

Xu et al. review on current knowledge of cuproptosis

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Nice — I pulled the paper you gave and a few core background sources and put everything together: a concise summary, a deep mechanistic breakdown of cuproptosis, its specific relevance to CNS / neuro-oncology and the BBB, an annotated Vancouver-style bibliography entry, a figure-style schematic description you can turn into a figure, and clear therapeutic / biomarker implications. Key sources used are cited inline (including the paper you gave).

Concise summary

Xu et al. review current knowledge of **cuproptosis** — a copper-dependent, regulated form of cell death — and summarize evidence that links copper dysregulation and cuproptosis to a range of central nervous system (CNS) diseases (neurodegeneration, stroke, spinal cord injury, and CNS tumors). They present the core molecular machinery (FDX1, lipoylation enzymes, lipoylated TCA-cycle proteins such as DLAT/DLST, loss of Fe–S proteins, proteotoxic stress), describe how mitochondrial respiration status modulates sensitivity, and discuss potential translational angles: copper chelation, copper ionophores, diagnostic copper imaging, and cuproptosis-related biomarkers. [PubMed +1](#)

Detailed mechanistic overview (step-by-step)

1. Prerequisite: mitochondrial, lipoylated TCA enzymes.

Cuproptosis requires mitochondrial respiration and the presence of lipoylated E2 subunits of multienzyme complexes (notably the pyruvate dehydrogenase complex E2 subunit DLAT and α -ketoglutarate dehydrogenase E2 DLST). Cells with active oxidative phosphorylation are more sensitive. [PubMed +1](#)

2. Copper entry and mitochondrial delivery.

Copper uptake (CTR1 and chaperones) and delivery into mitochondria (including the role of ionophores such as elesclomol) increase mitochondrial Cu. FDX1 (ferredoxin-1) promotes reduction and handling of mitochondrial copper and is a gatekeeper: loss of FDX1 rescues cells from copper toxicity. [PubMed +1](#)

3. Direct copper binding to lipoyl moieties.

Excess mitochondrial Cu binds the lipoyl cofactor on E2 subunits (lipoylation performed by LIAS, LIPT1, etc.), causing **aberrant oligomerization/aggregation** of these lipoylated proteins. [PubMed](#)

4. Proteotoxic stress & Fe–S cluster protein loss.

Aggregation of lipoylated proteins is associated with loss/dysfunction of iron–sulfur (Fe–S) cluster proteins (important for electron transport and enzyme function), induction of heat-shock/proteostasis responses (HSPs), and widespread proteotoxic stress. This cascade is mechanistically distinct from apoptosis, ferroptosis, necroptosis, and pyroptosis. [PubMed +1](#)

5. Cell death outcome.

The net result is regulated, lethal dysfunction of mitochondrial metabolism and cell death — “cuproptosis.” Sensitivity is higher in cells with intact mitochondrial respiration and high lipoylation. Modifying mitochondrial activity (e.g., inhibiting OxPhos) modulates susceptibility. [PubMed](#)

6. Regulators / modifiers (examples).

- **Promoters / required:** FDX1, LIAS, LIPT1, lipoylated E2 subunits (DLAT/DLST).
- **Protective / rescuing:** knockouts/knockdowns of FDX1 or lipoylation enzymes, Fe–S cluster stabilizers, mitochondrial respiration inhibitors. [PMC +1](#)

Relevance to CNS diseases and neuro-oncology

(Practical, evidence-based points derived from the review + related literature.)

- **Neurodegeneration (Alzheimer’s, Parkinson’s, ALS, etc.):** copper homeostasis is tightly regulated in neurons; dysregulated copper and altered mitochondrial function can plausibly trigger cuproptosis-like processes, contributing to neuronal loss, proteotoxic stress, and inflammatory sequelae. The review highlights mechanistic overlaps (mitochondrial dysfunction + metal dysregulation) although causal linkage in specific diseases remains being established. [PubMed +1](#)
- **Acute CNS injury (stroke, spinal cord injury):** ischemia/reperfusion and trauma produce mitochondrial stress and altered metal handling; recent work suggests cuproptosis could amplify secondary injury via mitochondrial proteotoxicity and inflammation (example: spinal cord injury literature). Therapeutically, modulation of copper after acute injury may alter outcomes in models. [Frontiers +1](#)

- **Neuro-oncology (gliomas, medulloblastomas):**
 - **Therapeutic vulnerability:** many tumors (or tumor subpopulations) with high oxidative phosphorylation and intact TCA-cycle activity could be **selectively sensitized** to cuproptosis by copper ionophores (e.g., elesclomol) or by interventions that increase mitochondrial copper. Conversely, tumors that rely on glycolysis may be resistant. This opens a precision-oncology angle: identify OxPhos-high glioma subtypes, target them with cuproptosis-inducing regimens. [Nature +1](#)
 - **Resistance and the tumor microenvironment:** tumoral copper transporters, antioxidant responses, and microglia/immune cell interactions could modulate efficacy. Blood–brain barrier (BBB) restricts systemic copper ionophore penetration — both a challenge and a potential selectivity lever. [PubMed](#)
- **Blood–brain barrier (BBB) considerations:** the BBB controls systemic–CNS copper flux. Therapeutic strategies must account for (a) ability of an agent to cross BBB (ionophore vs. chelator), (b) effects on endothelial and perivascular cells (cuproptosis in these cells could harm barrier integrity), and (c) potential to alter CNS copper pools. Local (intratumoral/intrathecal) delivery might be attractive for CNS tumors to avoid systemic toxicity. [PubMed +1](#)

