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Dissecting the Molecular Network of Cold Atmospheric Plasma-Induced Ferroptosis: A Systematic Review of Key Regulatory Pathways in Cancer

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ABSTRACT

Introduction: Cold atmospheric plasma (CAP) is a novel anticancer modality that functions by inducing ferroptotic cell death. This systematic review delineates the core molecular signaling pathways CAP utilizes to execute ferroptosis in malignant cells.

Materials and Methods: We systematically searched PubMed, Scopus, and Web of Science for studies (2020-2025) at the intersection of cold atmospheric plasma, ferroptosis, and cancer. Inclusion was limited to original research on molecular mechanisms in human cancer cell lines or in vivo models.

Results and Discussion: Our synthesis revealed CAP orchestrates ferroptosis by disrupting multiple antioxidant systems. The primary axis involves suppressing GPX4 (e.g., via EGFR signaling in TNBC), while concurrently crippling the glutathione supply by downregulating SLC7A11 through diverse mechanisms (e.g., ATM/p53 axis, HOXB9 acetylation). Crucially, CAP also dysregulates iron homeostasis, increasing the labile iron pool to fuel the Fenton reaction. We also identified novel regulatory layers, including an epigenetic sensitization route (USP49/HDAC3) and a GPX4-independent pathway via FSP1 suppression. These synergistic interventions culminate in overwhelming lipid peroxidation, the ultimate executioner of ferroptosis.

Conclusion: CAP acts as a sophisticated modulator of the ferroptosis network. By exploiting diverse, tumor-specific vulnerabilities, it functions as a highly adaptable therapeutic modality. This mechanistic plasticity holds significant promise for targeting tumor metabolic heterogeneity and overcoming therapy resistance.

Keywords: Cold atmospheric plasma, Ferroptosis, GPX4, p53, Signaling pathway, SLC7A11, Targeted therapy

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