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*Review*

# Research Status on the Combined Effects of Mitochondrial Dynamics/LncRNA/Ferroptosis/Cuproptosis in the Mechanisms of Antiplatelet Drugs

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**Abstract**

Antiplatelet agents such as aspirin, clopidogrel, ticagrelor, and abciximab are widely used as antithrombotic drugs. These drugs primarily inhibit platelet adhesion, activation, and aggregation by suppressing thromboxane $A_2$ synthesis or blocking the $P2Y_{12}$ adenosine diphosphate (ADP) receptor or the glycoprotein IIb/IIIa receptor. Common adverse effects include bleeding, rash, bronchospasm, thrombocytopenia, osteoporosis, allergic reactions, and hypotension. However, limitations in both efficacy and safety have driven the search for novel antiplatelet therapies. Recent studies suggest that antithrombotic drugs may act through mitochondrial dynamics, long noncoding RNAs (lncRNAs), ferroptosis, and cuproptosis. Nonetheless, the precise mechanisms involved remain incompletely understood.

**Keywords:** platelet aggregation inhibitors; mitochondrial dynamics; RNA, long noncoding; ferroptosis; cuproptosis; thrombosis

## 1. Introduction

Thrombotic disease refers to clinical conditions caused by thrombosis and thromboembolism that significantly threaten human health. These disorders rank among the leading causes of morbidity and mortality worldwide. Obstruction of blood flow after thrombosis, or the shedding of emboli, interrupts downstream circulation, leading to ischemia and tissue necrosis [1]. It is a significant contributor to different cardiovascular and cerebrovascular diseases [2]. Currently, the main clinical treatments of thrombotic diseases include anticoagulant, antiplatelet, and thrombolytic therapies and interventional or surgical procedures (Table 1). Among these, anticoagulant therapy remains the most widely used treatment, particularly for preventing and treating venous system thrombosis and intracardiac thrombus formation. Anticoagulants inhibit coagulation activity, prevent thrombus expansion, and facilitate gradual thrombus dissolution through the body's endogenous fibrinolytic system. Recently, novel oral anticoagulants, including rivaroxaban, apixaban, and dabigatran etexilate, have become the first choice in many clinical settings because of their rapid onset of action, minimal drug interactions, and lack of requirement for routine coagulation monitoring. Injectable anticoagulants, including low molecular weight heparin and unfractionated heparin, which require intravenous pumping and monitoring, are commonly used for acute-phase treatment or warfarin bridging therapy. Additionally, antiplatelet therapy is frequently used alongside anticoagulant therapy. Antiplatelet therapy is primarily used for arterial thrombosis prevention and treatment, including coronary heart disease, ischemic stroke, and peripheral arterial disease. The formation of arterial thrombosis typically begins with platelet aggregation at sites of ruptured atherosclerotic plaques. Commonly used antiplatelet agents include aspirin and $P2Y_{12}$ receptor inhibitors, such as clopidogrel, ticagrelor, and prasugrel. Dual antiplatelet therapy, usually consisting of aspirin combined with a $P2Y_{12}$ inhibitor, is widely used in patients with acute coronary syndrome or following coronary stent implantation to prevent stent thrombosis and recurrent cardiovascular events [3]. With the increasing prevalence and incidence of thrombotic diseases, the development of novel antithrombotic drugs has gradually become an important research focus. A previous study [4] demonstrated that the mechanisms of action of emerging antithrombotic drugs may be related to mitochondrial dynamics. The study of new antithrombotic drugs demonstrated that the triphenyl phosphonium cation and the bicyclic ortho-carbonyl hydroquinone are connected by a short alkyl chain, which can significantly enhance the antiplatelet effect. This structure increases mitochondrial reactive oxygen species (ROS) production and decreases mitochondrial membrane potential and oxygen consumption rate (OCR) by uncoupling oxidative phosphorylation, thereby disrupting the energy supply required for platelet activation. Notably, this effect depends on the integrity of the compound structure, rather than its individual components [4]. In platelets, mitochondrial dynamics regulate platelet activation through the $Ca^{2+}$-dependent signaling pathway and are closely associ-

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ated with long noncoding RNAs (lncRNAs). A recent study [5] demonstrated that the existing new antiplatelet drug, MITOCDNB, reduces platelet activation through its selective effect on mitochondrial thioredoxin reductase. Additionally, lncRNA Gm15441 regulates metabolic homeostasis and oxidative stress by modulating the expression of thioredoxin-interacting protein (TXNIP). As an endogenous thioredoxin inhibitor, TXNIP expression may affect the activity of the mitochondrial thioredoxin system through lncRNA-mediated transcriptional regulation. A recent study [6] demonstrated that the expression of 6109 lncRNAs was detected in human platelets, of which 338 were differentially expressed in high-responsive and low-responsive platelets. Bioinformatics analysis revealed that these expressed lncRNAs are closely associated with platelet activity and related functions [6]. For instance, PAR-lncRNA-1 (an lncRNA downregulated in highly reactive platelets) is significantly downregulated in platelets of patients with acute myocardial infarction. Notably, aspirin treatment can partially reverse this downregulation, indicating that lncRNA may be a regulator of platelet function. Ferroptosis may be associated with platelet activation [7]. Iron ions directly influence platelet activity in a concentration-dependent manner by promoting calcium mobilization and activating integrin αIIbβ3 and its downstream outward-inward signal transduction. *In vitro* experiments have demonstrated that iron chloride stimulation induces activation marker expression and protein phosphorylation in human and mouse platelets. Additionally, ferroptosis and platelet function can be bidirectionally regulated. Ferroptosis may directly compromise the platelet membrane structure and impair its function through lipid peroxidation products (PUFA-containing lipids). In a mouse model of iron deficiency anemia (IDA), the inhibition of platelet function may be related to the reduced lipid peroxidation resulting from iron deficiency. Conversely, platelets can affect endothelial ferroptosis by releasing inflammatory mediators or oxidative stress products, including ROS. Previous studies demonstrated that cuproptosis plays a fundamental role in cardiovascular diseases [8,9]. Cuproptosis, as a copper-dependent form of regulated cell death, plays an important regulatory role in cardiovascular diseases. Disruption of copper ion homeostasis can induce vascular endothelial injury and platelet activation through the cuproptosis pathway, providing a potential target for antiplatelet therapy. For instance, copper-chelating agents (ammonium tetrathiomolybdate) can alleviate cardiovascular disease by inhibiting the cuproptosis pathway.

Overall, antiplatelet drugs may be associated with mitochondrial dynamics/lncRNA/ferroptosis/cuproptosis. However, comprehensive studies systematically integrating these mechanisms remain limited. Therefore, this review summarizes current research to provide a theoretical basis for further research on precision therapy (Fig. 1).

## 2. Overview of Antiplatelet Drugs

Antiplatelet drugs are a class of agents that inhibit platelet activation and aggregation through distinct mechanisms, thereby preventing arterial thrombosis. They are primarily used for atherosclerotic thrombotic disease prevention and treatment, including myocardial infarction, ischemic stroke, and peripheral arterial disease. Under normal physiological conditions, vascular injury activates platelets, leading to adhesion and aggregation to form a hemostatic thrombus. The core role of antiplatelet drugs is to interfere with the key link in platelet activation. As illustrated in Fig. 2, the mechanisms of action of antiplatelet drugs include the following categories: (1) Thromboxane $A_2$ ($TXA_2$) pathway inhibitors: $TXA_2$ pathway inhibitors often include aspirin, terutroban, and ozagrel. The representative drug is aspirin. Aspirin irreversibly inhibits cyclooxygenase-1 (COX-1), the key enzyme in thromboxane $A_2$ synthesis. $TXA_2$ is a potent promoter of platelet aggregation and a vasoconstrictor. Aspirin deactivates COX-1 by acetylating it, thereby almost completely blocking $TXA_2$ production. Since platelets lack nuclei and cannot synthesize new COX-1 enzymes, this inhibition persists for the lifespan of platelets, approximately 7–10 days, until new platelets are generated. It may also downregulate TP receptor membrane expression through Pim kinase inhibitors. For instance, the mutant serine 57 site can disrupt TPαR function to indirectly inhibit the $TXA_2$ signal. This is independent of COX-1 inhibition or direct receptor antagonism and without increasing bleeding risk [10]. (2) $P2Y_{12}$ adenosine diphosphate (ADP) receptor antagonists: $P2Y_{12}$ ADP receptor antagonists, including clopidogrel, ticagrelor, and prasugrel, selectively block the platelet $P2Y_{12}$ receptor. The mechanism of action is that clopidogrel and prasugrel act irreversibly, and ticagrelor acts reversibly. $P2Y_{12}$ receptor on platelet surfaces is crucial for ADP-activated platelets, blocking the ADP pathway, which significantly weakens the amplification effect of platelet activation and markedly inhibits platelet aggregation [11]. It is implicated in platelet activation by inhibiting ADP-dependent signaling pathways [12]. IIb/IIIa receptor inhibitors, specifically glycoprotein IIb/IIIa receptor inhibitors, include abciximab, tirofiban, and eptifibatide. The mechanism of action is the inhibition of the final common pathway. Irrespective of the pathway of platelet activation, their final aggregation must be achieved by binding the GPIIb/IIIa receptor to fibrinogen. These drugs directly block the GPIIb/IIIa receptor, preventing its binding to fibrinogen, thereby effectively inhibiting platelet aggregation [13]. Phosphodiesterase inhibitors include cilostazol, dipyridamole, and tadalafil. PDE3A (cilostazol) and PDE5 (tadalafil) inhibitors enhance the inhibitory signals of these second messengers by inhibiting the degradation of cyclic adenosine monophosphate (cAMP)/cyclic guanosine monophosphate (cGMP), reducing platelet activation, aggregation, and procoagulant response. The pri-

