IMMUNOMODULATION BY TARGETING PDL-1 IN COLON CANCER USING NUCLEAR RECEPTOR 4A1 (NR4A1) ANTAGONISTS

Maen Abdelrahim*, Kumaravel Mohankumar, Keshav Karki, Stephen Safe. Houston Methodist Cancer Center, Houston, TX, United States; Texas A&M University, College Station, TX, United States.

Background The nuclear orphan receptor 4A1 (NR4A1, Nur77, TR3) is overexpressed in multiple solid tumors including colorectal tumors and is a negative prognostic factor for patient survival. NR4A1 is expressed in colon cancer cells and exhibit pro-oncogenic activity and results of examination of several colon cancer cell lines show that PD-L1 expression is limited and NR4A1 and PD-L1 are co-expressed in SW480 and RKO colon cancer cell lines. Previous studies showed that PD-L1 was regulated by NR4A1 which activates transcription factor Sp1 bound to the PD-L1 gene promoter. Knockdown of NR4A1 or Sp1 by RNA interference or treatment with mithramycin an inhibitor of Sp-mediated transcription decreased expression of PD-L1 in RKO and SW480 colon cancer cell lines.

Methods SW480, RKO and MC-38 cells were used in this study. Cells were treated for 24 hrs with DIM series of compounds.

Results Current data coupled with ongoing gene expression and PD-L1 promoter studies demonstrate that PD-L1 expression is regulated by NR4A1/Sp1 in colon cancer cells (figures 1–3). Bis-indole derived NR4A1 ligand that act as receptor antagonists have been developed in this laboratory and these compounds block pro-oncogenic NR4A1-regulated genes/pathways. Treatment of RKO and SW480 colon cancer cell lines with a series of potent 1,1-bis(3′-indolyl)-1-(3,5-disubstituted-phenyl) analogs decreased expression of PD-L1. These results show that bis-indole derived NR4A1 antagonists act as small molecule mimics of immunotherapeutics that target PD-L1. In vivo applications of NR4A1 ligands that target PD-L1 and their effects on tumor growth and immune surveillance are currently being investigated.

Conclusions Bis-indole derived NR4A1 antagonists inhibit PD-L1 expression. NR4A1/Sp1 regulates PD-L1 and is inhibited by NR4A1 antagonist. NR4A1 ligands such as DIM-3-Br-5-OCF3 were among the most potent of the substituted DIM compounds and ongoing in vivo studies show that this DIM compound also inhibits tumor growth in a syngenic mouse model (data not shown). Data from this study demonstrate the pro-oncogenic activity of NR4A1 and show that the synthetic buttressed analog DIM-3-Br-5-OCF3 acts as an NR4A1 antagonist and inhibits PD-L1 expression. These drugs can be developed for future clinical applications.

REFERENCES


http://dx.doi.org/10.1136/jitc-2021-SITC2021.725