Advances in Obstetrics and Gynecology Research, 2024, Volume 2, Issue 5
https://ojs.bbwpublisher.com/index.php/AOGR
Online ISSN: 2981-8060

Exploring the Role of Cuproptosis-Associated Genes in Cancer Progression and Therapy Resistance: A Comprehensive Analysis Across Multiple Cancer Types

Yasir Hameed*

Department of Biotechnology, Institute of Biochemistry, Biotechnology, and Bioinformatics, The Islamia University of Bahawalpur, Bahawalpur 63100, Punjab, Pakistan

***Corresponding author:** Yasir Hameed, yasirhameed2011@gmail.com

Copyright: © 2024 Author(s). This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 4.0), permitting distribution and reproduction in any medium, provided the original work is cited.

Abstract: This review provides a comprehensive overview of the role of cuproptosis-associated genes across various cancer types, emphasizing their importance in tumor progression and therapy resistance. In breast cancer and colorectal cancer, the dysregulation of genes related to mitochondrial function and copper metabolism, such as *FDX1*, *LIAS*, *LIPT1*, *DLD*, *DLAT*, and *PDHA1/PDHB*, promotes metabolic reprogramming and enhances cancer cell survival. Ovarian cancer exhibits unique dysregulations in genes like *ATP7B*, *CCS*, and *COMMD1*, which influence copper metabolism and redox signaling pathways, thereby contributing to chemoresistance and tumor growth. In head and neck cancer, the upregulation of *MT1X*, *ATP7A*, and *CCS* potentially aids cancer cell survival under oxidative stress conditions. Lung cancer is characterized by distinct dysregulation of genes such as *SLC31A1*, *ATOX1*, and *COMMD1*, modulating copper homeostasis and redox signaling to support tumor proliferation. Liver cancer and kidney cancer present unique sets of dysregulated cuproptosis-associated genes, such as *SLC39A4*, *SCO2*, and *ATP7A*, suggesting novel therapeutic targets specific to these cancer types. Pathway analysis reveals enrichment in mineral absorption pathways, highlighting the importance of these genes in maintaining cellular mineral homeostasis. Understanding the complex interplay between cuproptosis-associated genes and cancer biology offers insights into potential therapeutic strategies targeting copper metabolism for improved treatment outcomes across various cancer types.

Keywords: Cuproptosis; Cancer; Dysregulation; Therapeutic

Online publication: October 31, 2024

1. Introduction

Cancer remains one of the most formidable health challenges worldwide, accounting for millions of deaths each year [1]. Despite significant advances in early detection and treatment, the complexity and heterogeneity of

cancer continue to hinder effective management. A critical aspect of cancer biology that has garnered substantial attention in recent years is the regulation of cell death [1]. While apoptosis, necrosis, and ferroptosis have been extensively studied [2,3], a novel form of regulated cell death, known as cuproptosis, has emerged as a potential key player in cancer progression and treatment resistance [4,5].

Cuproptosis is a copper-dependent form of cell death that is fundamentally distinct from other cell death mechanisms [4]. It is characterized by the disruption of mitochondrial function due to copper accumulation, leading to protein aggregation and the loss of mitochondrial iron-sulfur (Fe-S) cluster proteins [6]. These disruptions ultimately result in cell death. The discovery of cuproptosis underscores the dual role of copper as both an essential trace element and a potential cytotoxic agent when dysregulated [7].

Copper is indispensable for various biological processes, including mitochondrial respiration, antioxidant defense, and iron metabolism [8]. Under normal physiological conditions, copper homeostasis is tightly regulated to prevent toxicity [9]. However, cancer cells often exhibit altered copper metabolism, leading to increased copper levels that can contribute to tumorigenesis and metastasis [10]. Understanding the molecular pathways involved in copper-induced cell death has, therefore, become a crucial area of research in cancer biology.

Central to the process of cuproptosis are several key genes that regulate mitochondrial function and copper metabolism [11]. These include *Ferredoxin 1* (*FDX1*), *Lipoic Acid Synthetase* (*LIAS*), *Lipoyltransferase 1* (*LIPT1*), *Dihydrolipoamide Dehydrogenase* (*DLD*), *Dihydrolipoamide S-Acetyltransferase* (*DLAT*), and the *Pyruvate Dehydrogenase E1* subunits Alpha and Beta (*PDHA1* and *PDHB*) [12]. These genes play vital roles in maintaining mitochondrial integrity and metabolic homeostasis. Their dysregulation can lead to enhanced tumorigenicity, resistance to apoptosis, and altered cellular metabolism—hallmarks of cancer.

