TLR9-ACTIVATED B CELLS DIRECTLY LICENSE ADOPTIVELY TRANSFERRED CD8+ T CELLS WITH POTENT TUMOR IMMUNITY

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Background The use of immunotherapies such as immune checkpoint blockade or adoptive cell therapy has substantially improved outcomes for many patients with advanced malignancies. However, a majority of these patients still do not respond or relapse. Thus, extensive efforts are being made to improve these therapies. We and others have demonstrated that adoptive cell therapy can be improved by the co-administration of TLR agonists intratumorally. TLR agonists have also been administered to patients alongside a number of other immunotherapies, but often induce toxic side effects that may be exacerbated by cell therapy. We hypothesized that TLR agonists could alternatively be used in ex vivo cell culture to propagate a more potent cell therapy product.

Methods To address our question, we used a transgenic mouse model of tumor-infiltrating lymphocyte (TIL) therapy, pmel-1, in which CD8+ T cells express a TCR specific for a melanoma/melanocyte antigen. We activated CD8+ pmel-1 T cells with APCs and the Toll-like receptor 9 agonist, CpG. Cell therapy efficacy was determined against mice bearing established B16F10 melanoma. Mechanisms underlying TLR-improved T cell products were determined using ex vivo cell depletion strategies and blocking antibodies.

Results CpG-expanded pmel-1 T cell products were much more effective against B16F10 melanoma in vivo than traditionally expanded T cells; they conferred more durable antitumor responses and improved survival of mice. CD8+ T cells generated in the presence of CpG also had heightened engraftment and persistence in the mice. We found that CpG did not act directly on T cells in culture, but on B cells, as depletion of B cells alone (not DCs, macrophages, NK cells, or CD4 cells) ablated the effects of CpG. B cells in CpG-treated cultures expressed a unique cytokine profile and upregulated several costimulatory markers on their cell surface, so we next questioned whether CpG improved the B cell/T cell axis via a direct or indirect (soluble) factor. Together, cell supernatant transfer experiments and costimulatory blockade experiments revealed that the direct interaction between B and T cells was required for the CpG-mediated improvement of the T cell product.

Conclusions Our findings reveal a novel role for B cells in the generation of potent CD8+ T cell therapies against an aggressive solid tumor. These findings highlight a unique way B cells can become powerful APCs for generating effective antitumor CD8+ T cells and can be directly translated to improve cell therapy products for patients with advanced malignancies.

Ethics Approval All animal procedures performed at the Medical University of South Carolina or Emory University were approved by each university's Institutional Animal Care & Use Committee, protocol number 0488 or 201900225, respectively.

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