AIM2 MODULATES AZACYTIDINE-INDUCED ANTITUMOR IMMUNITY IN LUNG CANCER

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Background

Immune checkpoint inhibition (ICI) has been established as an essential treatment for lung and other cancers. Preclinical studies revealed that DNA-demethylating agents induced type I interferon (IFN-I) response and primed the tumor microenvironment (TME) to enhance antitumor immunity.1 2 However, this promising effect has not been successfully demonstrated in clinical trials of combined treatments of ICI and DNA hypomethylation agents in lung cancer.3 We hypothesize that azacytidine (AZA), a DNA hypomethylation agent and a broad-spectrum epigenetic programmer, might inevitably also activate key immune suppression mediator(s). We demonstrated that absent melanoma 2 (AIM2), a DNA sensing component of inflammasome, negatively impacts AZA-induced antitumor immunity in non-small cell lung cancer (NSCLC) by modulating IFN-I response and T effector cell tumor infiltration.

Methods

We tested gene expression upregulated by AZA in lung cancer cell lines and used genetic modeling to identify the mechanism mediating AZA-induced AIM2 expression. Aim2-deficient (Aim2−/−) tumor cells (CMT167 and LLC) were established with the CRISPR/Cas9 system. We adopted an immune-competent syngeneic mouse tumor model to investigate the impacts of AIM2 on TME and tumor growth. We measured tumor growth and analyzed tumor samples with flowcytometry (FCM) and immunohistochemistry staining (IHC).

Results

AIM2 expression was highly synergistically induced by AZA and IFN-γ in multiple human and mouse lung cancer cell lines. We demonstrated that AZA upregulated AIM2 expression through a RNA sensing mechanism. Analysis of AIM2 expression in 1925 NSCLC patients with KM-Plotter (https://kmplot.com/analysis/)4 showed that high AIM2 expression was associated with significantly shorter overall survival in NSCLC. We showed that AZA and IFN-γ induced IFN-I response was enhanced in Aim2−/− CMT167 cells comparing to Aim2+/+ cells. Using Aim2−/− and Aim2+/+ CMT167, and the immune-competent syngeneic mouse model, AZA treatment induced significant growth suppression of Aim2−/− tumors, but not Aim2+/+ tumors. FCM of the tumor tissue demonstrated that the number of CD8+ T cells was significantly increased after AZA treatment in both Aim2−/− and Aim2+/+ tumors, whereas IHC revealed AZA promoted significantly more CD8+ T cell infiltration into the TME in Aim2−/− tumors than in Aim2+/+ tumors. We demonstrated that CD8 depletion negated AIM2’s effect on AZA-treated tumor growth in vivo and indicated that the impact of AIM2 on tumor growth would depend on CD8+ T cells.

Conclusions

AIM2 is a key negative regulator for AZA-induced antitumor immunity and a potential novel therapeutic target in optimizing epigenetic and immune therapy in NSCLC.

REFERENCES