2. Copper metabolism in cancer

Copper's role in cancer is multifaceted. On one hand, copper is essential for the activity of several enzymes involved in oxidative stress response and cellular respiration, which are crucial for rapidly proliferating cancer cells [13]. On the other hand, excessive copper can be toxic, leading to oxidative damage and cell death [14]. This paradoxical nature of copper makes it a double-edged sword in cancer biology.

Cancer cells often exhibit increased copper uptake and accumulation. For instance, elevated levels of copper have been detected in various malignancies, including breast, lung, colorectal, and liver cancers [15]. This heightened copper accumulation can support the metabolic demands of cancer cells but also predispose them to copper-induced cytotoxicity, which can be therapeutically exploited.

3. The mechanism of cuproptosis

Cuproptosis is triggered by the intracellular accumulation of copper, which interferes with normal mitochondrial function. The primary mechanism involves copper binding to lipoylated components of the tricarboxylic acid (TCA) cycle within mitochondria. This binding leads to protein aggregation and the subsequent loss of Fe-S cluster proteins, which are essential for mitochondrial electron transport and metabolic function [16]. The resulting mitochondrial dysfunction precipitates a cascade of events that culminate in cell death [17].

The genes associated with cuproptosis are integral to this process. For example, *FDX1* is involved in electron transfer within mitochondria and the biogenesis of Fe-S clusters [18]. *LIAS* is critical for the synthesis of lipoic acid, a cofactor for key mitochondrial enzyme complexes [19]. *LIPT1* facilitates the attachment of lipoic

acid to these enzymes [19], while *DLD* and *DLAT* are components of the pyruvate dehydrogenase complex, which links glycolysis to the TCA cycle [20]. *PDHA1* and *PDHB* are also crucial for this metabolic link [20]. Dysregulation of any of these genes can disrupt mitochondrial function and increase sensitivity to copper-induced cell death [11].

4. Clinical implications

The discovery of cuproptosis and its associated genes opens new avenues for cancer therapy. By targeting copper metabolism and cuproptosis pathways, novel treatments may be developed to selectively induce cell death in cancer cells while sparing normal tissues. Therapeutic strategies such as copper chelation, gene modulation, and combination therapies are being explored to exploit the vulnerabilities of cancer cells with dysregulated copper metabolism.

This review aims to provide a comprehensive overview of the role of cuproptosis-associated genes in various cancers. By elucidating the mechanisms through which these genes influence tumor progression and resistance, we seek to highlight their potential as therapeutic targets and contribute to the development of more effective cancer treatments.

5. The role of cuproptosis-associated genes in cancer

5.1. The role of cuproptosis-associated genes in breast cancer

In breast cancer, cuproptosis-associated genes play critical roles in tumor progression and therapy resistance by regulating mitochondrial function and copper metabolism. Elevated levels of *FDX1*, *LIAS*, *LIPT1*, *DLD*, *DLAT*, and the pyruvate dehydrogenase complex subunits *PDHA1* and *PDHB* have been observed in breast cancer tissues, indicating their involvement in enhancing mitochondrial respiration, metabolic reprogramming, and energy production [21]. For instance, *FDX1* and *LIAS* contribute to mitochondrial electron transport and lipoic acid synthesis, respectively, supporting the high energy demands of proliferating cancer cells [22,23]. *LIPT1* and *DLD* are critical for maintaining mitochondrial enzyme complex functions, promoting metabolic flexibility and survival [24]. Additionally, DLAT and the PDHA1/PDHB subunits facilitate the conversion of pyruvate to acetyl-CoA, which is essential for linking glycolysis to the tricarboxylic acid (TCA) cycle [25,26]. These metabolic adaptations enable cancer cells to thrive in diverse microenvironments and resist therapeutic stress [27].

