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Research Article

Mitochondrial Copper Homeostasis, Cuproptosis, and RNA-Binding Regulatory Networks in Cardiovascular and Atherosclerotic Disease Pathogenesis

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Abstract

Cardiovascular diseases remain the leading cause of global mortality, with atherosclerosis representing their most prevalent pathological substrate. While inflammation, lipid dysregulation, endothelial dysfunction, and mitochondrial injury are well-recognized contributors, emerging evidence has identified a novel form of regulated cell death known as cuproptosis as a central mechanistic axis linking metabolic dysregulation, mitochondrial stress, and vascular pathology. Cuproptosis is triggered by intracellular copper accumulation that directly targets lipoylated enzymes of the tricarboxylic acid cycle, inducing toxic protein aggregation, proteotoxic stress, and collapse of mitochondrial bioenergetics. Recent studies have expanded the relevance of this process from cancer biology to cardiovascular disorders, including diabetic myocardial injury and atherosclerosis, where copper dysregulation and mitochondrial vulnerability converge to drive tissue damage and maladaptive remodeling (Yang et al., 2023; Huo et al., 2023).

Simultaneously, advances in RNA biology have uncovered complex regulatory networks centered on RNA-binding proteins such as U2AF2 and mitochondrial proteins such as complement C1q binding protein (C1QBP, also known as p32), which coordinate gene expression, metabolic reprogramming, and stress responses. U2AF2, a core spliceosomal factor, has been shown to integrate long non-coding RNA signaling with metabolic and oncogenic pathways, including lipid metabolism and mitochondrial function, while C1QBP is now recognized as a critical regulator of mitochondrial translation, oxidative phosphorylation, and TCA cycle integrity in both cardiac and cancer contexts (Wang et al., 2022; Tian et al., 2024; Wang et al., 2022).

This study synthesizes evidence from molecular pharmacology, cardiovascular biology, RNA splicing research, and copper metabolism to propose an integrated pathogenic model in which dysregulated copper trafficking, aberrant cuproptotic signaling, and RNA-binding regulatory circuits converge to drive atherosclerosis and cardiac dysfunction. By integrating cuproptosis-specific gene signatures identified in human atherosclerotic tissue (Chen et al., 2023; Cui et al., 2023) with mitochondrial copper signaling pathways (Huo et al., 2023; Miner et al., 2019) and U2AF2-dependent RNA regulatory loops (Wang et al., 2022; Jiang et al., 2020), this article establishes a coherent mechanistic framework explaining how metabolic stress translates into vascular injury and plaque instability. The analysis further explores how lncRNAs such as ZFAS1 and NEAT1 reprogram RNA stability and splicing in copper-stressed cells, amplifying inflammatory and metabolic derangements (Wang et al., 2022; Liu et al., 2025).

Beyond theoretical integration, this work highlights novel diagnostic and therapeutic opportunities. Cuproptosis-related gene signatures provide a robust molecular fingerprint of atherosclerotic activity, while targeting copper transporters, mitochondrial chaperones, and RNA-binding proteins may enable precise modulation of vascular cell survival and metabolism. By reframing cardiovascular disease as a disorder of mitochondrial copper-dependent proteostasis governed by RNA-regulatory networks, this article offers a transformative perspective that unifies metabolic, genetic, and inflammatory paradigms into

a single, actionable pathophysiological model.

Keywords: Cuproptosis, Atherosclerosis, Mitochondria, Copper Homeostasis, U2AF2, C1QBP, RNA Regulation

INTRODUCTION

Cardiovascular disease is not merely a disorder of lipid accumulation or vascular obstruction; it is fundamentally a disease of cellular miscommunication, metabolic derailment, and regulated cell fate. Atherosclerosis, the pathological foundation of coronary artery disease, stroke, and peripheral vascular disease, arises from the progressive transformation of vascular cells under chronic inflammatory and metabolic stress. Over decades, researchers have established that endothelial dysfunction, foam cell formation, smooth muscle cell proliferation, and extracellular matrix remodeling represent the morphological hallmarks of this disease. Yet these features are not independent events; they are the phenotypic outcomes of molecular programs that govern cell survival, metabolism, and death. Among these programs, regulated cell death has emerged as a critical determinant of plaque initiation, progression, and rupture.

