COMBINATION OF FLT3L AND STING AGONISM SENSITIZES NON-T CELL-INFLAMED TUMORS TO CHECKPOINT BLOCKADE THERAPY

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Background STING agonists have been pursued as a strategy to trigger innate immune activation within the tumor microenvironment, which can lead to adaptive immunity and tumor regression in mice. However, clinically activity of STING agonists has been less impressive. We hypothesized that a low response rate clinically could be because most patients have non-T cell-inflamed (cold) tumors. We hypothesized that non-T cell-inflamed tumors may lack the required CD103⁺ dendritic cell (DC) subset for T cell priming, thus failing to make the bridge to adaptive immunity. To investigate this notion, we turned to a B-catenin-driven genetically engineered mouse melanoma model, which is non-inflamed and known to lack CD103⁺ DCs. We evaluated whether recruitment of CD103⁺ DCs via Flt3L might cooperate with a STING agonist to promote tumor control, alone or in combination with checkpoint blockade antibodies.

Methods We used the BRAF-activated, PTEN-deleted, B-catenin-stabilized (BPC) genetic melanoma model. Our laboratory previously showed that these tumors lack spontaneous CD103⁺ DC and T cell infiltration and have low expression of the chemokines known to recruit these cells, which closely resembles the biology of many non-T cell-inflamed human cancers. To recruit and activate CD103⁺ DCs to these tumors, we injected intratumoral Flt3L alone, the STING agonist DMXAA alone, and both in combination.

Results Intratumoral DMXAA injection led to significant increases in CD8⁺ T cells in BPC tumors five days post injection. However, the CD103⁺ DC numbers in these tumors were not increased. Moreover, T cells recruited following DMXAA treatment were unable to control tumors alone or with anti-PD-L1 + anti-CTLA-4. This led us to adopt an additional strategy aimed at promoting CD103⁺ DC accumulation directly. A single injection of Flt3L was able to drive CD103⁺ DC accumulation in BPC tumors. However, Flt3L alone with a subsequent DMXAA injection had minimal effects on tumor growth. Excitingly, Flt3L and DMXAA injection followed by anti-PD-L1 + anti-CTLA-4 mAB therapy led to significant tumor control.

Conclusions Injection of Flt3L + DMXAA supported intratumoral accumulation of both CD8⁺ T cells and CD103⁺ DCs. This enabled subsequent therapeutic activity of anti-CTLA-4 + anti-PD-L1 mAb therapy in this very challenging cold tumor model. Inasmuch as tumors in this model fail to respond to vaccination, adoptive T cell therapy, and checkpoint blockade strategies, the activity of this regimen is highly significant. Clinical investigation of intratumoral Flt3L + STING agonists should be prioritized for future study in anti-PD-1-refractory patients.

Ethics Approval This study obtained ethics approval by the Institutional Animal Care and Use Committee (IACUC) at the University of Chicago as outlined in the animal protocol #71621. The IBC protocol number is IBC1309(3).