5.2. The role of cuproptosis-associated genes in colorectal cancer

Cuproptosis-associated genes play crucial roles in the progression and therapy resistance of colorectal cancer (CRC) by regulating mitochondrial function and copper metabolism. Similar to breast cancer, genes such as *FDX1*, *LIAS*, *LIPT1*, *DLD*, *DLAT*, and the *PDHA1/PDHB* subunits are often dysregulated in CRC, enhancing mitochondrial respiration and metabolic reprogramming to meet the high energy demands of tumor cells [28]. For instance, *FDX1* enhances mitochondrial electron transport and Fe-S cluster biogenesis [29,30]. ***DLD* and *DLAT*, key components of the pyruvate dehydrogenase complex, facilitate the conversion of pyruvate to acetyl-CoA**, which is crucial for energy production and biosynthesis [31,32]. *PDHA1* and *PDHB* further promote mitochondrial respiration and anabolic processes [33]. These metabolic adaptations help CRC cells survive under various conditions and resist therapeutic stress [34]. Consequently, targeting these genes could disrupt cancer cell metabolism, reduce tumor growth, and enhance sensitivity to treatments [35].

5.3. The role of cuproptosis-associated genes in ovarian cancer

In ovarian cancer, specific cuproptosis-associated genes exhibit unique patterns of dysregulation not commonly observed in breast cancer and CRC, highlighting distinct pathways of metabolic reprogramming and therapeutic resistance. One such gene is *ATP7B*, a copper-transporting ATPase that plays a crucial role in regulating intracellular copper levels. In ovarian cancer, *ATP7B* is frequently overexpressed, facilitating increased copper efflux and protecting cancer cells from copper-induced toxicity. This overexpression contributes to chemoresistance, particularly to platinum-based drugs, by enhancing the efflux of platinum compounds, thereby reducing their intracellular accumulation and cytotoxicity [36].

Another unique gene is *Copper Chaperone for Superoxide Dismutase* (*CCS*), which is involved in delivering copper to the antioxidant enzyme superoxide dismutase 1 (SOD1). In ovarian cancer, elevated levels of *CCS* enhance the activity of SOD1, thereby increasing the antioxidant capacity of cancer cells and promoting their survival under oxidative stress conditions commonly induced by the tumor microenvironment and chemotherapy [37].

Additionally, the gene *Copper Metabolism Domain Containing 1* (*COMMD1*) plays a distinct role in ovarian cancer. *COMMD1* is involved in the regulation of NF-κB signaling and copper homeostasis. In ovarian cancer, aberrant expression of *COMMD1* has been linked to altered NF-κB activity, promoting inflammation, cell proliferation, and resistance to apoptosis. By influencing these pathways, *COMMD1* supports tumor growth and survival, making it a potential target for therapeutic intervention [38].

These unique dysregulations in *ATP7B*, *CCS*, and *COMMD1* underscore the complex interplay between copper metabolism and cancer cell survival in ovarian cancer, presenting novel opportunities for targeted therapies that could disrupt these specific pathways and enhance treatment efficacy. Further research into the precise mechanisms by which these genes contribute to ovarian cancer progression and resistance will be essential for developing effective therapeutic strategies [39,40].

5.4. The role of cuproptosis-associated genes in head and neck cancer

Among the important dysregulated cuproptosis-associated genes in head and neck cancer, *Metallothionein 1X* (*MT1X*) stands out. Metallothioneins (MTs) are a family of low molecular weight, cysteine-rich proteins that play critical roles in metal homeostasis and detoxification. *MT1X*, in particular, has been implicated in copper metabolism and redox regulation. In head and neck cancer, *MT1X* expression is often upregulated, possibly as a cellular response to increased copper levels within the tumor microenvironment. This upregulation may provide a survival advantage to cancer cells by mitigating the cytotoxic effects of copper overload, thereby promoting tumor progression and resistance to therapy [41].

Another notable gene is *ATP7A*, which encodes a copper-transporting P-type ATPase involved in copper efflux from cells. While *ATP7A* dysregulation has been implicated in various cancers, including breast and ovarian cancer, its role in head and neck cancer appears to be distinct. In head and neck cancer, *ATP7A* expression levels may be finely tuned to balance the copper requirements for cell proliferation and survival, without tipping over into cytotoxic cuproptosis. This nuanced regulation of *ATP7A* highlights its importance as a potential therapeutic target in head and neck cancer [42].

Furthermore, the *CCS* gene stands out as a key player in head and neck cancer. CCS plays a crucial role in delivering copper to SOD, an antioxidant enzyme that neutralizes reactive oxygen species (ROS) [43].