**Table 1. Summary of main treatment methods for clinical thrombotic diseases.**

| Treatment | Action mechanism | Representing a drug or technology |
|---|---|---|
| Anticoagulant therapy | Inhibit the activity of coagulation factors to prevent new thrombosis and the expansion of existing thrombosis. | Warfarin, heparin, low molecular weight heparin, and direct oral anticoagulants (DOACs) such as rivaroxaban and apixaban. |
| Antiplatelet therapy | Inhibit platelet activation and aggregation, prevent arterial thrombosis. | Aspirin, clopidogrel, ticagrelor, dipyridamole. |
| Thrombolytic therapy | The fibrinolytic system is activated by drugs to rapidly dissolve the formed thrombus. | Alteplase, urokinase, reteplase. |
| Interventional and surgical treatment | Use physical methods to remove, bypass, or block the thrombus, or to block the source of the thrombus. | Catheter thrombectomy, balloon dilatation/stent implantation, thrombectomy, inferior vena cava filter implantation, and arterial bypass grafting. |

DOACs, Direct Oral Anticoagulants.

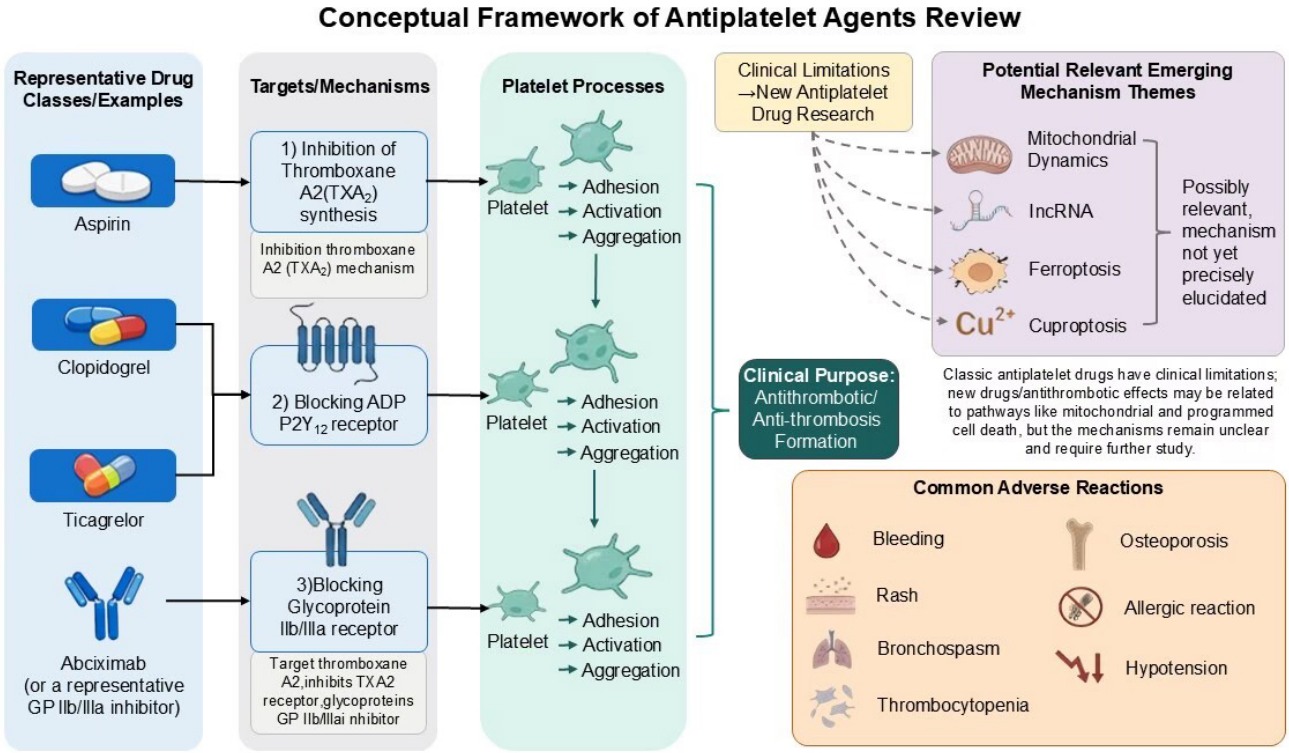



**Fig. 1. Conceptual framework of antiplatelet agents review**. ADP, adenosine diphosphate; lncRNA, long noncoding RNA.

mary mechanism of action is increasing cAMP concentration in platelets by inhibiting phosphodiesterase. Elevated cAMP levels can inhibit platelet activation. Dipyridamole can enhance this effect by inhibiting adenosine reuptake [14]. Protease-activated receptor 1 (PAR-1) is a thrombin-activated platelet receptor of the G protein-coupled receptor family. Thrombin exposes new ligand-binding sites by cutting the N-terminus of PAR-1, thereby activating downstream signaling pathways that promote platelet aggregation and thrombosis. PAR-1 antagonists selectively inhibit this process, thereby blocking thrombin-mediated platelet activation by antagonizing PAR-1. PAR-1 is the main receptor of thrombin on platelets [15]. The mechanism of action of antiplatelet drugs is diverse. However, there are few systematic studies or literature reports. In the development of precision treatment, the systematic and comprehensive study of the mechanism of action of antiplatelet drugs may become a research focus in this field in the future.

## 3. Research Progress of Mitochondrial Dynamics/LncRNA/Ferroptosis/Cuproptosis Regulatory Network

### *3.1 Research Progress of Mitochondrial Dynamics and LncRNA*

Current research primarily focuses on the regulation of mitochondrial dynamics by lncRNAs and their impact on platelet function. LncRNAs are RNA molecules longer

