SIRP α -DEFICIENT MACROPHAGES ACTIVATE POLYCLONAL TISSUE-RESIDENT CYTOTOXIC CD8 T CELLS TO ELIMINATE IRRADIATION-REFRACTORY NON-SMALL CELL LUNG CARCINOMA

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Background Radiotherapy (RT) is a mainstay treatment for cancer and may not only eliminate irradiated tumors but also induce cytotoxic CD8 T cell immunity to regress abscopal metastases. However, even when combining RT with immunomodulatory agents, adequate immune-mediated tumor elimination is limited, especially when tumors are advanced and highly immunosuppressive. Thus, revealing the mechanisms by which tumors resist RT and resolving methods to enhance RT-induced immunity are needed. SIRP α is a myeloid-expressed receptor that inhibits macrophages from phagocytosing self-cells by interacting with its ligand CD47. Cancers often increase their CD47 to suppress macrophages. Although merely depleting SIRP α -mediated inhibition (SIRP α -deficient) does not elicit phagocytosis, activating SIRP α -deficient macrophages with certain proinflammatory cytokines or TLR agonists enables them to phagocytose cancer cells. Given that macrophages are abundant in solid tumors and often contribute to RT-resistance, we postulated that RT-induced damage in the tumor microenvironment (TME) would stimulate TLRs on SIRP α -deficient macrophages to then phagocytose cancer cells and better control RT-resistant tumors.

Methods Tumors were established by engrafting syngeneic non-small cell lung carcinoma (LLC) into wild-type (WT) or SIRP α -deficient C57BL6 mice. Tumors were allowed to progress to various stages, then mice were treated with tumor-directed RT (4–15Gy). In some cases, RT was combined with intravenous or intratumoral adoptive transfer of macrophages. To compare the therapeutic efficacy of RT plus macrophage transfer, head-to-head studies were conducted using anti-CD47 antibodies or SIRP α -Fc fusion-proteins with cancer-specific antibodies and RT. Flow cytometry, Nanostring RNA sequencing, and several cell function assays were used to analyze responses to treatments.

Results Global knockout of SIRP α in mice sensitizes their otherwise RT-resistant tumors to low-dose RT and achieves up to 100% complete response and 100% overall survival. SIRP α -deficient macrophages are essential to the therapeutic response, as depleting them abrogated efficacy while transferring them recapitulated this efficacy in WT mice. SIRP α -deficient macrophages not only eliminate tumors by phagocytosing cancer cells but more so by conducting in situ antigen presentation to CD8 T cells that are highly cancer-specific and cytotoxic. In addition, RT synergizes with activated SIRP α -deficient macrophages to reprogram the TME into a pro-inflammatory niche infiltrated by cytotoxic NK cells and neutrophils but comprising few CD4 T regulatory cells (Tregs) and myeloid-derived suppressor cells (MDSCs).

Conclusions The results demonstrate that SIRP α predominantly underlies tumor resistance to RT and provide proof-of-principle for SIRP α -deficient macrophage-based therapies to cure lung cancer, including those at advanced stages with poor immunogenicity and metastases.

Acknowledgements The authors thank the Georgia State University Animal Resources Program for assisting many experiments; This work was supported, in part, by grants from National Institutes of Health (CA241271 and AI106839), a Georgia Research Alliance (GRA) Venture Development grant,

a Bioclicity Innovation & Commercialization grant, a Careers in Immunology fellowship from American Association of Immunologist (Z.B.), a Molecular Basis of Disease fellowship from Georgia State University (K.K.) and an Ahmed T. Abdelaal Molecular Genetics and Biotechnology fellowship from Georgia State University (K.K.).

Ethics Approval All experiments using animals and procedures of animal care and handling were carried out following protocols approved by the Institutional Animal Care and Use Committee (IACUC) of Georgia State University.

<http://dx.doi.org/10.1136/jitc-2021-SITC2021.214>