5.5. The role of cuproptosis-associated genes in lung cancer

In lung cancer, one of the significantly dysregulated cuproptosis-associated genes is *SLC31A1*, which encodes the copper transporter protein CTR1. While CTR1 dysregulation has been implicated in several cancers, its role in lung cancer appears to be distinct. CTR1 is responsible for copper uptake into cells, a crucial step in maintaining cellular copper homeostasis and regulating cuproptosis. In lung cancer, CTR1 expression levels may be finely regulated to support the heightened metabolic demands and proliferation of cancer cells, while avoiding excessive cuproptosis. This nuanced regulation of CTR1 highlights its importance as a potential therapeutic target in lung cancer, differing from its roles in other cancer types [44].

Another notable gene is *ATOX1*, which encodes a copper chaperone protein involved in delivering copper to ATP7A, a copper-transporting ATPase. Although *ATOX1* dysregulation has been observed in various cancers, its role in lung cancer is particularly significant. *ATOX1* may modulate copper homeostasis and redox signaling pathways to support cancer cell survival and proliferation. Targeting *ATOX1*-mediated copper trafficking could offer a novel therapeutic approach in lung cancer, distinct from its roles in other cancer types [45].

Additionally, *COMMD1* stands out as a unique player in lung cancer. *COMMD1* regulates copper homeostasis and cuproptosis by interacting with various copper transporters and signaling molecules. Its dysregulation may disrupt copper homeostasis and redox signaling pathways, contributing to lung cancer progression through mechanisms distinct from those in breast, colorectal, ovarian, and head and neck cancers [46].

5.6. The role of cuproptosis-associated genes in liver cancer

In liver cancer, a distinct set of cuproptosis-related genes is implicated in tumorigenesis, presenting unique molecular targets not shared with other cancers, such as breast, colorectal, ovarian, head and neck, and lung cancers. These genes are critical for copper homeostasis, redox regulation, and cell survival in the context of liver cancer. One such gene is *SLC39A4*, which encodes the zinc transporter ZIP4. While primarily involved in zinc transport, ZIP4 also plays a role in copper uptake. Dysregulation of ZIP4 in liver cancer may affect copper homeostasis and redox signaling pathways, promoting tumor growth and progression. Targeting ZIP4-mediated copper transport could offer a novel therapeutic approach specific to liver cancer [47].

Another key gene is the *Synthesis of Cytochrome c Oxidase 2* (*SCO2*), which is involved in assembling cytochrome c oxidase, a crucial component of the mitochondrial electron transport chain. Dysregulation of *SCO2* in liver cancer may impair mitochondrial function and disrupt redox balance, contributing to tumorigenesis through mechanisms different from those observed in other cancers. Targeting *SCO2*-mediated mitochondrial pathways could provide a promising therapeutic strategy for liver cancer [48].

Additionally, *CCS* plays a critical role in liver cancer. *CCS* facilitates the delivery of copper to SOD, an antioxidant enzyme that neutralizes ROS. Dysregulation of *CCS* in liver cancer may impair copper homeostasis and redox signaling, promoting tumor growth and metastasis through mechanisms that differ from those in other cancers [49].

5.7. The role of cuproptosis-associated genes in kidney cancer

In the complex landscape of kidney cancer, certain cuproptosis-associated genes play pivotal roles, distinct from those observed in other common cancer types, such as breast, colorectal, ovarian, head and neck, lung, and liver cancers. One such gene is *ATP7A*, which encodes a copper-transporting ATPase involved in copper efflux from cells. While dysregulation of *ATP7A* has been implicated in various cancers, its role in kidney cancer appears to be unique. *ATP7A* may modulate copper homeostasis and redox signaling pathways in kidney tumorigenesis,

potentially promoting cancer cell survival and proliferation through mechanisms independent of those seen in other cancer types [50,51].

Furthermore, *ATOX1*, which encodes a copper chaperone protein involved in delivering copper to the ATP7A transporter, is another key player in kidney cancer. *ATOX1*-mediated copper trafficking pathways may play a distinct role in kidney tumorigenesis, potentially influencing copper homeostasis and redox signaling to promote cancer cell proliferation and survival [52,53].

