Abstract

Inhibitory T cell responses to low frequency antigenic peptides from the HLA-A*02:01 restricted PD-L1 ligand PD-L1 have been reported to impact the antitumor efficacy of immunotherapies. Here, we demonstrate that class I HDAC inhibitor mocetinostat, through upregulation of PD-L1 ligand and MICA/B, demonstrates synergy with multiple PD-L1 blockade therapies to enhance antitumor activity.

Methods

PanCancer specific gene expression analyses were performed in the CT26 model. 13 mice per group were treated with an isotype control, mocetinostat (500 nm) or LTF (10 mg/kg). Mice were treated for 3 or 5 days. Individual tumor volumes were measured twice a week with the following formula: length * width * length. Tumor response was defined as: microscopically complete response (MCR) or partial response (PR) if tumor regression was at least 35% or 15% respectively. Mice were sacrificed when tumors reached 15 mm in diameter. Tumor tissues were fixed in 10% formalin and processed for paraffin-embedded snap sections. Sections were stained with antibodies recognizing PD-L1, HLA-A, HLA-B, HLA-C, HLA-DRA, HLA-DRB, HLA-DPA, HLA-DPB, MIC-A, MIC-B and MICA/B.

Results

Class I HDAC inhibitor mocetinostat, induces expression of PD-L1 and tumor antigen presentation machinery and modifies tumor immune cellular subsets providing a rationale for immune checkpoint inhibitor combinations.

Conclusions

• Mocetinostat upregulates PD-L1, co-repression molecules, class I and Class II MHC, genes as well as CD107a, CD107b, and GPR173 ligands MICA and MICB in several NSCLC cell lines tested. FACS analysis confirmed the increased surface protein expression. Similar observations were made in pancreatic cancer models in vivo.

• Mocetinostat increases PD-L1 and MICA/B+ cells. CD8+ cells were also increased in the spleen following mocetinostat treatment.

• The combination of mocetinostat and an anti- PD-L1 antibody resulted in greater antitumor activity compared to either agent alone.

References

13. Jaffe ES, Harris NL, Stein H, Vardiman JW. Pathology and genetics of tumors of haematopoietic and lymphoid tissues. IARC Press; 2001
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