THE CX3CL1-CX3CR1 CHEMOKINE AXIS CAN CONTRIBUTE TO TUMOR IMMUNE EVASION AND BLOCKADE WITH A NOVEL CX3CR1 MONOCLONAL ANTIBODY ENHANCES RESPONSES TO ANTI-PD-1 IMMUNOTHERAPY

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Background Immune suppressive myeloid population defined as CX3CR1+CD206+ strongly influence the outcome of the response to anti-PD-1 therapy since tumor-CX3CR1+CD206+ myeloid cells were reduced after response to anti-PD-1 in a T3 sarcoma mouse model. Non-responders to anti-PD-1 in non-small cell lung cancer showed an increase in the plasma concentrations of the CX3CR1 ligand, CX3CL1. Thus, a failure to reduce CX3CR1+ myeloid populations may result in non-response to anti-PD-1 immunotherapy. CX3CR1 binds to its ligand, CX3CL1. The CX3CL1-CX3CR1 axis promotes chemotaxis of CX3CR1+ cells towards soluble CX3CL1 as well as adhesion of CX3CR1+ cells to membrane-bound CX3CL1. CX3CR1 activation induces signaling events and following interaction with CX3CL1, CX3CR1 signaling supports tumorigenesis.

This led us to investigate whether blockade of CX3CL1-CX3CR1 axis using an antibody approach would augment the response to anti-PD-1 therapy and increase the number of responders in preclinical models whilst offering clinical translatability.

Methods We generated a novel monoclonal antibody against mouse CX3CR1 in CX3CR1 knockout mouse. Hybridomas were screened for reactivity with Jurkat and 300 cells transfected to express mouse CX3CR1 and a lack of reactivity with un-transfected Jurkat cells and 300.19 cells. The CX3CR1 antibody showed binding to mouse CX3CR1 with an EC-50 value of 0.09 µg/ml indicating an apparent binding affinity of 0.6 nM. The antibody blocked and antagonized the CX3CL1-CX3CR1 interaction.

Results Our CX3CR1 monoclonal antibody reduces migration of tumor cells and decreases secretion of immune suppressive soluble mediators from the tumor. In combination with anti-PD-1 immunotherapy, this CX3CR1 monoclonal antibody enhances survival in an immunocompetent mouse colon carcinoma model through a decrease in tumor-promoting myeloid populations. We further explore the immune evasion strategies implemented by this axis and find that it initiates a resistance program in cancer cells that results in 1) facilitation of tumor cell migration, 2) secretion of soluble mediators to generate a pro-metastatic niche, 3) secretion of soluble mediators to attract myeloid populations 4) generation of tumor-inflammation. Thus, this axis is involved in the mechanisms of resistance to anti-PD-1 immunotherapy.

Conclusions We observe an improvement in response to anti-PD-1 therapy in an immunocompetent mouse model of colon carcinoma. Mechanistically, combined PD-1 and CX3CR1 blockade reduces the migration of tumor cells, decreases the abundance of immune suppressive myeloid cells in the tumor, increases mature macrophages in the tumor and reduces secretion of soluble mediators from the tumor. In summary, the CX3CR1 antibody can mitigate CX3CL1-CX3CR1 mediated pro-tumorigenic effects of aberrant myelopoiesis during cancer progression.

Ethics Approval Animal experiments were performed as per the IACUC guidelines (protocol 04–047) of the Dana-Farber Cancer Institute.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0808