

SEX-LINKED DIFFERENCES IN OBESITY MARKEDLY IMPACT THE ANTI-TUMOR EFFICACY OF PD-1 BLOCKADE

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Background Immune checkpoint inhibitors (ICIs) particularly those targeting the PD-1/PD-L1 axis have markedly impacted cancer immunotherapy resulting in significant therapeutic responses across an increasingly wide variety of cancers. While obesity is often associated as a negative prognostic indicator in cancer and therapeutic outcomes, it has surprisingly been linked to greater anti-tumor efficacy and survival in multiple cancers following immune checkpoint blockade both in pre-clinical models and clinical outcomes. Clinical data have demonstrated that the increased clinical efficacy was only observed in high body mass index (BMI) males and not females, indicating that sex-linked differences of obesity as it pertains to immunotherapy may exist with regard to the “obesity paradox” in cancer immunotherapy.

Methods We assessed the effects of sex on obesity-associated immune checkpoint therapy responses using a diet induced obese (DIO) mouse model following placement on high fat diet (HFD) versus control diets for a period of several months. Mice then received tumors and the tumor-bearing male and female mice were treated by targeting PD-1/PDL-1 as a monotherapy. We then characterized the immune signature of the different cohorts before and after immunotherapy. To determine if hormonal pathways were indeed involved, we then assessed effects of anti-PD-1 therapy in ovariectomized DIO and lean tumor bearing mice. Stratification of immunotherapy outcomes in high versus low BMI male and female cancer patients was also assessed.

Results Tumor progression was observed greater in both male and female DIO mice compared to control diet recipients. Immunotherapy using anti-PD-1 resulted in significant anti-tumor effects in DIO male mice but not DIO female nor the lean male and female recipients. Ovariectomy of female mice resulted in markedly greater weight gain when placed on HFD as well as accelerated tumor growth but it also resulted in significant efficacy of anti-PD-1 monotherapy comparable to male DIO mice. Stratification of patient outcomes following checkpoint blockade for melanoma on both BMI and sex demonstrated that significant increases in survival and efficacy were only observed in high BMI male patients mirroring the effects observed in the mouse models.

Conclusions These data reveal potential implications in taking sex into account when using obesity as a predictive biomarker for effective use of ICI and provides potential insights on how to potentially improve immunotherapy efficacy by targeting hormonal pathways.

Ethics Approval All animal were housed in AAALAC-accredited animal facilities at University of California Davis and all animal protocols were approved by the University of California Davis Institutional Animal Care and Use Committee (IACUC). All studies maintained compliance with guidelines and regulation from the IACUC.

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