6. Cuproptosis-associated genes dysregulated pathways

Figure 1 presents a comprehensive analysis of pathway enrichment related to cuproptosis-associated genes. **Figure 1A** highlights various metabolic pathways with their respective fold enrichment, showing "Mineral absorption" as the most significantly enriched pathway, supported by its high fold enrichment and the large number of cuproptosis-associated genes involved (**Figure 1A**). The color gradient of the dots indicates statistical significance, with redder dots representing higher significance levels. Additionally, **Figure 1B** provides a detailed KEGG pathway map of "Mineral absorption," where key components such as DMT1, TF, and ATP7A are marked in red, underscoring their crucial role in this process. These cuproptosis-associated genes participate in the transcellular and paracellular transport of minerals like Ca^{2+}, Mg^{2+}, Fe^{2+}, and Zn^{2+} through the intestinal epithelium into the bloodstream.

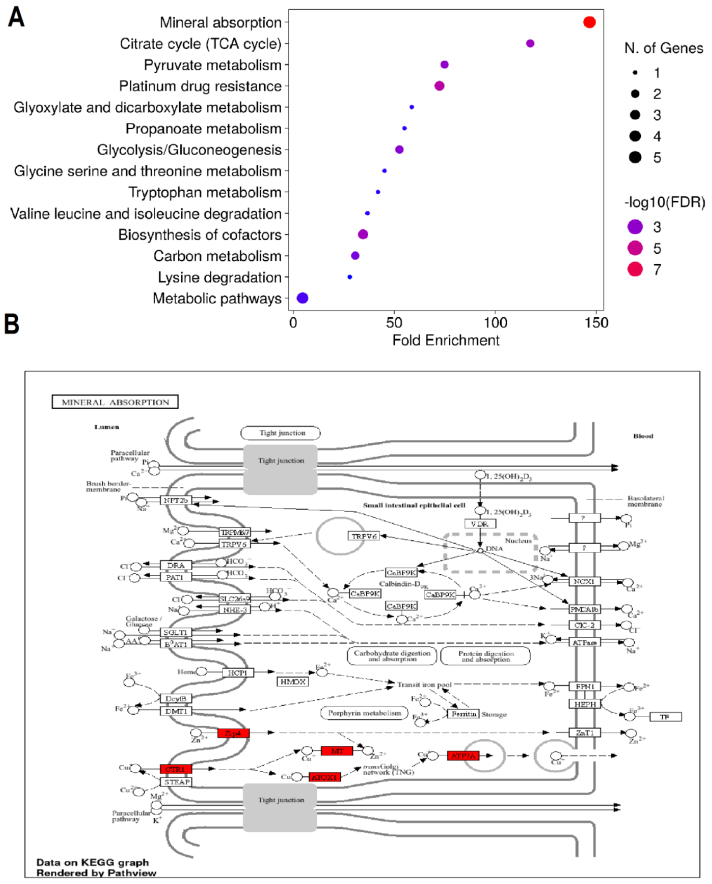

Figure 1. Cuproptosis-associated genes and related pathways. **(A)** A bubble graph illustrating cuproptosis-associated genes and related pathways. **(B)** KEGG map of the most significantly associated pathway.

7. Conclusion

From this comprehensive review of the literature, several conclusions can be drawn:

First, cuproptosis-associated genes exhibit tissue-specific dysregulation patterns, indicating unique molecular pathways driving tumorigenesis in each cancer type. For example, *ATP7B* overexpression is prominent in ovarian cancer, while *ATP7A* dysregulation is notable in kidney cancer. These genes play different roles—or may not be dysregulated at all—in other cancer types, such as breast, colorectal, head and neck, lung, and liver cancers. This highlights the importance of considering tissue-specific contexts when studying the role of cuproptosis-associated genes in cancer.

Second, cuproptosis-associated genes contribute to various aspects of cancer progression, including metabolic reprogramming, therapy resistance, and redox signaling modulation. For instance, in breast and colorectal cancers, dysregulated genes such as *FDX1*, *LIAS*, *LIPT1*, *DLD*, *DLAT*, *PDHA1*, and *PDHB* enhance mitochondrial respiration and metabolic flexibility, promoting tumor growth and survival. In contrast, in liver cancer, dysregulated genes like *SLC39A4*, *SCO2*, and *CCS* play crucial roles in copper homeostasis and redox regulation, influencing tumor progression and metastasis.

