeted miRNA modulation as a viable DR intervention strategy [55].

On the other hand, miRNAs that inhibit ferroptosis have been shown to slow DR progression. For instance, miR-200b has been closely linked to DR and ferroptosis. By modulating the VEGF signaling pathway, miR-200b influences angiogenesis in the context of ferroptosis[33, 56, 57]. Intravitreal injection of miR-200b mimics has been shown to prevent diabetes-induced increases in VEGF mRNA and protein levels while suppressing glucose-induced vascular permeability and angiogenesis. Zhou et al.[58] reported that blocking miR-338-3p regulates SLC1A5 and inhibits high-glucose-induced ferroptosis in retinal epithelial cells. miR-138-5p suppression activates the Sirt1/Nrf2 signaling axis, augmenting cellular redox defenses to counteract ferroptotic pathways, preserve cell viability, and impede diabetic retinopathy advancement[59]. In streptozotocin (STZ)-induced DR models, miR-7-5p was shown to suppress ferroptosis by negatively regulating ACSL4, reducing intracellular iron levels and lipid peroxidation, and maintaining the expression of GPX4. This protective effect shielded endothelial cells from high-glucose-induced damage and further inhibited DR progression[60](Fig. 2).

4. Conclusion

Diabetic retinopathy persists as the primary etiology of acquired blindness in diabetic populations. Emerging evidence delineates ferroptotic pathways as central drivers of DR pathogenesis, with miRNAs demonstrating master regulatory control over these iron-dependent cell death mechanisms. This regulatory hierarchy positions miRNAs as dual-function entities – serving both as early diagnostic indicators and therapeutic modulators. This review provides a comprehensive overview of the involvement of iron overload and ferroptosis in DR progression. Moreover, it presents compelling

evidence supporting the dual role of miRNAs as both inducers and inhibitors of ferroptosis, shedding light on the shared molecular mechanisms underlying DR and identifying promising therapeutic targets. The ferroptosis regulatory axis in DR extends beyond miRNAs to encompass circRNA/lncRNA networks, with emerging evidence positioning these non-coding RNAs as critical modulators of iron-dependent cell death pathways. However, the precise mechanisms through which they contribute to this process remain largely unexplored and warrant further investigation. As discussed in this review, a deeper understanding of these molecular pathways could lead to the identification of novel biomarkers and the development of innovative therapeutic strategies, ultimately offering new perspectives for DR management.

Declarations

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Author Contribution

Lamusi A: Writing-original draft, Methodology, Writing-review & editing, Formal analysis, Data curation, Conceptualization, Funding acquisitionRina Sa: Writing-original draft, Formal analysis, Data