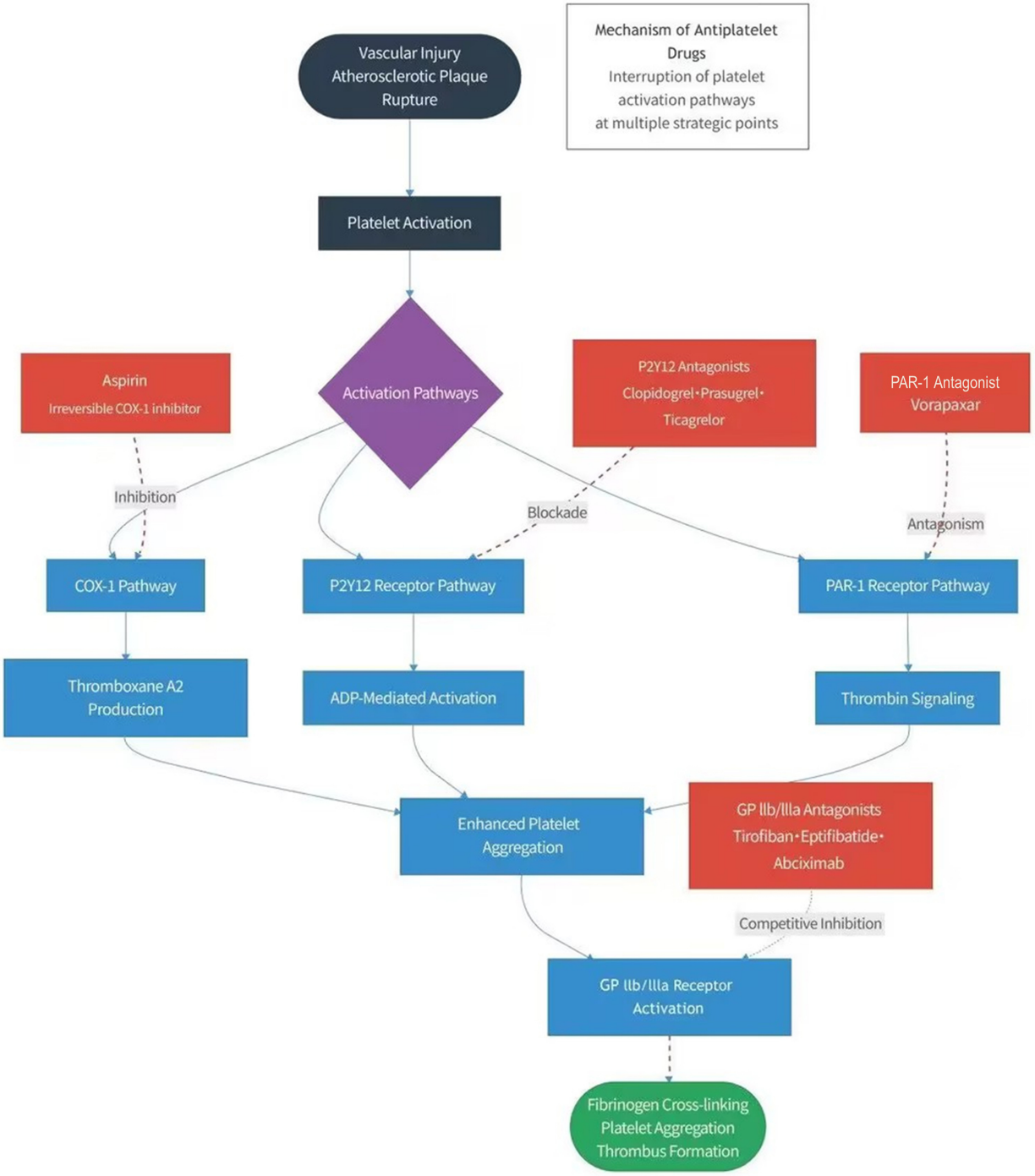



**Fig. 2. The main mechanism of antiplatelet drugs.** Note: Blue represents physiological processes, red represents drug actions, and green represents the final results. COX-1, cyclooxygenase-1; PAR-1, protease-activated receptor 1.

than 200 nucleotides that do not encode proteins. As important epigenetic regulators, they can regulate gene transcription, mRNA stability, and translation. Mitochondrial dynamics, governed by the balance between mitochondrial fission and fusion, are essential for platelet activation [16]. Emerging evidence suggests that lncRNAs may influence platelet function by regulating mitochondrial dynamics through several potential mechanisms:

#### 3.1.1 LncRNA Regulates the Expression of Genes Involved in Mitochondrial Dynamics

(1) MicroRNA (miRNA) regulatory network: The establishment of the lncRNA-00742/miR-116/CD74 regulatory network revealed that lncRNA can indirectly regulate mitochondrial function through miRNA. A previous study demonstrated that vanadium (V)-induced mitochondrial damage and mitochondrial apoptosis-related factor expression are upregulated, and miR-116 knockdown can al-

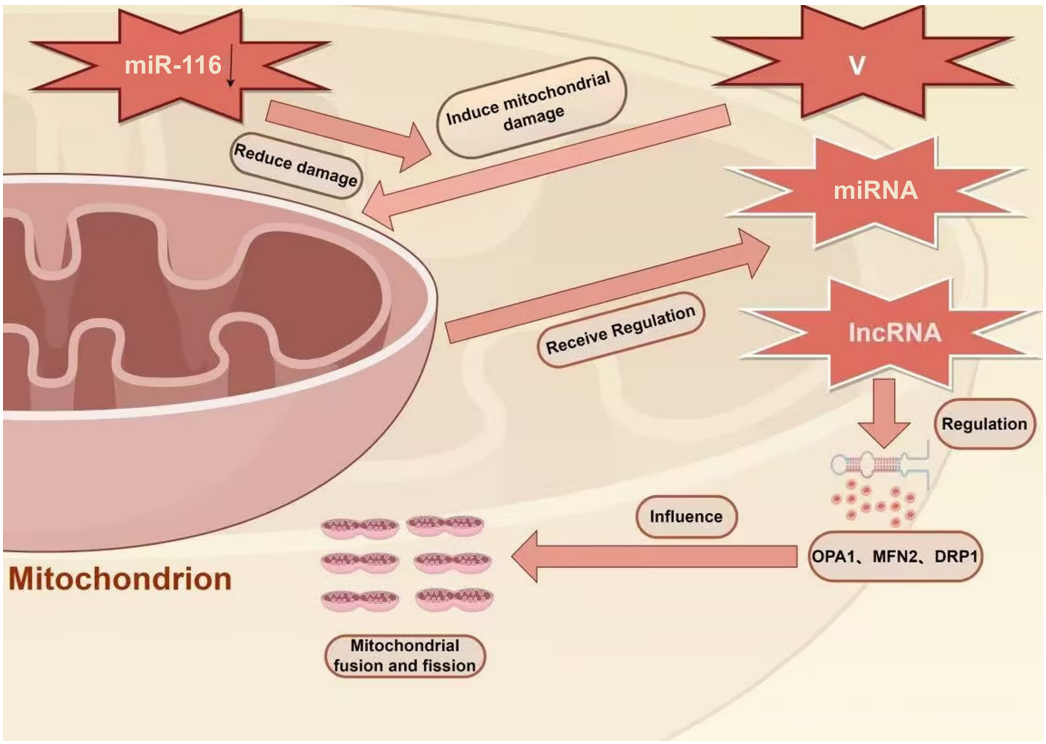



**Fig. 3. Partial mechanism map of lncRNA and mitochondrial dynamics**. OPA1, optic atrophy 1; MFN2, mitofusin-2; DRP1, dynamin-related protein 1. The downward-pointing arrow indicates downregulation.

leviate this damage [17]. (2) Direct regulation of mitochondrial fusion/fission genes study demonstrated the regulation of the expression of mitochondrial dynamics key genes, including optic atrophy 1 (OPA1, which mediates inner membrane fusion), mitofusin-2 (MFN2, responsible for outer membrane fusion), and dynamin-related protein 1 (DRP1, a critical mediator of mitochondrial fission), thereby affecting mitochondrial fusion and division processes (Fig. 3). Furthermore, the nuclear genome-encoded lncRNA can function as a critical epigenetic regulator of mitochondrial metabolism in liver cancer cells [18].

#### 3.1.2 Mitochondrial Functional Status (ROS Production) Can Subsequently Modulate LncRNA Expression

(1) Regulated by oxidative stress and lncRNA expression. In diabetic retinopathy, hyperglycemia-induced mitochondrial dysfunction elevates ROS levels and significantly changes the expression patterns of multiple lncRNAs [19]. Both nuclear genome-encoded lncRNAs (LL22NC03-N14H11.1) and mitochondrial DNA-encoded lncRNAs (lncMtDloop) are sensitive to mitochondrial ROS (Fig. 4). LncMtDloop contributes to the maintenance of aging-related mitochondrial homeostasis by preserving mitochondrial RNA levels and functions, which may be affected by ROS accumulation nuclear reverse signaling pathway [20]. Mitochondrial dysfunction (calcium homeostasis imbalance and excessive ROS) can affect lncRNA transcription through nuclear-mitochondrial interaction. In hepatocellular carcinoma cells, mitochondrial metabolic disturbances regulate nuclear-mitochondrial transport of lncRNA through RNA transporter HuR and the mitochondrial transmembrane protein MTCH2, thereby regulating epigenetic modification [18].

### *3.2 Combined Research Progress of Mitochondrial Dynamics and Ferroptosis*

Mitochondrial dynamics represent a central regulatory hub influencing cellular sensitivity to ferroptosis. Mitochondrial dynamics include fusion and fission: fusion is mediated by outer mitochondrial membrane proteins MFN1/2 and inner membrane protein OPA1. Fusion supports mitochondrial networking, content exchange, and buffer pressure and maintains mitochondrial function. Fission is mainly mediated by the DRP1 protein and its receptor. Division helps separate damaged mitochondria for clearance through mitophagy, but is also associated with apoptosis and several diseases. Ferroptosis is an iron-dependent type of cell death characterized by excessive accumulation of lipid peroxides, driven by three main mechanisms: (1) The antioxidant defence system, especially glutathione peroxidase 4 (GPX4)-GSH system failure, GPX4 enzyme requires GSH to reduce lipid peroxides. System $Xc^-$ comprises SLC7A11 and SLC3A2, a key channel for cellular uptake of cystine to synthesize GSH. (2) Iron metabolism disorder: Intracellular free iron catalyzes lipid peroxidation through the Fenton reaction. (3) Lipid metabolism changes: phospholipids rich in polyunsaturated fatty acids are prone to peroxidation.

