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Activation of STING in Response to Partial-Tumor Radiation Exposure

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Abstract
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Abstract

Objective: The potential of radiotherapy (RT) to induce immune recognition of cancer cells is a growing topic of research. It has been suggested that partial volume irradiation used in GRID therapy/Lattice RT, a type of RT in which radiation does not cover the entire tumor intentionally but rather is spatially fractionated, sometimes induces an immune response. We previously showed that a single dose of radiation delivered to half of the tumor (50% RT) activated an anti-tumor immune response comparable to the response in a fully-irradiated tumor in the immunogenic 67NR murine tumor model (breast carcinoma) and in the less immunogenic and more radioresistant Lewis lung carcinoma (LLC) tumor model. We have also demonstrated that this immune response was due to the infiltration of CD8+ T cells along with an increased expression of ICAM adhesion molecules. Treatment with either anti-CD8 or anti-ICAM antibodies abrogated the hemi-RT response. Furthermore, a significant abscopal effect was observed after partial irradiation with a single dose of 10Gy in a bilateral 67NR tumors model. It has been shown that ionizing radiation can mediate antitumor immunity via the activation of the cytosolic DNA sensor cGAS/STING pathway. Therefore, in this study, we tested whether the hemi-irradiation-mediated immune response involves the cGAS/STING canonical pathway, or the non-canonical activation of STING, in the 67NR or LLC tumor models. It has been reported that STING can be activated, independently of cGAS, via non-canonical activation of STING, involving ATM and TRAF6, among other factors.

Methods: We investigated 67NR murine orthotopic breast tumors in Balb/c mice and LLC cells injected in the flank of C57Bl/6, cGAS, or STING KO mice. RT was delivered to 50% or 100% of the tumor volume using a 2X2 cm collimator on a microirradiator allowing precise irradiation. Tumors were collected at different time points post-RT and assessed for different measurements.

Results: There was a significant activation of the cGAS/STING pathway in the hemi-irradiated tumors as compared to control and to 100% exposed 67NR tumors. Interestingly, the increased expression of the cGAS/STING pathway was found in the hemi-irradiated tumor and also in the non-irradiated part of the tumor, indicative of communications between the irradiated and the non-irradiated areas of the partially exposed tumors. Remarkably, it seems that a non-canonical activation of STING was involved in the LLC model. Using both cGAS and STING KO mice, we demonstrated that the partial exposure RT-mediated immune response in the LLC tumor model was dependent on STING activation in the host while cGAS was dispensable, as previously reported for full tumor exposure to RT. The tumor response to partial exposure RT was completely abrogated when the LLC tumors were implanted in the STING KO mice, while there is no effect on tumor response when these tumors were implanted in the cGAS KO mice, demonstrating that STING is crucial for LLC tumor response to partial RT while cGAS is not essential.

Conclusion: These results demonstrate the involvement of STING in the partial exposure RT-mediated by activation of different STING pathways in different tumor models.