Third, targeting dysregulated cuproptosis-associated genes presents promising opportunities for cancer therapy. By disrupting specific pathways involved in copper metabolism, mitochondrial function, and redox signaling, novel therapeutic strategies could be developed to selectively target cancer cells while sparing normal tissues. For example, targeting *ATP7B*-mediated copper efflux in ovarian cancer or *SCO2*-mediated mitochondrial pathways in liver cancer could represent effective therapeutic approaches tailored to the unique biology of each cancer type.

Overall, the comprehensive understanding of the role of cuproptosis-associated genes in cancer underscores the intricate interplay between copper metabolism, mitochondrial function, and redox signaling in tumorigenesis. Further research into the precise mechanisms underlying dysregulated cuproptosis-associated genes and their tissue-specific effects is essential for developing targeted therapies with improved efficacy and reduced toxicity for cancer patients.

Disclosure statement

The author declares no conflict of interest.

References

[1] Horgan D, Mia R, Erhabor T, et al., 2022, Fighting Cancer Around the World: A Framework for Action. Healthcare, 10(11): 2125.

[2] Tang R, Xu J, Zhang B, et al., 2020, Ferroptosis, Necroptosis, and Pyroptosis in Anticancer Immunity. Journal of Hematology & Oncology, 13: 1–18.

[3] Yang J, Hu S, Bian Y, et al., 2022, Targeting Cell Death: Pyroptosis, Ferroptosis, Apoptosis and Necroptosis in Osteoarthritis. Frontiers in Cell and Developmental Biology, 9: 789948.

[4] Brady DC, Crowe MS, Turski ML, et al., 2014, Copper is Required for Oncogenic BRAF Signalling and Tumorigenesis. Nature, 509(7501): 492–496.

[5] Yang Z, Feng R, Zhao H, 2024, Cuproptosis and Cu: A New Paradigm in Cellular Death and Their Role in Non-Cancerous Diseases. Apoptosis, 29(9): 1330–1360.

[6] Du J, Huang Z, Li Y, et al., 2023, Copper Exerts Cytotoxicity Through Inhibition of Iron-Sulfur Cluster Biogenesis on ISCA1/ISCA2/ISCU Assembly Proteins. Free Radical Biology and Medicine, 204: 359–373.

[7] Vo TTT, Peng T-Y, Nguyen TH, et al., 2024, The Crosstalk Between Copper-Induced Oxidative Stress and Cuproptosis: A Novel Potential Anticancer Paradigm. Cell Communication and Signaling, 22(1): 353.

[8] Chen J, Jiang Y, Shi H, et al., 2020, The Molecular Mechanisms of Copper Metabolism and Its Roles in Human Diseases. Pflügers Archiv-European Journal of Physiology, 472: 1415–1429.

[9] Chen L, Min J, Wang F, 2022, Copper Homeostasis and Cuproptosis in Health and Disease. Signal Transduction and Targeted Therapy, 7(1): 378.

[10] Shanbhag VC, Gudekar N, Jasmer K, et al., 2021, Copper Metabolism as a Unique Vulnerability in Cancer. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 1868(2): 118893.

[11] Zhao R, Sukocheva O, Tse E, et al., 2024, Cuproptosis, the Novel Type of Oxidation-Induced Cell Death in Thoracic Cancers: Can It Enhance the Success of Immunotherapy? Cell Communication and Signaling, 22(1): 379.

[12] Liu WQ, Lin WR, Yan L, et al., 2024, Copper Homeostasis and Cuproptosis in Cancer Immunity and Therapy. Immunological Reviews, 321(1): 211–227.

[13] Ruiz LM, Libedinsky A, Elorza AA, 2021, Role of Copper on Mitochondrial Function and Metabolism. Frontiers in Molecular Biosciences, 8: 711227.

[14] Xue Q, Kang R, Klionsky DJ, et al., 2023, Copper Metabolism in Cell Death and Autophagy. Autophagy, 19(8): 2175–2195.

[15] Lelièvre P, Sancey L, Coll J-L, er al., 2020, The Multifaceted Roles of Copper in Cancer: A Trace Metal Element with Dysregulated Metabolism, but Also a Target or a Bullet for Therapy. Cancers, 12(12): 3594.

[16] Tsvetkov P, Coy S, Petrova B, et al., 2022, Copper Induces Cell Death by Targeting Lipoylated TCA Cycle Proteins. Science, 375(6586): 1254–1261.