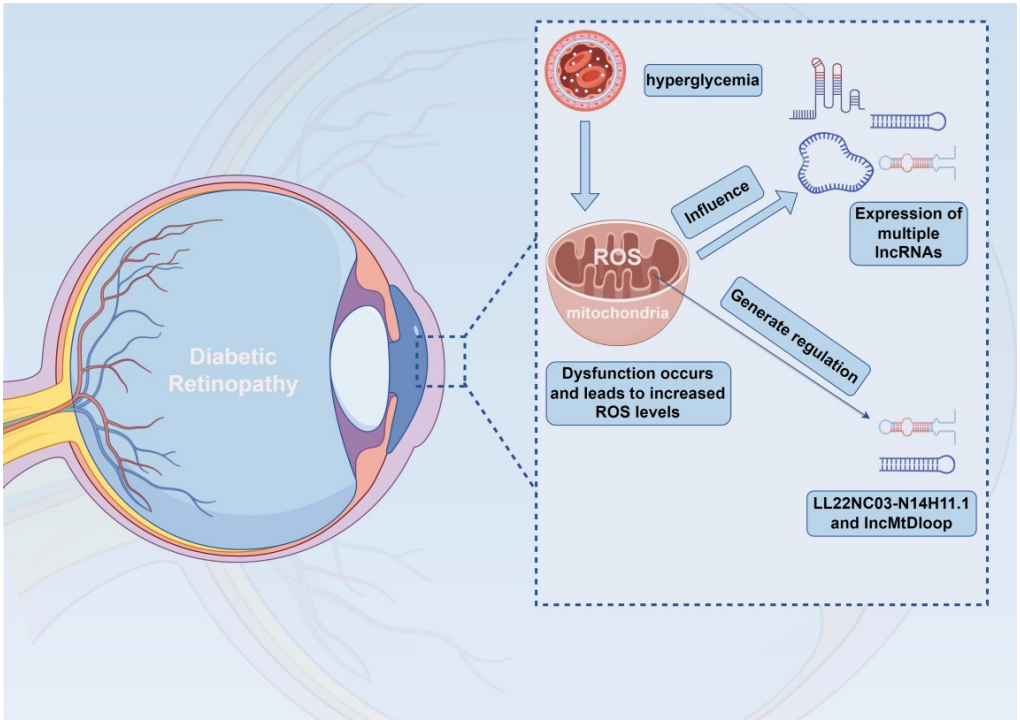



**Fig. 4. Partial mechanism map of lncRNA and mitochondria in diabetic retinopathy**. ROS, reactive oxygen species.

3.2.1 Mitochondrial Fission Promotes Ferroptosis

Mitochondrial fission enhances ferroptosis by generating mitochondrial fragments more susceptible to lipid peroxidation, thereby exacerbating intracellular oxidative stress [21], which is a primary source of ROS in cells, and the oxidative phosphorylation process contributes to ROS accumulation. These ROS directly facilitate lipid peroxidation, the principal indicator of ferroptosis. In ferroptosis, increased ROS production destroys cell membrane lipids, resulting in membrane rupture and cell death. For instance, mitochondrial dysfunction (including damage to the electron transport chain) increases ROS levels, which subsequently induces ferroptosis and mitochondrial fission [22]. Evidence suggests that mitochondrial fission can facilitate the onset of ferroptosis [23]. During ferroptosis, mitochondria undergo notable morphological changes, including volume decrease, membrane density increase, loss of cristae, and outer membrane rupture. These changes are closely related to the mitochondrial fission process. DRP1-mediated mitochondrial fission increases mitochondrial membrane potential and ROS production [24].

3.2.2 Mitochondrial Fusion Inhibits Ferroptosis

Maintaining mitochondrial fusion status or promoting fusion can enhance cellular resistance to ferroptosis through the OPA1 protein. The mitochondrial fusion protein OPA1 (a dynamin-like GTPase) modulates ferroptosis sensitivity by maintaining mitochondrial homeostasis and function. A previous study [25] demonstrated that cells deficient in OPA1 exhibit significant resistance to ferroptosis, and reactivating its GTPase activity (non-fusion function dependence) can re-endow ferroptosis sensitivity. OPA1 promotes ferroptosis by promoting the production of mitochondrial lipid reactive oxygen species (ROS) and inhibiting the integrated stress response (ISR) mechanism mediated by activating transcription factor 4 (ATF4), indicating that OPA1 affects ferroptosis through a fusion-independent metabolic regulatory axis (Fig. 5). Another study [26] demonstrated a negative correlation between mitochondrial fusion and ferroptosis in the acute ozone exposure model; the decrease in mitochondrial fusion (decrease of OPA1 expression) is accompanied by an increase of ferroptosis, whereas the recovery of fusion by drug (ferrostatin-1) or gene intervention (TRPA1 knockout) can inhibit ferroptosis. Enhanced mitochondrial fusion (OPA1 activation through the PI3K/Akt pathway) can reduce inflammation and oxidative stress, therefore decreasing ferroptosis.

*3.3 Joint Research Progress of Mitochondrial Dynamics and Cuproptosis*

Cuproptosis is a new type of programmed cell death distinct from apoptosis, necrosis, pyroptosis, or ferroptosis. The fundamental traits are copper dependence and mitochondrial respiratory regulation. It is a protein oligomerization induced by the aberrant binding of copper ions to lipoic acylated proteins, which leads to proteotoxic stress and cell death. This mechanism of death does not depend on known cell death pathways, including caspase activation or lipid peroxidation, and is classified as an independent type of death [27,28].

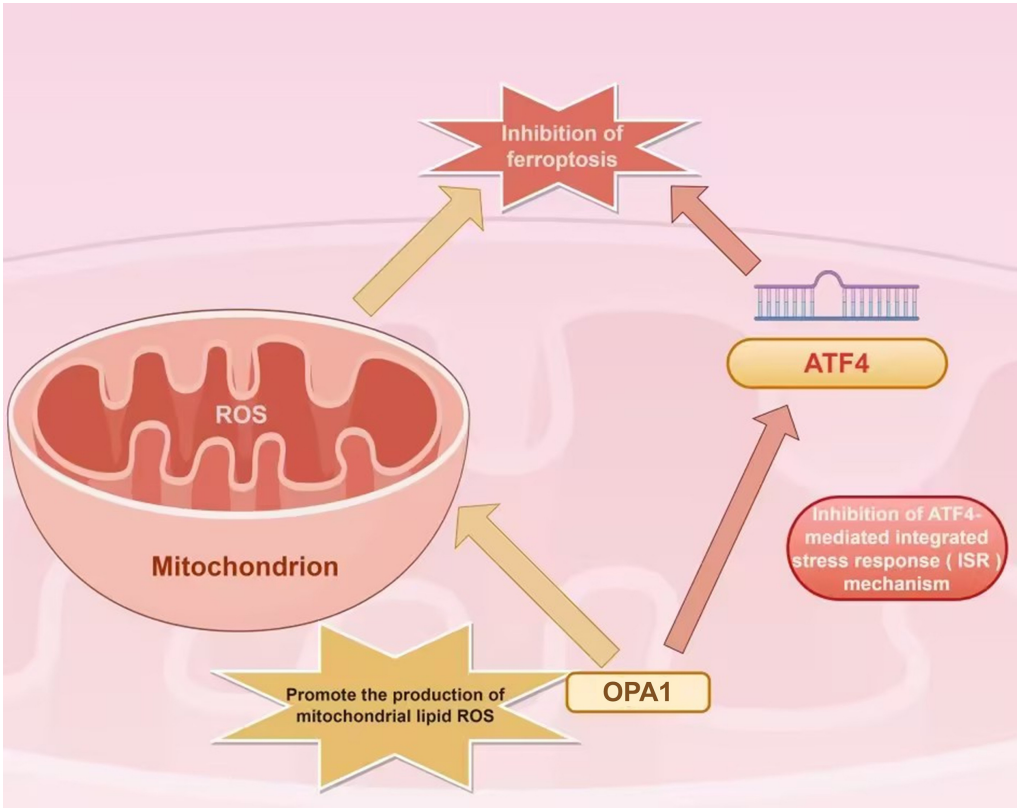



**Fig. 5. Mechanism map of mitochondria and ferroptosis**. ATF4, activating transcription factor 4.

3.3.1 Mitochondria-Dependent Mechanism of Cuproptosis

Cuproptosis is a copper-dependent, mitochondrial metabolism-associated type of programmed cell death. The fundamental mechanism entails the direct binding of copper ions with acylated proteins in the mitochondrial tricarboxylic acid cycle (TCA), causing abnormal protein aggregation and iron-sulfur (Fe-S) cluster protein depletion, resulting in mitochondrial dysfunction [29,30]. Copper exacerbates mitochondrial damage by inducing oligomerization of dihydrolipoamide S-acetyltransferase (DLAT) [31]. Cuproptosis depends on mitochondrial respiration, which is in contrast to the Warburg effect of glycolysis-dominated tumor metabolism, indicating that regulation of mitochondrial metabolism can enhance cuproptosis sensitivity [32].

