ANTITUMOR AND METABOLIC EVALUATION OF IMMUNE CHECKPOINT INHIBITION IN DIET-INDUCED OBESE MICE

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Background Obesity is an epidemic in the Western world and a risk factor for at least 13 types of cancer. Cancer rates are rising for several obesity-related cancers, such as liver, pancreatic, thyroid, and uterine cancer, as well as for colorectal cancer in patients under 55. Preclinical studies for new cancer drugs are often performed in models of cancer that are hosted in mice that are metabolically healthy and of normal weight. To establish models of cancer in hosts that are more reflective of the clinical population we established the tumor growth kinetics of commonly used murine models of cancer in diet induced obese (DIO) mice.

Methods Syngeneic tumor models, MC38, Hepa1–6, implanted in 18-week-old DIO C57BL6 mice showed accelerated tumor growth when compared to the growth rate in age-match control C57BL6 mice. We also studied the growth of three other C57BL/6J syngeneic tumor models MB49, TC-1 and PAN 02. We then tested the response of anti-mPD-1 (αPD-1) against MC38 syngeneic mouse tumor model comparing response to αPD-1 in 18-week-old DIO mice versus age matched control diet (CD) mice.

Results The αPD-1 treatment showed a strong anti-tumor response (TGI=53%) against MC38 in DIO mice compared to a no response rate (TGI=0%) in CD mice. Evaluation of the tumor microenvironment (TME) on Day 13 revealed comparable numbers of CD8+ T Cells in 18-week-old DIO mice tumors compared to CD tumors. Treatment with αPD-1 resulted in a statistically significant increase in CD8+ T Cells in DIO mouse tumors compared to CD tumors (p<0.008). An increase in LAG3+ cells were detected in αPD-1 treated DIO tumors compared to CD (p<0.05). A global metabolomics assessment of serum metabolites showed significant alterations in metabolites between CD and DIO mice. Thirty-six metabolites increased after αPD-1 treatment in DIO mice but were decreased after αPD-1 treatment in CD mice. Amongst these was an alterations in the pentose phosphate pathway particularly with ribose 5-phosphate intermediates.

Conclusions DIO accelerated MC38 tumor growth and showed improved sensitivity to αPD-1 treatment compared to CD in 18 week old mice. The significant increase in LAG3+ cells in the TME of DIO MC38 tumors treated with αPD-1 could represent an opportunity for greater antitumor efficacy. Use of syngeneic tumor models in DIO mice could provide improved models for the identification and development of immunomodulatory test agents, in a more metabolically challenged, clinically relevant system.

Ethics Approval All studies were conducted at TD2.inc performed following the recommendation of the Guide and were reviewed and overseen by the attending veterinarian and IACUC.

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