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BRD4 inhibition sensitizes diffuse large B-cell lymphoma cells to ferroptosis

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Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma and characterized by an aggressive clinical course. In approximately one-third of DLBCL patients, first line multiagent immunochemotherapy fails to produce a durable response due to molecular heterogeneity and therapy resistance, including evasion of apoptosis. Ferroptosis, an iron-dependent, lipid peroxidation-driven form of regulated cell death, has emerged as an alternative strategy to eliminate apoptosis-refractory lymphoma cells. Here, we systematically screened a compound library of epigenetic modulators to identify compounds that enhance ferroptotic killing in DLBCL. Bromodomain and extra-terminal domain (BET) inhibitors robustly sensitized germinal center B-cell–like (GCB) DLBCL cells to multiple ferroptosis inducers, including dimethyl fumarate and RSL3, resulting in synergistic cell death *in vitro* and improved antitumor efficacy *in vivo*. Mechanistically, we identify the BET protein BRD4 as a critical transcriptional regulator of ferroptosis suppressor protein 1 (FSP1), thereby maintaining a ferroptosis-resistant state in GCB-DLBCL. Genetic or pharmacologic BRD4 inhibition downregulated FSP1 expression, increased susceptibility to lipid peroxidation, and rendered DLBCL cells highly vulnerable to ferroptosis induction. Collectively, our data establishes BRD4 as a critical regulator of ferroptosis resistance in GCB-DLBCL and provides a strong preclinical rationale for combining BET inhibitors with ferroptosis-inducing agents as a novel therapeutic approach for DLBCL.