3.3.2 Role of Mitochondrial Dynamics in Cuproptosis

Mitochondrial fusion and fission imbalance are closely associated with cuproptosis. Excessive copper ions disrupt mitochondrial protein homeostasis, including the stability of Fe-S cluster proteins, leading to mitochondrial depolarization, swelling, and membrane potential collapse [33]. While the mitochondrial unfolded protein response (UPRmt) normally preserves mitochondrial protein import and homeostasis [34], the disruption of UPRmt and mitophagy during cuproptosis may further amplify the cell death signal [30,33]. The loss of iron-sulfur cluster proteins induced mitochondrial $Ca^{2+}$ overload and ROS burst, resulting in a self-amplified damage cycle [31].

*3.4 Research Progress on the Combined Regulation of LncRNA-Ferroptosis/LncRNA-Cuproptosis*

3.4.1 Research Progress on the Combination of LncRNA and Ferroptosis

Long noncoding RNAs (lncRNAs) are essential regulatory molecules that modulate cellular sensitivity to ferroptosis, either promoting or inhibiting this form of programmed cell death by interfering with its core signaling pathways. Mechanistically, lncRNAs frequently function as competing endogenous RNAs (ceRNAs) to competitively bind miRNAs and indirectly regulate key ferroptotic proteins. For instance, lncRNA H19 inhibits ferroptosis by sponging miR-19b-3p, leading to the upregulation of ferritin heavy chain 1 (FTH1) expression [35], whereas lncRNA-CASC2 enhances gastric cancer cell sensitivity to ferroptosis by stabilizing the SOCS2 protein [36]. At the transcriptional level, upstream transcription factors, including POU6F1, can directly bind to the lncRNA-CASC2 promoter to promote its expression, activating the ferroptosis pathway [36]. Conversely, lncRNAs can guide transcription factors; for instance, LINC02936 binds to SIX1 to upregulate ceruloplasmin (CP) expression, which inhibits ferroptosis and enhances endometrial carcinoma progression [37]. Furthermore, lncRNAs actively intervene in broader stress and metabolic signaling cascades. In renal ischemia-reperfusion injury (IRI), exosomal lncRNA TUG1 derived from urine stem cells significantly attenuates ferroptosis and acute kidney injury through the SRSF1/ACSL4 axis, a

protective effect evident in hypoxia/reoxygenation-treated HK-2 cells [38]. Similarly, lncRNA URB1-AS1 regulates ferroptosis sensitivity through the MAPK cascade in hepatocellular carcinoma [39].

Previous studies [39,40] demonstrated that the combined study of lncRNA and ferroptosis is promising in tumor therapy. In HCC treatment, lncRNA URB1-AS1 and MIR6852 inhibit tumor growth by modulating ferroptosis-related pathways, and lncRNAs play a key role in sorafenib-induced ferroptosis.

#### 3.4.2 Combined Research Progress of LncRNA and Cuproptosis

The theoretical relevance of lncRNA-cuproptosis networks to cardiovascular biology.

The interaction between lncRNAs and cuproptosis has been primarily investigated in oncology, with prognostic models developed for malignancies including leukemia, lung adenocarcinoma, and pancreatic cancer [41,42,43]. Mechanistically, cuproptosis-related lncRNAs (HAGLR) modulate copper-induced toxicity through ceRNA networks, epigenetic modifications, and metabolic reprogramming of the tricarboxylic acid (TCA) cycle [41,42,43,44,45].

Although these prognostic models are exclusively tumor-focused, they offer an essential translational blueprint for thrombosis research. A robust rationale for this extrapolation lies in the common metabolic plasticity between solid tumors and hyperactivated platelets. In a pro-thrombotic, localized ischemic microenvironment, platelets experience significant metabolic reprogramming (balancing glycolysis and oxidative phosphorylation) and enduring severe oxidative stress, reminiscent of the tumor microenvironment. Therefore, the molecular nodes characterized in oncological models—particularly how lncRNAs manage mitochondrial copper overload and metabolic exhaustion—represent compelling hypothetical targets for designing next-generation antiplatelet therapies designed to deliberately induce platelet metabolic collapse [46].

### *3.5 Research Progress on the Combination of Ferroptosis and Cuproptosis*

Ferroptosis and cuproptosis, two metal ion–dependent forms of regulated cell death, have recently been recognized for their significant synergistic potential in cancer treatment. Recent studies have explored their molecular mechanisms, cross-pathways, and synergistic effects in cancer treatment.

#### 3.5.1 Shared Molecular Mechanisms and Cross-talk Pathways

Ferroptosis depends on iron metabolism dysregulation and lipid peroxidation, whereas cuproptosis is associated with copper ion accumulation, acylated protein aggregation, and Fe-S cluster protein damage. Despite these distinct pathways, intersections exist between the two processes. Glutathione serves as the central hub, and the depletion of GSH is the cross-regulatory node of the two types of death. Cuproptosis aggravates ferroptosis by interfering with GSH synthesis. Both processes result in mitochondrial dysfunction; however, cuproptosis directly targets the acylated protein in the TCA cycle [29], whereas ferroptosis compromises mitochondrial membrane integrity through lipid peroxidation.

#### 3.5.2 Synergistic Effect in Tumor Therapy

Co-induction of ferroptosis and cuproptosis has demonstrated enhanced therapeutic efficacy in liver cancer treatment. This combination inhibits the proliferation of liver cancer cells and activates anti-tumor immunity through immunogenic cell death (ICD) [46,47]. Nano-delivery systems for the treatment of tumors, such as HA-Z Cu nanoparticles, potentiate the ferroptosis effect by inducing GSH synthesis disorder through cuproptosis.

## 4. Research the Status of Antiplatelet Drugs in Mitochondrial Dynamics/LncRNA/Ferroptosis/Cuproptosis Regulatory Network

Before examining these intersections, an important biological caveat must be established: human platelets are anucleate. Consequently, classical nucleus-dependent cell death and *de novo* lncRNA transcription differ in platelets compared to nucleated tumor or somatic cells. Therefore, some mechanisms discussed below are supported by direct platelet data; others are hypothesis-driven extrapolations drawn from nucleated cell models (oncology and cardiovascular tissue models) to provide a theoretical basis to guide antiplatelet strategies.

A critical ontological question must be addressed: Do ferroptosis and cuproptosis genuinely occur in platelets, or are the observed effects indirect? Although platelets are anucleate, they are well-established to undergo classical intrinsic apoptosis. However, unlike nucleated cells where cell death pathways can be regulated by *de novo* gene transcription, ferroptosis and cuproptosis in platelets are executed directly through cytosolic lipid peroxidation and mitochondrial protein aggregation, respectively [48]. Consequently, we critically appraise that “ferroptosis” and “cuproptosis” in platelets should not be viewed as transcriptionally regulated programmed cell death, but rather as instances of “terminal metabolic exhaustion” and “accelerated structural clearance”. Antiplatelet drugs targeting these pathways do not induce death via nuclear degradation; instead, they trigger severe lipid or proteotoxic stress that disrupts platelet activation machinery and precipitates rapid clearance from circulation.