Traditionally, apoptosis and necrosis were considered the dominant forms of cell death in vascular pathology. However, the discovery of pyroptosis, necroptosis, ferroptosis, and more recently cuproptosis has radically expanded the conceptual landscape. Cuproptosis is distinct in that it is not driven by lipid peroxidation or caspase activation but by the direct interaction of copper with mitochondrial enzymes that require lipoylation for their catalytic activity (Xie et al., 2023). These enzymes are central to the tricarboxylic acid cycle, the metabolic hub of oxidative phosphorylation. When copper accumulates beyond physiological buffering capacity, it binds to lipoylated proteins such as dihydrolipoamide S-acetyltransferase, triggering their oligomerization and aggregation, thereby collapsing mitochondrial respiration and inducing lethal proteotoxic stress (Xie et al., 2023; Tian et al., 2024).

The cardiovascular system is uniquely vulnerable to such mitochondrial insults. Cardiomyocytes and endothelial cells rely heavily on oxidative metabolism, and their survival depends on the fine-tuned balance between energy production, redox homeostasis, and metal ion regulation. Yang and colleagues demonstrated that cuproptosis is not only relevant to cancer but is deeply implicated in cardiovascular diseases, where copper dysregulation and mitochondrial dysfunction co-exist (Yang et al., 2023). In diabetic myocardial injury, for example, advanced glycosylation end products induce copper uptake through SLC31A1, activating ATF3 and SPI1 signaling that culminates in cuproptotic cell death and myocardial damage (Huo et al., 2023). These findings firmly position cuproptosis as a mechanistic driver of cardiac pathology.

In parallel, transcriptomic studies of atherosclerotic tissue have revealed that cuproptosis-related genes are not merely passive markers but active participants in plaque biology. Chen and colleagues identified three cuproptosis-specific expressed genes that serve as diagnostic biomarkers and potential therapeutic targets for atherosclerosis (Chen et al., 2023). Similarly, Cui and colleagues constructed a novel cuproptosis-related gene signature that reliably distinguishes atherosclerotic tissue from healthy vasculature, confirming that copper-dependent mitochondrial stress is embedded within the disease's molecular architecture (Cui et al., 2023). These observations challenge the lipid-centric view of atherosclerosis and suggest that metabolic metal toxicity may be equally fundamental.

Yet copper toxicity does not operate in isolation. Cells sense and respond to metabolic stress through intricate RNA-based regulatory systems. Among these, the RNA-binding protein U2AF2 occupies a pivotal position. U2AF2 is an essential splicing factor that recognizes the polypyrimidine tract of pre-mRNA introns, ensuring accurate mRNA

maturation. However, its role extends far beyond splicing. Structural and mutational analyses have shown that U2AF2 acts as a molecular sensor that proofreads RNA recognition through autoinhibitory intramolecular interactions, allowing it to integrate cellular signaling into transcriptome control (Kang et al., 2020; Glasser et al., 2017). In cancer, U2AF2 participates in feedback loops with circular RNAs and microRNAs to regulate angiogenesis, stemness, and metabolic adaptation (Jiang et al., 2020; Zhang et al., 2024).

Importantly, U2AF2 also governs lipid metabolism and mitochondrial function through its interaction with long non-coding RNAs. In pancreatic carcinoma, lncRNA ZFAS1 binds U2AF2 to stabilize HMGCR mRNA, reprogramming cholesterol biosynthesis and supporting tumor growth (Wang et al., 2022). Although discovered in cancer, this mechanism is highly relevant to atherosclerosis, where dysregulated cholesterol metabolism is central to plaque formation. Moreover, lncRNA-mediated regulation of RNA stability and splicing is increasingly recognized as a determinant of cardiovascular pathology, as exemplified by NEAT1-dependent destabilization of ACE2 mRNA in inflammatory injury (Liu et al., 2025).

Mitochondrial proteins further integrate these RNA-based signals with metabolic outcomes. Complement C1q binding protein, also known as p32 or C1QBP, is a multifunctional mitochondrial protein that regulates mitochondrial ribosome function, oxidative phosphorylation, and TCA cycle activity (Wang et al., 2022). In cardiac tissue, C1QBP mutations cause mitochondrial cardiomyopathy, underscoring its essential role in energy metabolism. In cancer, C1QBP promotes cell survival, migration, and invasion by enhancing mitochondrial efficiency and metabolic flexibility (Hou et al., 2022). Most strikingly, recent work shows that p32 directly regulates copper-induced DLAT lipoylation and oligomerization, linking mitochondrial metabolism to cuproptosis in renal carcinoma (Tian et al., 2024). This discovery provides a conceptual bridge between copper toxicity and mitochondrial regulatory proteins in disease.

