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The molecular mechanisms of cuproptosis and its role in central nervous system diseases

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Abstract

Copper is an essential micronutrient in the brain, serving as a critical enzymatic cofactor indispensable for neuronal function and homeostasis. In recent years, cuproptosis, a new regulated form of cell death mechanistically distinct from pyroptosis and ferroptosis, has emerged as a pivotal player in the pathogenesis of central nervous system disorders. This review provides a systematic synthesis of brain-specific copper homeostasis, detailing the roles of blood-brain barrier transporters, glial-mediated copper buffering, and neuron-specific copper chaperones in maintaining cerebral copper balance. We delineate three core molecular pathways driving cuproptosis in the CNS and highlight their cell-type-specific manifestations. Furthermore, by converging clinical observations with preclinical evidence, we elucidate the pathogenic links between cuproptosis and major CNS disorders, including acute injuries, neurodegenerative disorders, and gliomas, clarifying the distinct triggers and disease-specific contributions of cuproptosis in each condition. Building on these insights, we propose a disease-classified therapeutic strategy targeting cuproptosis, identify promising diagnostic and prognostic biomarkers and advocate for future research into organ-specific cuproptosis regulation. This review offers a conceptual foundation for advancing mechanistic understanding and developing precision therapeutics for CNS diseases rooted in copper dysregulation.

Keywords: Brain; Cell death; Cognitive function; Copper; Cuproptosis; Nervous system.