allied academies Joint Event on
International Conference on
CELL AND GENE THERAPY
&
World Congress on
CLINICAL AND MEDICAL MICROBIOLOGY
September 10-11, 2018 | Dublin, Ireland
Biomed Res 2018, Volume 29 | DOI: 10.4066/biomedicalresearch-C3-008

TARGETING CD38 ON TUMOR CELLS TO REVERSE THE RESISTANCE TO ANTI-PD-1/PD-L1 IMMUNOTHERAPY OF CANCER

Limo Chen, Lixia Diao, B Leticia Rodriguez, Ignacio I Wistuba, Jing Wang, John V Heymach, F Xiao-Feng Qin and **Don L Gibbons**
The University of Texas MD Anderson Cancer Center, USA

Although strategies incorporating immune checkpoint inhibition are achieving unprecedented successes and rapidly being incorporated into standard of care regimens for lung cancer patients, high rates of therapeutic resistance limit their potential efficacy. Thus, successful immunotherapy of lung cancer requires a thorough understanding of the biological process of resistance. In immunocompetent syngeneic and K-ras$^{LA1/+}$p53$^{R172H\Delta g/+}$ spontaneous animal models of lung cancer, we have explored the resistance mechanisms using pharmacological and genetic approaches (PD-1/PD-L1 monoclonal antibody treatment and CRISPR/Cas9-mediated editing). The molecular and immune profiles of the tumor microenvironment were evaluated. More importantly, to determine the applicability to patients, 793 lung cancer specimens were immunohistochemically stained for CD38, and multiple large independent patient datasets (TCGA, PROSPECT, BATTLE-2) of non-small cell lung cancer (~1430 tumors) were analyzed by using integrated bioinformatics. We identified the up-regulation of CD38 on tumor cells as the marker of resistance to anti-PD-1/PD-L1 treatment. The same resistance mechanism caused by CD38 was also observed in PD-L1 KO mice bearing PD-L1 KO Lewis lung tumors edited with the CRISPR/Cas9 system. *In vitro* and *in vivo* studies revealed that CD38 inhibited CD8 T cell function via adenosine receptor signaling, and that CD38 blockade served as an effective strategy to overcome the treatment resistance to PD-1/PD-L1 axis blockade. In lung cancer patients, 15-23% of cases exhibited positive staining for CD38 on tumor cells, showing a great potential benefit for treatment. Multiple large datasets of lung cancer patients suggested a strong correlation between CD38 and an intratumoral immune signature.