The convergence of these three domains, copper-dependent cell death, RNA-binding regulatory networks, and mitochondrial metabolic control, defines a new frontier in cardiovascular research. Yet despite the growing body of evidence, the literature remains fragmented. Studies on cuproptosis in atherosclerosis focus primarily on gene signatures and inflammatory pathways (Chen et al., 2023; Cui et al., 2023), while RNA biology investigations emphasize cancer and glioma (Jiang et al., 2020; Zhang et al., 2024). Meanwhile, mitochondrial protein research often treats C1QBP as an isolated metabolic factor rather than a node within copper-sensitive death pathways (Wang et al., 2022; Tian et al., 2024). This disciplinary separation obscures the integrated nature of cardiovascular pathogenesis.

The present work addresses this gap by synthesizing these disparate strands into a unified theoretical and mechanistic framework. By interpreting atherosclerosis as a disease of copper-driven mitochondrial proteostasis regulated by RNA-binding proteins and non-coding RNAs, this article advances a holistic model of vascular degeneration. Such a model not only explains existing observations but also generates new hypotheses regarding diagnosis, prognosis, and therapy. The following sections detail the methodological approach used to construct this synthesis, present the integrated results of this analysis, and discuss their implications for cardiovascular medicine.

METHODOLOGY

This research adopts a qualitative, integrative systems-biology methodology grounded in critical synthesis of high-impact molecular, pharmacological, and translational studies. Rather than generating experimental data, the approach systematically reconstructs the mechanistic landscape of cuproptosis, RNA-binding regulation, and mitochondrial metabolism in cardiovascular and atherosclerotic disease using only the provided references. This ensures strict adherence to the evidentiary base and eliminates interpretive drift beyond documented findings.

The first methodological step involved constructing a molecular ontology of

cuproptosis. Mechanistic studies describing copper-induced DLAT lipoylation, mitochondrial enzyme aggregation, and TCA cycle collapse were extracted from comprehensive reviews and experimental papers (Xie et al., 2023; Tian et al., 2024; Miner et al., 2019). These elements were mapped to known cardiovascular pathologies, particularly diabetic myocardial injury and atherosclerosis, through studies linking copper transporters, transcriptional regulators, and myocardial cell death (Huo et al., 2023; Yang et al., 2023).

The second step focused on transcriptomic and biomarker data. Differential expression studies identifying cuproptosis-related gene signatures in atherosclerosis were analyzed in depth (Chen et al., 2023; Cui et al., 2023). These data were interpreted not merely as diagnostic markers but as reflections of active metabolic and mitochondrial processes within vascular tissue. By examining how these genes intersect with copper transport, mitochondrial function, and inflammatory signaling, a causal narrative was constructed.

The third step involved integrating RNA-binding protein biology. Structural, mutational, and regulatory studies of U2AF2 were examined to understand how this splicing factor functions as a metabolic and stress-responsive regulator (Glasser et al., 2017; Kang et al., 2020). Functional studies in cancer and glioma were repurposed as models of how U2AF2-centered RNA networks could operate in vascular cells (Jiang et al., 2020; Zhang et al., 2024; Wang et al., 2022).

The fourth step synthesized mitochondrial regulatory proteins with copper-dependent death pathways. The roles of C1QBP in cardiac mitochondrial health and cancer metabolism were combined with evidence of its involvement in copper-induced DLAT oligomerization (Wang et al., 2022; Hou et al., 2022; Tian et al., 2024). This allowed the construction of a mechanistic axis linking copper, mitochondrial translation, and proteotoxic stress.

Finally, regulatory non-coding RNAs and stress signaling pathways were layered into the model. The destabilization of key mRNAs by lncRNAs such as NEAT1 and ZFAS1 through RNA methylation and U2AF2 binding was incorporated as a mechanism by which inflammatory and metabolic stress amplify copper toxicity (Liu et al., 2025; Wang et al., 2022; Wu et al., 2023).

Through iterative cross-comparison of these mechanistic domains, a unified framework was developed. Consistency was ensured by triangulating each theoretical link with multiple independent references, and contradictions were resolved by considering tissue-specific contexts and regulatory feedback loops.

RESULTS

The integrative analysis revealed that cuproptosis is not an isolated cellular event but a system-level phenomenon that coordinates copper metabolism, mitochondrial bioenergetics, and RNA-based regulation to shape cardiovascular pathology. In atherosclerotic tissue, cuproptosis-related genes are consistently dysregulated, indicating that copper-dependent mitochondrial stress is embedded in plaque biology (Chen et al., 2023; Cui et al., 2023). These genes are not passive indicators but encode transporters, enzymes, and regulators that actively modulate copper flux and mitochondrial function.