[17] Li Y, Qi P, Song S-Y, et al., 2024, Elucidating Cuproptosis in Metabolic Dysfunction-Associated Steatotic Liver Disease. Biomedicine & Pharmacotherapy, 174: 116585.

[18] Lill R, Freibert S-A, 2020, Mechanisms of Mitochondrial Iron-Sulfur Protein Biogenesis. Annual Review of Biochemistry, 89(1): 471–499.

[19] Cronan JE, 2020, Progress in the Enzymology of the Mitochondrial Diseases of Lipoic Acid Requiring Enzymes. Frontiers in Genetics, 11: 510.

[20] Pavlu-Pereira H, Silva MJ, Florindo C, et al., 2020, Pyruvate Dehydrogenase Complex Deficiency: Updating the Clinical, Metabolic and Mutational Landscapes in a Cohort of Portuguese Patients. Orphanet Journal of Rare Diseases, 15: 1–14.

[21] Huang T, Liu Y, Li J, et al., 2022, Insights Into Prognosis and Immune Infiltration of Cuproptosis-Related Genes in Breast Cancer. Frontiers in Immunology, 13: 1054305.

[22] Dreishpoon MB, Bick NR, Petrova B, et al., 2023, FDX1 Regulates Cellular Protein Lipoylation Through Direct Binding to LIAS. Journal of Biological Chemistry, 299(9): 105046.

[23] Zhao Q, Qi T, 2023, The Implications and Prospect of Cuproptosis-Related Genes and Copper Transporters in Cancer Progression. Frontiers in Oncology, 13: 1117164.

[24] Zhang L, Deng R, Guo R, et al., 2024, Recent Progress of Methods for Cuproptosis Detection. Frontiers in Molecular Biosciences, 11: 1460987.

[25] Echeverri Ruiz NP, Mohan V, Wu J, et al., 2021, Dynamic Regulation of Mitochondrial Pyruvate Metabolism Is Necessary for Orthotopic Pancreatic Tumor Growth. Cancer & Metabolism, 9: 1–12.

[26] Duarte I, Caio J, Moedas M, et al., 2021, Dihydrolipoamide Dehydrogenase, Pyruvate Oxidation, and Acetylation-Dependent Mechanisms Intersecting Drug Iatrogenesis. Cellular and Molecular Life Sciences:1–18.

[27] Zhao H, Li Y, 2021, Cancer Metabolism and Intervention Therapy. Molecular Biomedicine, 2(1): 5.

[28] Shao Y, Fan X, Yang X, et al., 2023, Impact of Cuproptosis-Related Markers on Clinical Status, Tumor Immune Microenvironment, and Immunotherapy in Colorectal Cancer: A Multi-Omic Analysis. Computational and Structural Biotechnology Journal, 21: 3383–403.

[29] Zhang X, Han X, 2024, Targeting Cuproptosis for Cancer Therapy: Focus on the Anti-Tumor Immune System. Cancer Pathogenesis and Therapy, 2: E76.

[30] Crispin A, 2017, HSCB, a Co-Chaperone in Mitochondrial Iron-Sulfur Cluster Biogenesis, Is a Novel Candidate Gene for Congenital Sideroblastic Anemia. Blood, 130(Supplement 1): 79.

[31] Mathias RA, Greco TM, Oberstein A, et al., 2014, Sirtuin 4 Is a Lipoamidase Regulating Pyruvate Dehydrogenase Complex Activity. Cell, 159(7): 1615–1625.

[32] Chen Q, Wang Y, Yang L, et al., 2022, PM2.5 Promotes NSCLC Carcinogenesis Through Translationally and Transcriptionally Activating DLAT-Mediated Glycolysis Reprograming. Journal of Experimental & Clinical Cancer Research, 41(1): 229.

[33] Lazzarino G, O'Halloran P, Di Pietro V, et al., 2022, Pyruvate Dehydrogenase Complex, Metabolic Enzymes, and Energy Derangement in Traumatic Brain Injury. Cellular, Molecular, Physiological, and Behavioral Aspects of Traumatic Brain Injury, Elsevier, Amsterdam, 207–218.

[34] Neitzel C, Demuth P, Wittmann S, et al., 2020, Targeting Altered Energy Metabolism in Colorectal Cancer: Oncogenic Reprogramming, the Central Role of the TCA Cycle and Therapeutic Opportunities. Cancers, 12(7): 1731.

