Abstract

Blockade of the PD-1/L1 negative immune checkpoint interaction with therapeutic antibodies leads to unprecedented numbers of long lasting responses in patients with multiple metastatic cancers, thereby rapidly becoming standard of care treatment for patients with metastatic melanoma, carcinomas of the head and neck, lung, kidney and bladder, Merkel cell carcinoma and Hodgkin's disease, among a rapidly growing list.

Primary resistance to PD-1 blockade therapy is most frequently mediated by a lack of intratumoral tumor antigen-specific T cell infiltration {Tumeh, 2014 #6520;Ribas, 2015 #6482}. Furthermore, biopsy of metastatic melanomas lesions taken from patients who did not l respond to PD-1 blockade had a transcriptome that was dominated by mesenchymal, regeneration and stemness gene expression which collectively we termed innate anti-PD-1 resistance signature (IPRES) {Hugo, 2016 #6574}.

In occasional cases we have been able to map a genetic mechanism of primary resistance to PD-1 blockade therapy. A putative pre-existing immunoediting process had led to the cancer cells being genetically unable to respond to interferons through biallelic loss of function mutations in *JAK1* and *JAK2*. These two kinases control signaling downstream of the interferon gamma receptor, which would then prevent PD-L1 upregulation on melanoma cells upon interferon gamma exposure {Shin, 2017 #6661}. Therefore, in these cases it would not be useful to try to block PD-1:PD-L1 interactions with antibody therapy as the cancer cells cannot express PD-L1 due to the *JAK* mutations.

Furthermore, approximately 25-30% of patients with metastatic melanoma who initially had an objective tumor response to therapy, being cases of acquired resistance. Using genetic analyses approaches we described that similar loss of function mutations in the interferon gamma signaling pathway (*JAK1* or *JAK2*) and the antigen presentation pathway (*beta-2 microglobulin – B2M-*) can allow the relapse of acquired resistant lesions {Zaretsky, 2016 #6647}.

We have modeled these mutations in syngeneic mouse cancer systems that have a response to anti-PD-1/L1 therapy. Indeed, CRISPR/Cas9 knock out of *JAK1* or *JAK2* or *B2M* results in complete abrogation of anti-PD-1 responses in the MC38 high mutational load colon carcinoma and in the YUMM2.1 *BRAFV600E* mutated melanoma models syngeneic to C57BL/6 mice.

We hypothesize that modeling these resistance mechanism will allow us to understand their mechanisms and test combination therapies that may prevent or overcome resistance.