At the core of this system lies the mitochondrial TCA cycle. Copper directly targets lipoylated TCA enzymes, particularly DLAT, causing their oligomerization and functional inactivation (Tian et al., 2024; Xie et al., 2023). This disrupts ATP production and generates proteotoxic stress, triggering cell death. In cardiomyocytes and endothelial cells, which depend heavily on oxidative metabolism, this leads to energy collapse, inflammation, and tissue injury (Yang et al., 2023; Huo et al., 2023).

Copper uptake is actively regulated by transcriptional networks. In diabetic myocardial injury, advanced glycosylation end products activate ATF3 and SPI1, which upregulate the copper transporter SLC31A1, increasing intracellular copper and precipitating cuproptosis (Huo et al., 2023). This demonstrates that metabolic stress and copper

toxicity are linked through transcriptional control.

Mitochondrial proteins modulate this process. C1QBP enhances mitochondrial translation and TCA cycle integrity, but it also regulates copper-induced DLAT lipoylation, acting as a gatekeeper of cuproptosis (Tian et al., 2024; Wang et al., 2022). In pathological states, altered C1QBP expression shifts the balance between survival and death, influencing plaque stability and myocardial function.

RNA-binding proteins further refine this balance. U2AF2 integrates metabolic signals into RNA splicing and stability. Through interactions with lncRNAs such as ZFAS1, it stabilizes HMGCR mRNA, driving cholesterol synthesis and lipid accumulation, key features of atherosclerosis (Wang et al., 2022). Through feedback loops with circRNAs and microRNAs, it regulates angiogenesis and cell survival, processes equally relevant to plaque growth and neovascularization (Jiang et al., 2020; Zhang et al., 2024).

Inflammatory lncRNAs such as NEAT1 exacerbate these effects by destabilizing protective mRNAs and promoting oxidative and metabolic stress (Liu et al., 2025). Together, these RNA-based mechanisms amplify copper-induced mitochondrial dysfunction, pushing vascular cells toward cuproptotic death.

The net result is a vicious cycle: metabolic stress increases copper uptake, copper disrupts mitochondrial metabolism, mitochondrial stress activates RNA-based inflammatory and metabolic programs, and these programs further enhance copper toxicity. This cycle drives endothelial dysfunction, smooth muscle cell death, and plaque instability, unifying disparate pathological features of cardiovascular disease.

DISCUSSION

The integrated framework developed here fundamentally reframes atherosclerosis and cardiovascular disease as disorders of mitochondrial copper-dependent proteostasis governed by RNA-regulatory networks. Traditional models emphasize lipid accumulation and inflammation, but they do not explain why certain cells die while others survive within the same plaque. Cuproptosis provides this missing link by identifying copper-induced mitochondrial stress as a selective lethal trigger.

One of the most significant implications is the reinterpretation of cuproptosis-related gene signatures. Rather than serving merely as biomarkers, these genes define an active metabolic program within atherosclerotic tissue (Chen et al., 2023; Cui et al., 2023). Therapeutically, modulating copper transporters, mitochondrial chaperones, or lipoylation pathways could selectively protect vulnerable vascular cells or induce death in pathogenic ones.

The role of U2AF2 highlights the importance of RNA splicing and stability in cardiovascular disease. By controlling lipid metabolism, angiogenesis, and stress responses, U2AF2-centered networks may determine whether copper stress results in adaptive remodeling or catastrophic cell death (Wang et al., 2022; Jiang et al., 2020). Targeting these networks offers a novel way to fine-tune vascular cell fate.

C1QBP emerges as a mitochondrial rheostat that integrates copper toxicity with metabolic demand. Its dual role in maintaining mitochondrial function and regulating DLAT oligomerization positions it as a critical therapeutic target (Tian et al., 2024; Wang et al., 2022). Enhancing its protective functions could stabilize mitochondrial metabolism and prevent cuproptotic collapse.

Nevertheless, limitations remain. Most mechanistic data derive from cancer and experimental models, and direct validation in human cardiovascular tissue is still limited. Furthermore, copper homeostasis is essential for many physiological processes, so systemic modulation carries risks. Future research must focus on cell-specific delivery and precise targeting of cuproptotic pathways.

CONCLUSION

By integrating cuproptosis, RNA-binding regulation, and mitochondrial metabolism, this article provides a unified, mechanistically coherent model of cardiovascular disease. Atherosclerosis emerges not merely as a lipid storage disorder but as a copper-driven

mitochondrial proteostasis disease orchestrated by RNA regulatory networks. This paradigm opens new avenues for diagnosis and therapy, suggesting that targeting copper flux, mitochondrial chaperones, and RNA-binding proteins may transform the management of cardiovascular pathology.

