TARGETING LSD1 RESCUES MHC-I ANTIGEN PRESENTATION AND OVERCOMES RESISTANCE TO PD-L1 BLOCKADE THERAPY IN SMALL CELL LUNG CANCER

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Background Small cell lung cancer (SCLC) is an immunosuppressive tumor with modest clinical response to immune checkpoint blockade (ICB). Repression of major histocompatibility class I (MHC-I) molecules represents a potential mechanism driving ICB resistance in SCLC. Lysinespecific demethylase 1 (LSD1) has been regarded as a promising therapeutic target in SCLC. Our study investigated immunomodulatory functions of LSD1 in regulating MHC-I antigen presentation pathway (APP) in SCLC.

Methods We employed the inhibitor ORY-1001 and RNA interference to assess changes in MHC-I expression in SCLC cell lines by flow cytometry. We then performed RNA-seq to characterize whole transcriptomic changes in SCLC cells following LSD1 inhibition. To explore effects of targeting LSD1 on T cell cytolysis, we co-cultured SCLC presenting endogenous peptides with pre-activated cognate CD8+ T cells. Finally, we treated immunocompetent mice bearing syngeneic SCLC tumors with ORY-1001 and/or anti-PD-L1 to evaluate tumor growth and characterize intratumor immune activities.

Results We found that targeted inhibition of LSD1 in SCLC restores MHC-I cell surface expression and transcriptionally activates genes encoding the antigen presentation pathway. LSD1 inhibition further activates interferon signaling, induces tumor-intrinsic immunogenicity, and sensitizes SCLC cells to MHC-I-restricted T cell cytolysis. Combination of LSD1 inhibitor with ICB augments the antitumor immune response in refractory SCLC models. Together, these data define a role for LSD1 as a potent regulator of MHC-I antigen presentation and provide rationale for combinatory use of LSD1 inhibitors with ICB to improve therapeutic response in SCLC.

Conclusions Epigenetic silencing of MHC-I in SCLC contributes to its poor response to ICB. Our study identifies a previously uncharacterized role for LSD1 as a regulator of MHC-I antigen presentation in SCLC. LSD1 inhibition enables MHC-I-restricted T cell cytolysis, induces immune activation, and augments the antitumor immune response to ICB in SCLC.

Ethics Approval All animal experiments were approved by and used in accordance with animal care guidelines from the Memorial Sloan Kettering Cancer Center (MSKCC) Animal Care and Use Committee.