### *4.1 Possible Correlation Between Antiplatelet Drugs and Mitochondrial Dynamics*

#### 4.1.1 Platelet Activation Depends on Mitochondrial Function

A previous study [49] demonstrated that platelet activation is critically reliant on mitochondrial respiration and energy metabolism. Stimuli such as collagen induce the maximum respiratory response of mitochondria, promoting platelet aggregation and activation. This mechanism represents the principal target for antiplatelet drugs, as modulation of mitochondrial dynamics (such as reducing respiratory efficiency) can effectively inhibit platelet activation and thrombosis. Mitochondrial dynamics imbalance, including excessive fission, can impair mitochondrial function, disrupt calcium homeostasis, and increase ROS production. These factors collectively enhance platelet reactivity and the procoagulant phenotype of platelets [50,51].

#### 4.1.2 Development of Novel Mitochondria-Targeted Antiplatelet Drugs

Recent research has shifted to the development of mitochondria-specific antiplatelet drugs to reduce the side effects of conventional drugs (bleeding risk). For instance, MITOCDNB (a methanesulfonate with a butyl chain) significantly reduces collagen-induced mitochondrial maximal respiration by selectively inhibiting mitochondrial thioredoxin reductase 2 (TrxR2) activity, thereby inhibiting platelet activation. This compound exhibits high mitochondrial specificity, low cytotoxicity, and minimal systemic risk, providing a new strategy for antiplatelet therapy [5]. Compounds targeting mitochondrial respiration can collapse inner membrane potential, and OCR is required for platelet energy production, thereby preventing activation [4]. Collectively, these findings highlight mitochondrial dynamics regulation as a key direction for developing the next generation of antiplatelet drugs.

#### 4.1.3 Mitochondrial Dynamics and Drug Application in Antiplatelet-Related Diseases

In pathological conditions, including cardiovascular diseases, mitochondrial dynamics disorders (fission and fusion imbalance) increase thrombosis risk. Therefore, drugs (mitochondrial ROS scavengers and kinetic regulators) can improve mitochondrial function and be used to treat diseases such as atrial fibrillation, representing a novel antiplatelet therapy [50,51,52]. However, a previous study [51] demonstrated that traditional antiplatelet drugs (aspirin and clopidogrel) may exhibit reduced efficacy in specific patients, partly due to interference with mitochondrial calcium-dependent mechanisms. These observations highlight the need for future drug development to prioritize mitochondrial specificity [5]. Mitochondrial dynamics is the core mechanism of the antiplatelet effect, providing opportunities for new drug development and challenges in addressing the limitations and bleeding risks associated with existing therapies [51].

### *4.2 Possible Correlation Between Antiplatelet Drugs and LncRNA*

#### 4.2.1 Regulation of LncRNAs in Platelet Function

Some lncRNAs are directly implicated in platelet hyperresponsiveness. For instance, analysis of platelets from patients with acute myocardial infarction revealed significant downregulation of a specific lncRNA, which was partially restored following aspirin treatment [6]. This suggests that certain lncRNAs may act as negative regulator of platelet function, with their expression changes linked to thrombosis. Mechanistically, lncRNA can regulate platelet function by regulating mitochondrial ROS levels, polarization, and apoptosis through the miRNA axis (lncRNA Snhg1 targeting miR-361-5p, which subsequently affects mitochondrial protein OPA1), thereby mitigating cellular damage in ischemia/reperfusion injury [53,54]. These findings indicate that lncRNAs represent a novel class of platelet regulators involved in maintaining platelet homeostasis.

#### 4.2.2 Effects of Antiplatelet Drugs on LncRNA Expression

Antiplatelet drugs can modulate lncRNA dynamics directly or indirectly. For instance, aspirin inhibits the release of platelet lncRNA dose-dependently, especially under collagen and ADP stimulation [52]. This suggests a multi-faceted mechanism: beyond conventional coagulation inhibition, antiplatelet drugs can alter lncRNA profiles [52], which in turn may modulate mitochondrial function (such as ROS levels and energy metabolism, as demonstrated in hypoxic cellular models [55]). Some diseases (hepatocellular carcinoma and kidney disease) and lncRNAs (LL22NC03-N14H11.1 or Meg3) regulate mitochondrial fission and homeostasis. Such mechanisms can be used for antiplatelet-related therapies through drug targeting [56,57,58].

#### 4.2.3 The Potential of LncRNA as a Therapeutic Target

LncRNA represents a promising target for new antiplatelet drug development. Gene-based intervention targeting lncRNA or small molecule compounds (BTZO-1) has demonstrated the potential to regulate mitochondrial apoptosis and function. For instance, in the duck liver model, the lncRNA-00742/miR-116/CD74 axis modulates vanadium-induced mitochondrial damage [17]. These findings suggest that lncRNA-targeted drugs serve as an adjuvant therapy to reduce the bleeding risk of conventional antiplatelet drugs.

### *4.3 Research Progress of Antiplatelet Drugs, Mitochondrial Dynamics, and LncRNA*

#### 4.3.1 Comprehensive Mechanism

A previous study [59] demonstrated that mitochondrial dynamics and lncRNA form an interactive network in platelets. For instance, lncRNA (Snhg1 or Oip5-as1) affects ROS levels and mitochondrial respiration by regulat-

ing OPA1-mediated inner membrane fusion. Antiplatelet drugs, including MITOCDNB and aspirin, directly interfere with these processes, attenuating activation signals. In the myocardial ischemia/reperfusion model, lncRNA Oip5-as1 regulates mitochondrial dynamic balance, and its disorder aggravates injury [59]. Similarly, regulating mitochondrial oxidative stress (via endogenous SOD2) directly inhibits platelet-dependent thrombin generation and thrombosis [60], supporting the potential of combining mitochondrial-targeted agents with lncRNA regulation. These mechanisms are applied in pathological contexts (atrial fibrillation or cancer) for drug combination strategies (mitochondrial ROS scavengers and lncRNA inhibitors) to reduce the side effects of antiplatelet therapy [61].

#### 4.3.2 New Research Directions and Therapeutic Potential

Current research focuses on the development of 'dual-target' strategies, wherein drugs simultaneously target mitochondrial dynamics and lncRNAs to enhance efficacy. Mitochondrial autophagy/mitophagy modulators, for example, improve mitochondrial quality and affect lncRNA expression to restore mitochondrial function in cardiovascular disease [62]. Studies have demonstrated that drugs such as GSK669 demonstrate synergistic antioxidant and antiplatelet effects, potentially reducing bleeding risk [63]. A combination of natural drug components or mitochondrial-specific compounds with lncRNA regulation offers a promising avenue for drug development. However, research challenges include drug delivery barriers (such as mitochondrial targeting) and heterogeneous expression, which necessitate further validation by models (the use of nematode or plasma EV analysis) in the future [64,65].

### *4.4 The Possible Correlation Between Antiplatelet Drugs and Ferroptosis*

#### 4.4.1 Cross-Regulation of Antiplatelet Drugs and Ferroptosis

Platelet-derived molecules regulate ferroptosis: Platelet-derived microparticles increase cardiomyocyte susceptibility to ferroptosis by reducing stearic acid-phosphatidylcholine levels in cardiomyocytes. This suggests that antiplatelet therapy may protect cardiomyocytes by blocking this pathway, offering a multi-mechanism treatment approach for myocardial injury [66]. Conversely, ferroptosis modulators influence platelet function. Ferroptosis inhibitors (Lip-1 and Fer-1) alleviate iron overload-induced platelet dysfunction. The combination of ferroptosis inducers (RSL3) and the antiarrhythmic drug propafenone enhances the anti-tumor effect by inducing mitochondrial ferroptosis, highlighting interactions between ferroptosis and metabolic regulation [67].

Critical Appraisal of Current Evidence [68]: Despite these promising observations, significant contradictions and limitations exist in the current literature. First, there is a "ROS/Iron Paradox" in platelet biology. Although excessive ROS and iron can suppress platelet function through ferroptosis, physiological ROS bursts are essential for normal platelet activation and outside-in signaling. The precise quantitative threshold where ROS transitions from an "activation second messenger" to a "ferroptotic executioner" remains undefined. Furthermore, most studies rely on isolated platelets in static *in vitro* assays or non-platelet models (cardiomyocytes). These models fail to replicate the complex *in vivo* hemodynamic shear stress and the intricate cross-talk with vascular endothelial cells, making the direct *in vivo* translation of ferroptosis-inducing antiplatelet strategies highly premature.

The potential of mitochondrial targeted therapy: For instance, the ferroptosis inhibitor CuATSM (Copper(II) diacetyl-di(N4-methylthiosemicarbazone)) can reverse mitochondrial dynamics abnormalities and ferroptosis in vascular smooth muscle cells and inhibit pathological phenotype conversion [69], suggesting it may treat thrombosis-related vascular disease.