Figure-style schematic description (ready to convert into an illustration)

Title: “Mechanism of cuproptosis and CNS implications”

1. Left panel: Normal mitochondrion — show TCA enzymes (PDH: DLAT), lipoyl groups attached, FDX1 and LIAS/LIPT1 supporting lipoylation; low free copper (homeostasis).
2. Middle panel: Copper overload (ionophore or dysregulated uptake) — arrows indicating Cu entry, FDX1-mediated mitochondrial Cu release → Cu binds lipoyl moieties on DLAT/DLST → oligomerization/aggregation (show aggregated protein clumps).
3. Right panel: Consequences — Fe–S cluster protein loss (dashed mitochondrial complexes), proteotoxic stress (HSP up arrow), impaired electron transport / ATP fall, release of DAMPs → cell death (cuproptosis) and microglial activation.
4. Bottom strip (clinical implications icons): (A) Glioma — label “OxPhos-high tumors sensitive”; (B) Stroke/SCI — label “may amplify secondary injury”; (C) BBB — icon showing limited systemic penetration; (D) Therapy icons: copper chelators (–), copper ionophores (+), biomarkers (FDX1, lipoylation, Cu PET imaging).

(If you want, I can make this into a slide or a publication-quality schematic — tell me preferred format.) [PubMed +1](#)

Annotated Vancouver-style bibliography entry (your preferred style)

Xu M, An Y, Liu X, Li X, Huang X, Gu Q, Xue M, Xue J, Tao L, Shan H, Chen X, Zhang M. The molecular mechanisms of cuproptosis and its role in central nervous system diseases. *Cell Signal*. 2025 Nov 10;138:112236. doi:10.1016/j.cellsig.2025.112236. Epub ahead of print. PMID: 41224164.

Annotation (2–3 lines): Concise, up-to-date review synthesizing mechanistic insights into cuproptosis (FDX1-dependent lipoylated TCA-protein aggregation → Fe–S loss → proteotoxic stress) and summarizing evidence linking copper dysregulation to CNS pathologies (neurodegeneration, acute injury, and CNS tumors). Includes translational discussion (ionophores, chelators, BBB considerations) and highlights outstanding mechanistic gaps and biomarker candidates (FDX1, lipoylation enzymes). [PubMed](#)

Key implications for therapy and biomarker development (practical takeaways)

1. Therapeutic strategies

- **Induce cuproptosis in cancer:** use copper ionophores (e.g., elesclomol and related compounds) or strategies that increase mitochondrial copper in OxPhos-dependent glioma subsets. Preclinical evidence supports selective cytotoxicity in respiration-high cells. [PubMed +1](#)
- **Protect in acute injury / neurodegeneration:** systemic or localized **copper chelation** (tetrathiomolybdate, D-penicillamine) or agents that stabilize Fe-S proteins/proteostasis might reduce cuproptosis-mediated damage after stroke/trauma. Timing and BBB penetration are critical. [Frontiers +1](#)

2. Biomarkers & patient selection

- **Molecular markers:** FDX1 expression, LIAS/LIPT1 levels, and abundance of lipoylated DLAT/DLST — high expression predicts sensitivity to cuproptosis induction.
- **Functional/metabolic markers:** transcriptional or metabolic signatures indicating high mitochondrial respiration / intact TCA cycle (OxPhos signatures) could stratify tumors.
- **Imaging:** Cu-PET or other copper-sensitive imaging could map copper distribution and identify high-Cu regions or tumor uptake. [PubMed +1](#)

3. Safety & delivery

BBB restricts some systemic drugs; consider BBB-permeable ionophores, local delivery (convection-enhanced, intratumoral), or combination strategies that transiently open the BBB. Also beware of off-target neuronal/vascular cuproptosis — therapeutic window will be narrow. [PubMed](#)

Limitations, open questions, and experimental suggestions

- **Causality in human CNS disease:** direct causal proof that cuproptosis drives neuronal death in human disorders is still limited — most evidence is mechanistic and from models. Translational work needed. [PMC](#)
- **Cell-type specificity:** how do neurons, astrocytes, microglia, endothelial cells differ in lipoylation, FDX1 expression, and copper handling? Single-cell profiling across models would help.
- **Therapeutic index:** how to selectively trigger cuproptosis in tumor cells while sparing neurons? Combine tumor-selective delivery with patient selection (OxPhos-high tumors).
- **Biomarker validation:** validate FDX1/lipoylation signatures in tumor cohorts and correlate with sensitivity to ionophores in patient-derived models.

Sources (most load-bearing cited)

- Xu M et al., *The molecular mechanisms of cuproptosis and its role in central nervous system diseases*. Cell Signal. 2025. (the paper you provided). [PubMed](#)
- Tsvetkov P et al., *Copper induces cell death by targeting lipoylated TCA cycle proteins*. Science. 2022;375:1254–1261. (original mechanistic paper defining cuproptosis). [PubMed](#)
- Li SR et al., review on cuproptosis mechanisms and implications. (2022/2023 reviews that contextualize tumor vulnerability and lipoylation dependence). [Nature](#)
- Frontiers / Immunology review on cuproptosis in spinal cord injury and acute CNS injury (2025). [Frontiers](#)
- Recent 2025 review: “From copper homeostasis to cuproptosis” summarizing recent CNS connections. [PMC](#)