[35] Liu J, Lu Y, Dai Y, et al., 2022, A Comprehensive Analysis and Validation of Cuproptosis-Associated Genes Across Cancers: Overall Survival, the Tumor Microenvironment, Stemness Scores, and Drug Sensitivity. Frontiers in Genetics, 13: 939956.

[36] Lukanović D, Herzog M, Kobal B, et al., 2020, The Contribution of Copper Efflux Transporters ATP7A and ATP7B to Chemoresistance and Personalized Medicine in Ovarian Cancer. Biomedicine & Pharmacotherapy, 129: 110401.

[37] Kamiya T, 2022, Copper Biology in Health and Disease: Copper in the Tumor Microenvironment and Tumor Metastasis. Journal of Clinical Biochemistry and Nutrition, 71(1): 22.

[38] Wan R, Pan L, Wang Q, et al., 2024, Decoding Gastric Cancer: Machine Learning Insights Into the Significance of COMMDs Family in Immunotherapy and Diagnosis. Journal of Cancer, 15(11): 3580.

[39] Riera-Romo M, 2018, COMMD1: A Multifunctional Regulatory Protein. Journal of Cellular Biochemistry, 119(1): 34–51.

[40] Maung MT, Carlson A, Olea-Flores M, et al., 2021, The Molecular and Cellular Basis of Copper Dysregulation and Its Relationship With Human Pathologies. The FASEB Journal, 35(9): 21810.

[41] Karlsson H, Fryknäs M, Strese S, et al., 2017, Mechanistic Characterization of a Copper Containing Thiosemicarbazone with Potent Antitumor Activity. Oncotarget, 8(18): 30217.

[42] Chen X, Mims J, Huang X, et al., 2018, Modulators of Redox Metabolism in Head and Neck Cancer. Antioxidants & Redox Signaling, 29(16): 1660–1690.

[43] Boyd SD, Ullrich MS, Skopp A, et al., 2020, Copper Sources for Sod1 Activation. Antioxidants, 9(6): 500.

[44] Mu W, Zhi Y, Zhou J, et al., 2024, Endoplasmic Reticulum Stress and Quality Control in Relation to Cisplatin Resistance in Tumor Cells. Frontiers in Pharmacology, 15: 1419468.

[45] Qin X, Wang P, Liang H, et al., 2024, Curcumin Suppresses Copper Accumulation in Non-Small Cell Lung Cancer

by Binding ATOX1. BMC Pharmacology and Toxicology, 25(1): 54.

[46] Suraweera A, Duijf PH, Jekimovs C, et al., 2021, COMMD1, from the Repair of DNA Double Strand Breaks, to a Novel Anti-Cancer Therapeutic Target. Cancers, 13(4): 830.

[47] Weaver BP, Zhang Y, Hiscox S, et al., 2010, Zip4 (Slc39a4) Expression is Activated in Hepatocellular Carcinomas and Functions to Repress Apoptosis, Enhance Cell Cycle and Increase Migration. PloS one, 5(10): e13158.

[48] Allard D, Turcotte M, Stagg J, 2017, Targeting A2 Adenosine Receptors in Cancer. Immunology and Cell Biology, 95(4): 333–339.

[49] Zhou Y, Lei D, Hu G, et al., 2022, A Cell Cycle-Related 13-mRNA Signature to Predict Prognosis in Hepatocellular Carcinoma. Frontiers in Oncology, 2022(12): 760190.

[50] Li Y, 2020, Copper Homeostasis: Emerging Target for Cancer Treatment. IUBMB Life, 72(9): 1900–1908.

[51] Zhalsanova IZ, Fonova E, Zhigalina D, et al., 2023, The ATOX1 Gene Role in Copper Metabolism and the Pathogenesis of Copper-Induced Diseases. Russian Journal of Genetics, 59(3): 242–250.

[52] Zhang X, 2023, Copper Binding Proteins in Breast Cancer: Cellular and Molecular Mechanisms, thesis, Chalmers University of Technology.

[53] Arnesano F, Natile G, 2021, Interference Between Copper Transport Systems and Platinum Drugs. Seminars in Cancer Biology, 75: 176–188.

Publisher's note

Bio-Byword Scientific Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.