FTH1 silencing is required to overcome JQ1 resistance in aggressive non-small cell lung cancer via BRD2 by inducing ferroptosis

P-27-128

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Recent studies reported the presence of Ferritin in cell nuclei,specifically, the H Ferritin subunit (FTH1) emphasizing its involvement in alternative functions such as DNA protection from oxidative damage and transcriptional regulation.Bromodomain and extra terminal domain (BET) proteins act as epigenome readers for gene transcriptional regulation. Among BET family members, the role of BRD2 in non-small cell lung carcinoma (NSCLC) remains to be elucidated.In this study, we provide the first evidence of the functional interplay between nuclear FTH1 and BRD2. We show that nuclear FTH1 associates with BRD2, but not with BRD4, in a panel of NSCLC cell lines, particularly, in more aggressive types of NSCLC cells. We verified if FTH1 could affect the stability of BRD2 protein in NSCLC cells and observed a reduction of BRD2 protein levels in FTH1-silenced cells, only in more aggressive types of NSCLC cells, without affecting BRD2 mRNA levels. The combination treatment of JQ1, a BET inhibitor, with the FTH1 silencing induces an increase in mortality in JQ1-insensitive cells rather than JQ1-sensitive cells. The potential mechanism by which the combination treatment of JQ1 with the FTH1 silencing induces cell death was explored. The results show that ferroptosis is involved in the anticancer effect of JQ1 upon FTH1 silencing in JQ1-insensitive cells. Of note, the reactive oxygen species levels were increased by iron via the Fenton reaction, leading to ferroptosis. In addition, expression of ferroptosis-associated genes GPX4, SLC7A11, and SLC3A2 was downregulated under JQ1 treatment and FTH1 silencing, indicating that the cotreatment JQ1-FTH1 silencing may regulate ferroptosis by controlling the expression of ferroptosis-associated genes. In summary, for the first time, our data suggests that FTH1 silencing may serve as an effective anti-tumor strategy to enhance the activity of JQ1,acting to overcome the chemotherapy resistance in more aggressive non-small cell lung cancers.