Abstract citation ID: bvac150.1652

Thyroid

OR11-2

RNA Sequencing Reveals Unique Transcriptomic Signatures of the Thyroid in a Murine Lung Cancer Model Treated with PD-1 and PD-L1 Antibodies

Rivka Dresner-Pollak, Zvi G Fridlender, Irina Gurt, Naomi Kaisar-Iluz, Natan Lishinsky, Rena Pollack, Merav E Shaul , and Joshua Stokar

Immune checkpoint inhibitors (ICI) have revolutionized cancer therapy, however, are associated with immune-related adverse events (irAEs). Thyroid dysfunction is among the most common irAEs, yet its mechanism has not been fully elucidated. To further explore the molecular mechanism of ICI-induced thyroid dysfunction, we profiled changes in transcription induced by PD-1/PD-L1 antibody treatment in a non-small cell lung cancer murine model using RNA-seq. We used bioinformatic tools to compare transcriptional changes in our model to previously published transcription data sets of drug-induced thyroiditis. C57BL6/129SvJ mice harboring LKR-M (Lung cancer K-ras metastatic tumor) flank tumors were treated with PD-1 antibody, PD-L1 antibody, or vehicle every 3 days over a period of 7 days when mice were sacrificed, and thyroid glands were removed. The tumor volume increased in the control mice (1.38 ± 0.19) and decreased in the anti PD-1 treated (0.64 ± 0.15; P=0.0001) and PD-L1 treated mice (0.74 ± 0.11; P=0.004). RNA-seq was performed in the LKR-M tumor-bearing control mice and in the anti PD-1/PD-L1 treated mice (n=4 per group). A total of 952 differentially expressed genes (DEGs), including 265 upregulated and 688 downregulated, were identified with anti PD-1 treatment (fold-change ≥1.8, FDR ≤0.05). Only 35 genes

were differentially expressed with anti PD-L1 treatment, and we therefore chose to focus on the anti PD-1 treated group alone. Using Ingenuity Pathway Analysis (IPA), we determined that of the DEGs in the PD-1 treatment group, 362 were associated with functions of cell death and survival, with a predicated activation of pathways for apoptosis and necrosis (Z=2.89 and 3.21, respectively) and negative activation of pathways for cell viability and cell survival (Z=-6.22 and -6.45, respectively). When compared to previously published datasets of interleukin-1β and interferon gamma-treated human thyroid cells, the apoptosis pathways were similarly activated. To our knowledge this is the first study to evaluate transcriptomic changes in thyroid tissue following ICI therapy. Our data suggest that there are unique changes in gene expression in the thyroid associated with anti PD-1 therapy. ICI-induced thyroid dysfunction may be mediated by increased tissue apoptosis resulting in destructive thyroiditis.

Presentation: Sunday, June 12, 2022 11:15 a.m. - 11:30 a.m.