#### 4.4.2 Clinical Significance and Prospect of Combined Regulation

Synergistic antithrombotic strategies: Inhibition of platelet energy metabolism (the combination of cangrelor and glycolysis/respiratory chain inhibitors) can synergistically enhance antiplatelet efficacy without compromising basal hemostasis, providing a potential approach to reduce bleeding risk [70]. New targets for disease treatment: Targeting mitochondrial dynamics (DRP1 inhibitors) and the ferroptosis pathway. Further research is expected to lay a possible foundation for neurodegenerative diseases and other disease treatments, including the following: Remote ischemic preconditioning (rIPC) reduces renal tubular mitochondrial dysfunction and ferroptosis by inhibiting NADPH oxidase 4 (NOX4), and improves acute kidney injury [71].

### *4.5 Hypothesized Cross-Talk Between Antiplatelet Drugs, lncRNAs, and Ferroptosis*

Research exploring the interplay among antiplatelet drugs, lncRNAs, and ferroptosis remains in the early stage, with a comprehensive mechanistic framework yet to be established. Preliminary evidence indicates that antiplatelet drugs (aspirin) can regulate the expression of specific lncRNA, thereby affecting platelet function, and lncRNA plays a critical role in ferroptosis regulation [39]. Data [66] indicate that antiplatelet therapy may alleviate myocardial injury through the ferroptosis protection mechanism. These observations highlight lncRNA as a potential therapeutic target and provide a rationale for future research to investigate whether antiplatelet drugs regulate ferroptosis through lncRNA.

### *4.6 Possible Correlation Between Antiplatelet Drugs and Cuproptosis*

Cuproptosis is a copper-dependent type of cell death reliant on mitochondrial respiration and the TCA cycle [33].

Its markers include the following: (1) Mitochondrial protein aggregation: copper-induced aggregation of acylated proteins (DLAT) and destabilization of Fe-S cluster proteins. (2) Mitochondrial dysfunction: Copper causes energy collapse by disrupting the electron transport chain (ETC) and protein homeostasis [72]. FDX1 is the key regulatory factor in cuproptosis, and its expression level is directly associated with cellular sensitivity to cuproptosis [73]. (3) Association with mitochondrial dynamics: Mitochondrial fusion/fission imbalance (dynamic imbalance), mitochondrial autophagy disorder, and the disruption of UPRmt-mediated protein homeostasis [34] collectively aggravate cell death during cuproptosis [30,33]. Similar to ferroptosis, cuproptosis depends on mitochondrial metabolic pathways. However, the specific mechanisms are different (copper-specific induction of acylated protein aggregation) [30]. Because of the absence of direct evidence of cuproptosis in platelets, we propose a theoretical intersection based on tumor biology extrapolations. (1) Shared metabolic vulnerabilities: Tumor cells evade cuproptosis through metabolic reprogramming (the Warburg effect) and high GSH levels [32]. Similarly, hyperactivated platelets demonstrate significant metabolic adaptations. Targeting mitochondrial respiration (through PDH kinase inhibition) [72] may concurrently facilitate platelet sensitivity to copper-induced stress and inhibit activation. (2) Mitochondrial targeting strategies: In oncology, copper ionophores (elesclomol) selectively eliminate cells dependent on mitochondrial respiration [74]. Similarly, next-generation antiplatelet drugs with mitochondrial-targeting moieties (MITOCDNB) [5] may inadvertently disrupt mitochondrial copper homeostasis, causing a metabolic energy collapse similar to cuproptosis. However, confirming the existence and functionality of lipoylated TCA proteins in anucleate platelets is essential for validating this hypothesis. It has the potential for combined therapy: a cuproptosis inducer combined with a GSH depletion agent can potentiate cell death [75], and mitochondrial oxidative stress regulation by antiplatelet drugs may act synergistically with this effect [76]. Nevertheless, applying the concept of cuproptosis into platelet biology has limitations, as circulating anucleate platelets depend predominantly on glycolysis rather than the TCA cycle, resulting in a metabolic environment markedly different from that of nucleated solid tumors.

### *4.7 Extrapolating From Disease Models: Potential Links Between Antiplatelet Drugs, lncRNAs, and Cuproptosis*

A potential interplay exists among antiplatelet drugs, lncRNA, and cuproptosis. In cardiovascular diseases, antiplatelet drugs modulate platelet activity and associated cell death mechanisms by altering lncRNA expression, while cuproptosis-associated lncRNA plays key roles in cell death pathways. These interactions may be indirectly connected through shared inflammatory or signaling pathways. The following are summarized from two aspects.

#### 4.7.1 Mechanism of Antiplatelet Drugs Extends to the Cell Death Pathway

Antiplatelet drugs (aspirin) reduce platelet miR-126 levels, thereby inhibiting platelet activation and thrombosis [53]. Although not limited to lncRNA, evidence [46] indicates that the lncRNA family (including lncRNA) regulates similar mechanisms. Cuproptosis involves mitochondrial metabolism (TCA cycle), and antiplatelet drugs may target mitochondria to mitigate platelet overactivation and potential risk of cell death and are mentioned in mitochondrial-related mechanisms, including calcium signaling.

#### 4.7.2 Interaction in Disease Context

In cardiovascular disease, platelet activation drives thrombosis and inflammation, with antiplatelet therapy being central to the disease treatment [77]. In cancer, cuproptosis-related lncRNA regulates tumor progression [41,42,43], and certain antiplatelet drugs (eptifibatide) can inhibit EMT markers (epithelial-mesenchymal transition) and partially restore endothelial integrity, potentially influencing cell death signals [78]. Additionally, in AML or colon cancer, cuproptosis-related lncRNA signatures are implicated in immune response [45].

### *4.8 Research Progress on the Correlation Between the Mechanism of Antiplatelet Drugs and Ferroptosis and Cuproptosis*

The interplay between antiplatelet drugs and ferroptosis or cuproptosis focuses on mitochondrial dysfunction, metal ion homeostasis disorder, and immune microenvironment modulation. The following is summarized from two aspects.

#### 4.8.1 Copper and Iron May Be Potential New Targets for Antiplatelet Drugs

(1) Mitochondrial targeting strategy: Platelet mitochondria contribute to hyperresponsiveness (drug resistance) through calcium-dependent signaling [50], whereas copper/ferroptosis is involved in mitochondrial metabolic dysfunction [79]. Mitochondria-targeted antiplatelet drugs (inhibition of calcium signaling) may inhibit the double death pathway by regulating metal ion homeostasis [51]. (2) Metal ion homeostasis regulation: Copper/iron ionophores (nanomaterial HA-ZCu) can simultaneously induce cuproptosis and ferroptosis, demonstrating a synergistic anti-tumor effect, indicating promise in the treatment of liver cancer. This suggests potential for antiplatelet drug development focused on metal ion modulation [47]. (3) Immune regulation: ferroptosis synergistic therapy can activate ICD [80]. Platelets affect the immune response by regulating the tumor microenvironment [81,82], indicating that antiplatelet drugs can regulate immunotherapy by interfering with the copper/ferroptosis pathway.