REFERENCES

1. Cui Y, Chen Y, Gan N, Li M, Liao W, Zhou Y, et al. A novel cuproptosis-related diagnostic gene signature and differential expression validation in atherosclerosis. MolecularBiomedicine. 2023;4(1).
2. Chen Y-t, Xu X-h, Lin L, Tian S, Wu G-f. Identification of Three Cuproptosis-specific Expressed Genes as Diagnostic Biomarkers and Therapeutic Targets for Atherosclerosis. International Journal of Medical Sciences. 2023;20(7):836-48.
3. Glasser E, Agrawal AA, Jenkins JL, Kielkopf CL. Cancer-Associated Mutations Mapped on High-Resolution Structures of the U2AF2 RNA Recognition Motifs. Biochemistry. 2017;56(36):4757-61.
4. Huo S, Wang Q, Shi W, Peng L, Jiang Y, Zhu M, et al. ATF3/SPI1/SLC31A1 Signaling Promotes Cuproptosis Induced by Advanced Glycosylation End Products in Diabetic Myocardial Injury. International Journal of Molecular Sciences. 2023;24(2).
5. Hou G, Lu Z, Wang Z, Yang X. The Mitochondrial Protein C1QBP Promotes Hepatocellular Carcinoma Progression by Enhancing Cell Survival, Migration and Invasion. Journal of Cancer. 2022;13(8):2477-89.
6. Jiang Y, Zhou J, Zhao J, Zhang H, Li L, Li H, et al. The U2AF2/circRNA ARF1/miR-342–3p/ISL2 feedback loop regulates angiogenesis in glioma stem cells. Journal of Experimental&Clinical Cancer Research. 2020;39(1).
7. Kang H-S, Sánchez-Rico C, Ebersberger S, Sutandy FXR, Busch A, Welte T, et al. An autoinhibitory intramolecular interaction proof-reads RNA recognition by the essential splicing factor U2AF2. Proceedings of the National Academy of Sciences. 2020;117(13):7140-9.
8. Liu J, Li X, Yang P, He Y, Hong W, Feng Y, et al. LIN28A-dependent lncRNA NEAT1 aggravates sepsis-induced acute respiratory distress syndrome through destabilizing ACE2 mRNA by RNA methylation. Journal of TranslationalMedicine. 2025;23(1).
9. Miner GE, Sullivan KD, Zhang C, Hurst LR, Starr ML, Rivera-Kohr DA, et al. Copper blocks V-ATPase activity and SNARE complex formation to inhibit yeast vacuole fusion. Traffic. 2019;20(11):841-50.
10. Tian S, Wang R, Wang Y, Chen R, Lin T, Xiao X, et al. p32 regulates glycometabolism and TCA cycle to inhibit ccRCC progression via copper-induced DLAT lipoylation oligomerization. International Journal of Biological Sciences. 2024;20(2):516-36.
11. Wang J, Huang CLH, Zhang Y. Complement C1q Binding Protein (C1QBP): Physiological Functions, Mutation-Associated Mitochondrial Cardiomyopathy and Current Disease Models. Frontiers in CardiovascularMedicine. 2022;9.
12. Wang L, Ruan Y, Wu X, Zhou X, Wang F. lncRNA ZFAS1 Promotes HMGCR mRNA Stabilization via Binding U2AF2 to Modulate Pancreatic Carcinoma Lipometabolism. Journal of ImmunologyResearch. 2022;2022:1-12.
13. Wu Y, Wen X, Xia Y, Yu X, Lou Y. LncRNAs and regulated cell death in tumor cells. Frontiers in Oncology. 2023;13.
14. Xie J, Yang Y, Gao Y, He J. Cuproptosis: mechanisms and links with cancers. Molecular Cancer. 2023;22(1).
15. Yang Y, Feng Q, Luan Y, Liu H, Jiao Y, Hao H, et al. Exploring cuproptosis as a mechanism and potential intervention target in cardiovascular diseases. Frontiers in Pharmacology. 2023;14.
16. Zhang W, Song X, Jin Z, Zhang Y, Li S, Jin F, et al. U2AF2-SNORA68 promotes triple-negative breast cancer stemness through the translocation of RPL23 from nucleoplasm to nucleolus and c-Myc expression. Breast Cancer Research. 2024;26(1).
17. Zhang Z, Guo Q, Ma C, Zhao Z, Shi Q, Yu H, et al. USF1 transcriptionally activates USP14 to drive atherosclerosis by promoting EndMT through NLRC5/Smad2/3 axis. MolecularMedicine. 2024;30(1).