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Figures

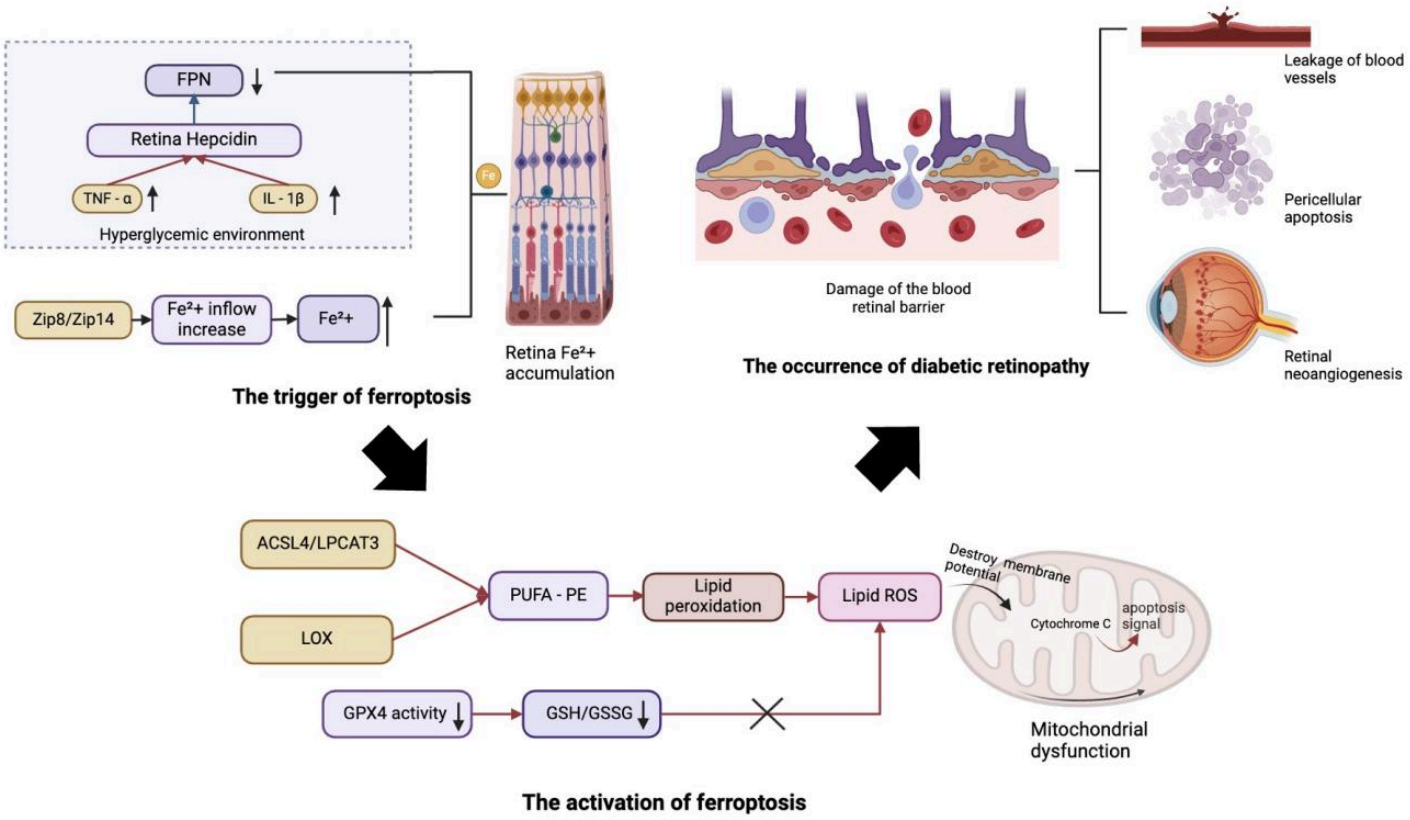


Figure 1

Ferroptosis in Diabetic Patients Induces Diabetic Retinopathy

(In diabetic patients, retinal iron levels are significantly elevated, leading to iron accumulation through the upregulation of Zip8/Zip14 (iron transporters) and downregulation of the iron exporter FPN. Iron overload induces lipid peroxidation of polyunsaturated fatty acids (PUFAs) catalyzed by lipoxygenase (LOX) and ACSL4/LPCAT3, resulting in the production of lipid ROS. The antioxidant defense system against iron overload, such as GPX4 and GSH, becomes impaired and is unable to eliminate lipid ROS, ultimately causing cell membrane rupture and ferroptosis. Iron overload generates ROS via the Fenton reaction, triggering oxidative stress, mitochondrial dysfunction, and inflammatory responses, which damage the blood-retinal barrier (BRB), leading to vascular leakage, pericyte apoptosis, and pathological neovascularization.)

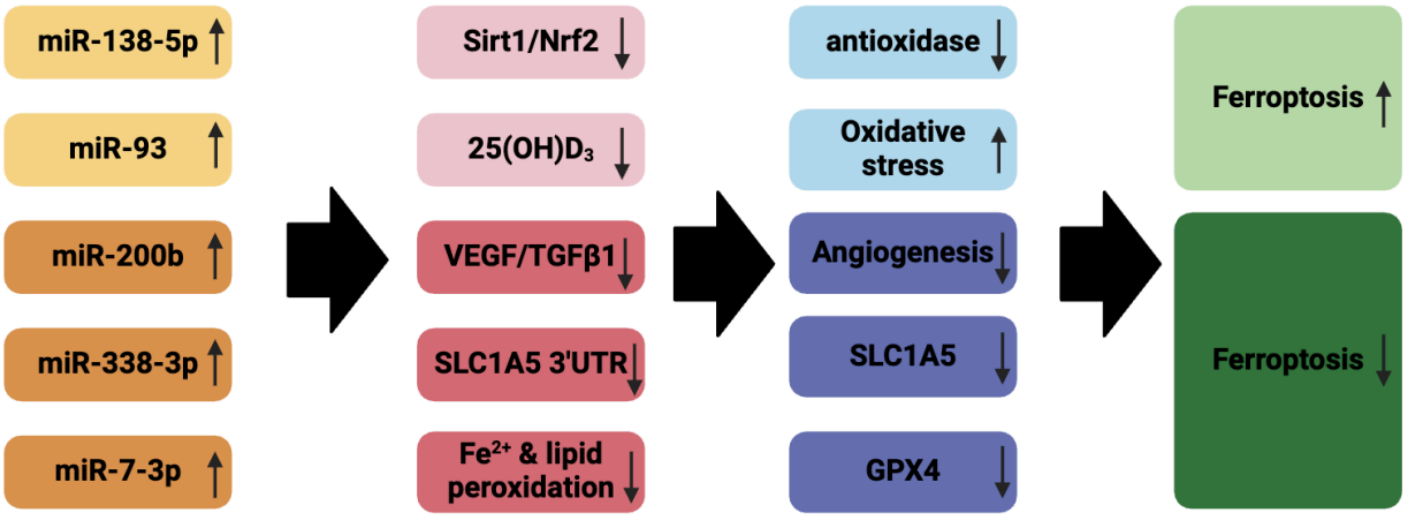


Figure 2

A Close Relationship Between miRNA and Ferroptosis in DR