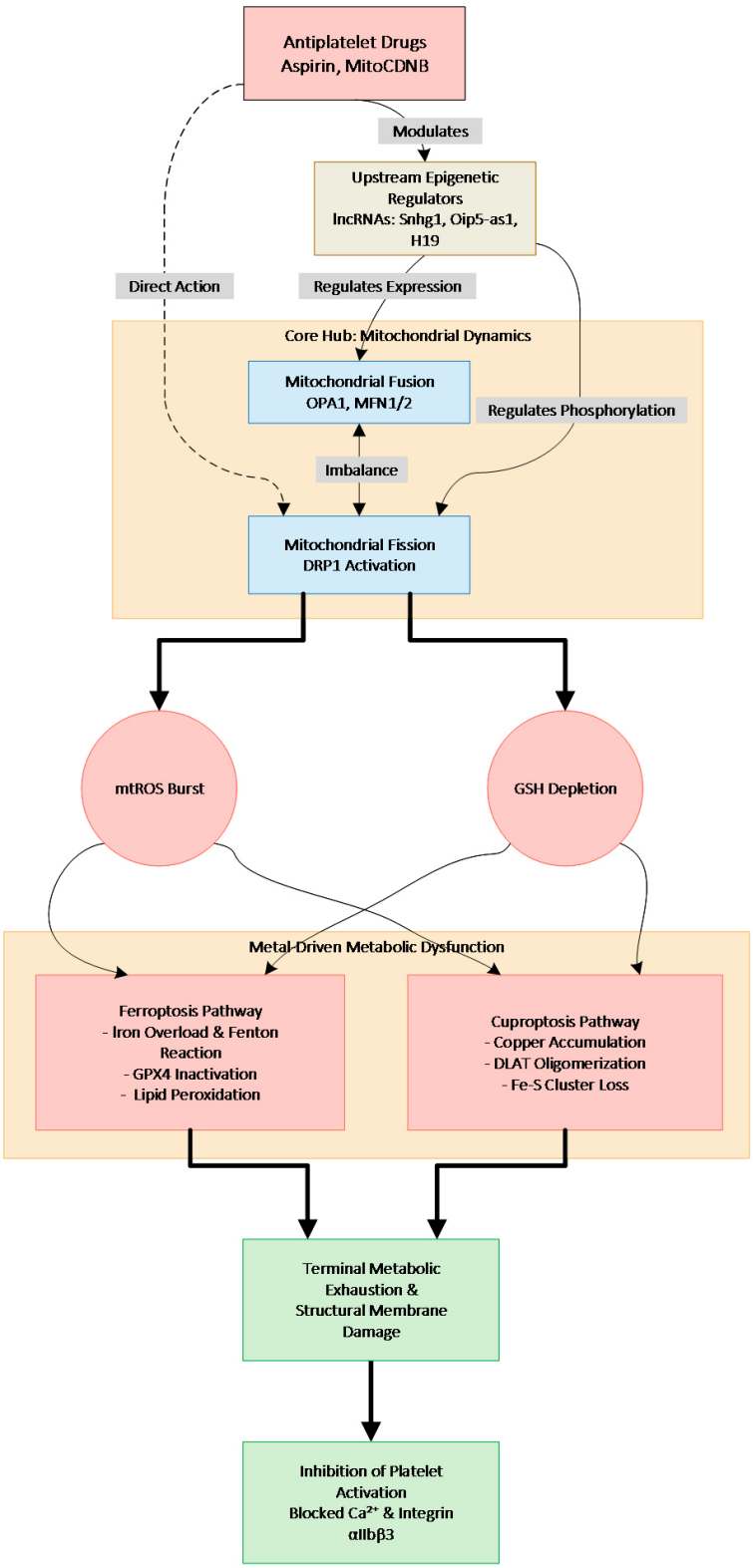



**Fig. 6. Final integrative model: the hypothesized antiplatelet drug–mitochondrial–metal cell death regulatory network**. GSH, glutathione; GPX4, glutathione peroxidase 4; DLAT, dihydrolipoamide S-acetyltransferase; Fe-S, iron-sulfur.

4.8.2 Combined Application of Copper and Iron in Disease Model

(1) Cardiovascular disease: In myocardial injury, inhibition of cuproptosis (rather than ferroptosis) underlies the cardioprotective effects of agents such as PHI [83]. Nevertheless, antiplatelet drugs can mitigate myocardial damage by blocking platelet-mediated ferroptosis [66]. (2) In the liver cancer model, simultaneous induction of cuprop-

tosis and ferroptosis exerts a synergistic anti-tumor effect through GSH depletion, lipid peroxidation accumulation, and mitochondrial damage and reshapes the immune microenvironment [47,80]. (3) In inflammatory diseases, periodontitis, and alcoholic hepatitis, dysregulated copper/-iron metabolism contributes to oxidative stress and M1 macrophage infiltration, highlighting potential therapeutic targets for anti-inflammatory and antiplatelet drugs [82,84].

### *4.9 Hierarchical Regulation Among Mitochondrial Dynamics, lncRNA, Ferroptosis, and Cuproptosis*

Mitochondrial dynamics represent a central regulatory node for both ferroptosis and cuproptosis. During ferroptosis, mitochondria undergo significant morphological changes, including increased membrane density, decreased cristae, enhanced oxidative phosphorylation, and increased ATP production. Additionally, mitochondrial fission is induced, and disruption of these mitochondrial dynamics modulates ferroptosis [85]. In cuproptosis, copper overload triggers mitochondrial dysfunction, leading to TCA cycle enzyme aggregation and the instability of iron-sulfur cluster proteins, thereby inducing proteotoxic stress. Furthermore, cuproptosis is accompanied by alterations in mitochondrial morphology and function [72]. This evidence indicates that mitochondrial dynamics is a common downstream effector or execution platform for ferroptosis and cuproptosis. Second, lncRNAs, as upstream regulators, may interfere with ferroptosis and cuproptosis by affecting mitochondrial function or directly regulating cell death pathways. Previous studies [37,38,57,86] demonstrated that lncRNAs can regulate the biological behavior of cancer cells by binding RNA, or protein and play a regulatory role in several diseases. Some studies have begun to identify lncRNAs associated with ferroptosis and indicated that they may affect ferroptosis by regulating lipid peroxidation, iron homeostasis, or redox systems [87]. Similarly, in cuproptosis, although the mechanism is unclear, several studies have identified cuproptosis-related lncRNAs (CRLs) and constructed CRL-based prognostic models in hepatocellular carcinoma, laryngeal squamous cell carcinoma, oral squamous cell carcinoma, and pancreatic cancer [42]. These findings suggest that lncRNAs occupy an upstream position within the regulatory hierarchy, modulating ferroptosis and cuproptosis through mitochondrial-related pathways or directly influencing death-executing molecules. Overall, the following hierarchical relationship can be preliminarily constructed: lncRNAs, as upstream regulatory molecules, modulate ferroptosis and cuproptosis by influencing mitochondrial dynamics and associated metabolic pathways; mitochondrial dynamics, as a core effect platform, integrates these upstream signals from lncRNAs and mediates the morphological and functional alterations characteristic of two metal-dependent cell deaths. Furthermore, GSH depletion and mtROS accumulation represent the critical molecular crosstalk nodes where ferroptosis and cuproptosis converge. Antiplatelet drugs targeting mitochondrial dynamics may exploit this dual-death mechanism by compromising platelets' antioxidant defense (GSH) and metabolic machinery.

## 5. Conclusion and Outlook

Existing studies have individually characterized mitochondrial dynamics, lncRNA, ferroptosis, and cuproptosis, with emerging evidence suggesting mechanistic interconnections among these processes. However, a comprehensive and systematic framework integrating the mitochondrial dynamics/lncRNA/ferroptosis/cuproptosis regulatory network remains lacking. Current research on antiplatelet drugs has largely focused on their isolated relationships with mitochondrial dynamics, lncRNAs, ferroptosis, or cuproptosis. Comprehensive regulatory network research on antiplatelet drugs is very commonly used in clinical treatment. Elucidating the precise mechanisms underlying antiplatelet drugs is, therefore, of critical importance and warrants further investigation. The correlation between antiplatelet drugs and mitochondrial dynamics/lncRNA/ferroptosis/cuproptosis regulatory networks is an essential breakthrough point. Future research should prioritize bridging the translational gap between nucleated tumor models and platelet-specific biology, distinguishing true intrinsic metabolic exhaustion from indirect bystander effects.

This study has several limitations. First, many of the proposed mechanisms are based on hypothesis-driven extrapolations from nucleated solid tumor models, which fail to reflect the unique anucleate nature and specific metabolic demands (the profound reliance on glycolysis in the resting state) of circulating platelets. Second, the "ROS Paradox" remains unresolved; although excessive ROS promotes terminal metabolic exhaustion, physiological ROS is essential for normal platelet activation, thereby rendering the therapeutic window for ferroptosis-inducing drugs exceedingly narrow. Most existing evidence derives from static *in vitro* assays, which fail to replicate the complex *in vivo* hemodynamic shear stress and complex interactions with the vascular endothelium. Accordingly, future research should prioritize validating these specific molecular executioners (FDX1, lipoylated DLAT, and GPX4) within the human platelet proteome under physiological flow conditions, strictly distinguishing intrinsic metabolic exhaustion from indirect bystander effects. To synthesize these complex interactions, we propose a final integrative model illustrating the hypothesized antiplatelet drug–mitochondrial–metal cell death regulatory network (see Fig. 6).

## Author Contributions

XX and YL conceptualized and designed the study. XK and BF conducted the comprehensive literature search and data extraction. XK drafted the initial manuscript and prepared the figures. BF assisted in manuscript formatting and literature organization. XX and YL provided strict supervision and critically revised the manuscript. All authors

contributed to critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

## Ethics Approval and Consent to Participate

Not applicable.

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## Conflicts of Interest

The authors declare no conflicts of interest.

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