Abstract #23 | Poster

Hyperthermia increases ferroptosis susceptibility of diffuse large B-cell lymphoma

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Background:
Despite advances in immunochemotherapy, patients with diffuse large B-cell lymphoma (DLBCL) who relapse or develop refractory disease have poor prognosis. Novel therapeutic strategies are urgently needed. Ferroptosis, an iron-dependent form of regulated cell death driven by lipid peroxidation and redox imbalance, represents a potential vulnerability in malignant B cells. Fever is an evolutionarily conserved hyperthermal response that supports immune function, and externally applied hyperthermia is clinically used as an adjunct in selected solid tumors. However, its role in hematologic malignancies remains unclear. In particular, the effect of hyperthermic temperatures on ferroptosis susceptibility in lymphoma cells has not been investigated. We therefore examined whether physiologic-range hyperthermia enhances ferroptosis induction in DLBCL cells.

Methods:
DLBCL cell lines were preincubated at 41°C and subsequently treated with ferroptosis inducers (dimethyl fumarate, erastin, RSL3) or conventional cytotoxic agents. Treatment response was assessed by viability assays, lipid peroxidation measurements, intracellular glutathione quantification, cystine uptake assays, and molecular analyses of key ferroptosis- and redox-regulatory proteins and transcripts.

Results:
Hyperthermia alone did not significantly affect cell viability. However, preincubation at 41°C markedly increased sensitivity to ferroptosis induced by dimethyl fumarate, erastin, and RSL3. No sensitization was observed for vincristine or cyclophosphamide, indicating pathway-specific effects rather than general chemosensitization. Hyperthermia-induced sensitization was fully rescued by α-tocopherol and N-acetyl-cysteine, confirming a lipid peroxidation- and glutathione-dependent mechanism. Mechanistically, hyperthermia reduced cystine uptake and altered intracellular glutathione homeostasis under redox stress. These changes were associated with decreased protein abundance of the cystine/glutamate antiporter SLC7A11, while mRNA levels remained largely unchanged, suggesting post-transcriptional regulation.

Conclusion:
Physiologic-range hyperthermia primes DLBCL cells for ferroptotic cell death without nonspecific cytotoxicity. By impairing cystine uptake and glutathione-dependent redox defense, hyperthermia enhances the efficacy of ferroptosis-targeting strategies. These findings provide a translational rationale for integrating hyperthermia into ferroptosis-based therapeutic strategies.