Abstract

Intratumoral injection of STING agonists provokes potent tumor-intrinsic immune responses that lead to tumor regression. However, the mechanism underlying the tumor regression is yet to be fully understood. Two recent studies revealed that tumor cells regulate expression of STING and other members of the pathway, mainly cGAS, by means of epigenetic mechanisms. Here we sought to determine the role of tumor-STING in the context of ADU-S100 (MIW815) treatment, a small molecule derivative of the natural cyclic dinucleotide STING ligand. In mouse models, ADU-S100 (MIW815) treatment increases systemic tumor-specific T cells and results in tumor regression. The tumor-specific T cells and STING expression in both tumor cells and host cells were assessed by flow cytometry, and the results indicated that ADU-S100 (MIW815) treatment of STING-/- animals resulted in similar tumor-specific T cell responses and tumor control as ADU-S100 (MIW815) treatment of STING+/- animals. These findings support the hypothesis that tumor-STING signaling is dispensable for the changes in CD8+ T cell responses in vivo.

Lack of STING in tumor cells impairs the production of cytokines in the context of ADU-S100 in vitro

Figure 1. Intratumoral injection of ADU-S100 (MIW815) increases systemic tumor-specific T cells and results in tumor regression. ADU-S100 (MIW815) was administered intravenously to tumor-bearing mice, and tumor volume was measured. Overall, these results show that ADU-S100 (MIW815) activation of STING in host cells rather than in tumor cells is critical for tumor regression.

Tumor cell intrinsic STING signaling demonstrates minimal contribution to the anti-tumor response elicited by the STING agonist ADU-S100 (MIW815)

Figure 2. STING expression in tumor cells is dispensable for the changes in CD8+ T cell responses in vivo. ADU-S100 (MIW815) was administered intravenously to tumor-bearing mice, and tumor volume was measured. Overall, these results show that ADU-S100 (MIW815) activation of STING in host cells rather than in tumor cells is critical for tumor regression.

Summary

STING-deficient 4T1 and B16.SIY tumor cell lines were generated. Tumors of STING+/- clones failed to generate cytokines or upregulate expression of IFN-β in vitro after stimulation with ADU-S100 (MIW815). Treatment with ADU-S100 (MIW815) caused tumor regression and increased systemic tumor-specific T cells in vivo. In addition, injection of STING-sufficient or deficient tumor cell lines in vivo generated tumors with a comparable composition of innate and specific CD8+ T cells, induced similar systemic anti-tumor CD8 responses and presented similar growth rates. These findings support the hypothesis that tumor-STING signaling is dispensable for the changes in CD8+ T cell responses in vivo.

References


Figure 3. Tumor volume (mm^3) in mice bearing 4T1 STING+/- or 4T1 STING-/- tumors. Injection of ADU-S100 (MIW815) increases systemic tumor-specific T cells and results in tumor regression. ADU-S100 (MIW815) was administered intravenously to tumor-bearing mice, and tumor volume was measured. Overall, these results show that ADU-S100 (MIW815) activation of STING in host cells rather than in tumor cells is critical for tumor regression.

Figure 4. STING expression in tumor cells is dispensable for the changes in CD8+ T cell responses in vivo. ADU-S100 (MIW815) was administered intravenously to tumor-bearing mice, and tumor volume was measured. Overall, these results show that ADU-S100 (MIW815) activation of STING in host cells rather than in tumor cells is critical for tumor regression.

Figure 5. Injection of STING-deficient 4T1 and B16.SIY tumor cell lines failed to generate cytokines or upregulate expression of IFN-β in vitro after stimulation with ADU-S100 (MIW815). Tumor cell intrinsic STING signaling demonstrates minimal contribution to the anti-tumor response elicited by the STING agonist ADU-S100 (MIW815).