Abstract #18 | Poster

Identification of ferroptosis sensitizers for DLBCL treatment

J. Labisch[1], G. Lenz[1], A. Schmitt[1], S. Hailfinger[1]

[1] *University Hospital Münster, Münster, North Rhine-Westphalia, Germany*

Diffuse large B cell lymphoma (DLBCL) are the most common type of non-Hodgkin lymphoma in adults and have an aggressive clinical course. The immunochemotherapy R-CHOP results in a durable response in two-third of patients, but one-third of all patients relapse or are refractory after R-CHOP treatment, highlighting the need for new therapeutic strategies. Ferroptosis, an iron-dependent cell death characterized by lipid peroxidation, represents a promising treatment strategy for DLBCL. Recently, dimethyl fumarate (DMF) was described as a ferroptosis inducer in GCB-DLBCL by depleting the glutathione pool and thereby disrupting cellular antioxidant mechanisms. By analyzing a compound library, inhibitors of PI3K signaling were identified to synergize with DMF on provoking lipid peroxidation. Here we show that inhibitors blocking PI3K, AKT or mTOR activity synergize with DMF in the induction of ferroptosis in DLBCL. Interestingly, we were able to detect a decrease in mRNA and protein levels of SLC7A11 (a subunit of the cystine/glutamate antiporter system x_c^-), which is crucial for providing cysteine for glutathione synthesis, upon PI3K signaling inhibition. Accordingly, PI3K signaling was essential for sustaining glutathione levels and thus important for the protection of the lymphoma cells from ferroptosis. In conclusion, we demonstrate that PI3K signaling inhibition can sensitize DLBCL cells to ferroptosis by lowering SLC7A11 and glutathione expression, highlighting the potential of a combination treatment of PI3K signaling inhibitors with ferroptosis inducers.