combining the reduced affinity CAR with this exogenous control mechanism, we provide evidence that we can modulate and control CAR-mediated toxicity.

Ethics Approval All animal experiments were conducted in a facility accredited by the Association for Assessment of Laboratory Animal Care (AALAC) under Institutional Animal Care and Use Committee (IACUC) guidelines and appropriate animal research approval.

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DEVELOPMENT OF T CELL-BASED IMMUNOTHERAPIES TO TARGET DORMANT DISSEMINATED BREAST CANCER CELLS

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Background A significant fraction of breast cancer survivors develop metastases years or even decades after initial diagnosis.1–3 Mounting evidence suggests these late recurrences arise from dormant disseminated tumor cells (DTCs).4–6 However, no therapy currently exists for targeting DTCs for the purpose of metastasis prevention. Immunotherapy represents a promising avenue to target dormant DTCs. Yet, a functional relationship between adaptive immunity and dormant DTCs has not been established.

Methods Here, we have utilized a bone marrow organotypic microvascular niche co-culture model and immunocompetent murine models of breast cancer dormancy to study the relationship between the adaptive immune response and dormant DTCs and to develop immunotherapies for the purpose of eliminating dormant DTCs and preventing breast cancer metastasis.

Results Our data suggest that breast cancer cells downregulate MHC class I antigen presentation upon dormancy induction, identifying one mechanism of immune evasion. Strikingly, out-growing metastases re-express MHC I and presumably upregulate antigen presentation. These data suggest that MHC-dependent T cell-based immunotherapies may not effectively kill dormant DTCs, but that MHC-independent chimeric antigen receptor (CAR) T cells may be more applicable. Using the organotypic bone marrow microvascular niche co-culture system, we have shown that CAR T cells kill both proliferating and dormant tumor cells independent of tumor cell localization in the niche and independent of tumor cell cycle status. Further, we have established preclinical immunocompetent murine models of breast cancer dormancy to compare efficacy of engineered T cell receptor (TCR) and CAR T cells in eliminating dormant DTCs. From these models of breast cancer dormancy, we have found that CAR T cells eliminate both overt metastases and DTCs in the lung and bone marrow of mice. In contrast, preliminary data suggest that TCR T cells clear overt metastases but are less effective in clearing dormant disease, lending support that MHC I downregulation during dormancy may impact the efficacy of various T cell-based immunotherapies.

Conclusions Our findings identify CAR T cells as one potential immunotherapy to eradicate dormant disease, while simultaneously identifying both CAR and TCR T cells as effective treatments for the clearance of overt metastases. In sum, our findings lay the groundwork for developing adoptive cell therapies to eliminate dormant disease and prevent death from breast cancer metastasis.

REFERENCES

PRECLINICAL DEVELOPMENT OF A NOVEL iPSC-DERIVED CAR-MICA/B NK CELL IMMUNOTHERAPY TO OVERCOME SOLID TUMOR ESCAPE FROM NKG2D-MEDIATED MECHANISMS OF RECOGNITION AND KILLING

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Background MHC class I related proteins A (MICA) and B (MICB) are induced by cellular stress and transformation, and their expression has been reported for many cancer types. NKG2D, an activating receptor expressed on natural killer (NK) and T cells, targets the membrane-distal domains of MICA/B, activating a potent cytotoxic response. However, advanced cancer cells frequently evade immune cell recognition by proteolytic shedding of the α1 and α2 domains of MICA/B, which can significantly reduce NKG2D function and the cytolytic activity.

Methods Recent publications have shown that therapeutic antibodies targeting the membrane-proximal α3 domain inhibited MICA/B shedding, resulting in a substantial increase in the cell surface density of MICA/B and restoration of immune cell-mediated tumor immunity.1 We have developed a novel chimeric antigen receptor (CAR) targeting the conserved α3 domain of MICA/B (CAR-MICA/B). Additionally, utilizing our proprietary induced pluripotent stem cell (iPSC) product platform, we have developed multiplexed engineered, iPSC-derived CAR-MICA/B NK (iNK) cells for off-the-shelf cancer immunotherapy.

Results A screen of CAR spacer and ScFv orientations in primary T cells delineated MICA-specific in vitro activation and cytotoxicity as well as in vivo tumor control against MICA+ cancer cells. The novel CAR-MICA/B design was used to compare efficacy against NKG2D CAR T cells, an alternative MICA/B targeting strategy. CAR-MICA/B T cells showed superior cytotoxicity against melanoma, breast cancer, renal cell carcinoma, and lung cancer lines in vitro compared to primary NKG2D CAR T cells (p<0.01). Additionally, using an in vivo xenograft metastasis model, CAR-MICA/B T cells eliminated A2058 human melanoma metastases in the majority of the mice treated. In contrast, NKG2D CAR T cells were unable to control tumor growth or metastases. To translate CAR-MICA/B functionality into an off-the-shelf cancer immunotherapy, CAR-MICA/B was introduced into a clonal master engineered
ENGINEERED T CELLS DIRECTED AT TUMORS WITH DEFINED ALLELIC LOSS

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Background Cell therapy, with all its promise as a powerful solid-tumor modality, is still hampered by the fundamental obstacle of cancer therapy: the acute shortage of truly tumor-specific targets. It is well known that an average tumor contains loss of heterozygosity (LOH) at an astonishing frequency: ~20% genome wide. These losses are irreversible and absolutely distinguish the cancer from normal cells. Methods We describe a novel approach to cancer immunotherapy that draws on LOH as a large, so far untapped source of cancer targets. To exploit such allelic losses, we focus on polymorphic loci and target the remaining allelic product of a locus that has LOH. We engineer T cells with a modular signal-integration circuit designed to be activated only by tumor cells that have lost expression of one specific allele on their surface. Results We use the HLA locus which undergoes LOH at a frequency of 13%, and the HLA-A*02 allele specifically, as proof of concept. We present a large body of quantitative in vitro data, along with in vivo data, that support the use of a synthetic signal-integration circuit called Tmod as a cancer therapy. We also describe Tmod’s mechanistic properties, including thorough structure/function analysis of its components. Conclusions LOH is a rich source of new targets, provided a system of sufficient power can be devised to exploit them. Our Tmod signal integration system confers on engineered T cells the capacity to discriminate effectively between normal and tumor cells that contain specific allelic losses. Ethics Approval The animal study was approved by Explora BioLabs’ Ethics Board, protocol number EB17-010-059

REFERENCE

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