CIK cell therapy remodels the immune microenvironment and suppresses cutaneous metastatic breast cancer in preclinical models

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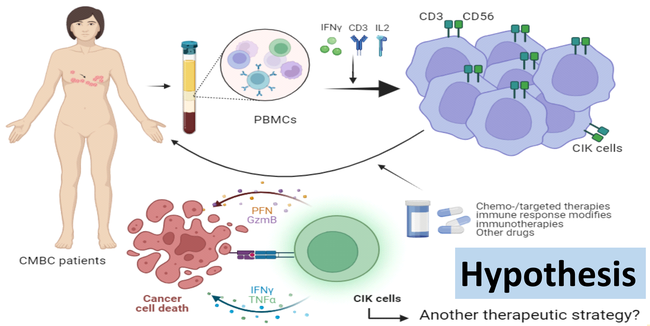
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Purpose

Cutaneous metastases in breast cancer (CMBC) are clinically challenging and associated with poor prognosis and limited therapeutic options. Conventional treatments offer minimal survival benefit and often fail to control skin lesions. Emerging data suggest that immunotherapy, particularly adoptive cell therapy, may offer therapeutic promise. This study evaluates the feasibility and immunologic impact of cytokine-induced killer (CIK) cells in preclinical models of CMBC.

Materials and Methods

We established in vitro and in vivo models using murine breast cancer cells with cutaneous metastatic potential. CIK cells were generated from peripheral blood mononuclear cells of murine splenocytes. Cytotoxicity assays, flow cytometry, and transcriptomic profiling were used to assess anti-tumor effects and immune-related changes. The impact of CIK therapy alone or in combination with a TLR7 agonist was also examined.



Hypothesis

We hypothesize that CIK cell therapy alone, or in combination with chemotherapeutic or immunomodulatory agents, can enhance anti-tumor efficacy in cutaneous metastatic breast cancer (CMBC).

Sequential Clinical Progression of CM in a Breast Cancer Patient



Figure 1. Clinical progression of a breast cancer patient with cutaneous metastasis (CM). (A) The inception of CM (B) CM continued to expand (C) CM continued uncontrollable.

Immunogenomic profiling highlights enhanced immune activation in human CMBC subgroup



Figure 2. Expression of immune-related genes varies across breast cancer tissues, with cutaneous metastasis showing elevated levels of both immune activation and suppression markers.

A novel CMBC-derived 848 cell line exhibits an immune-inflamed phenotype and enhanced sensitivity to CIK cell-mediated cytotoxicity

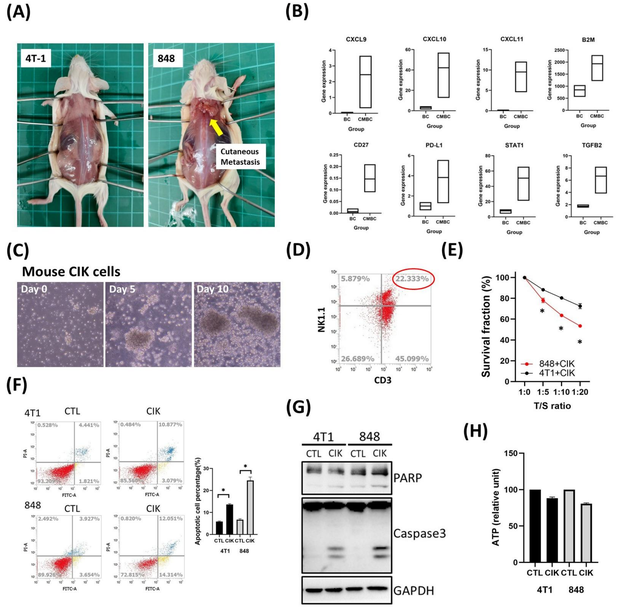


Figure 3. CIK cell therapy suppresses tumor growth and induces apoptosis in CMBC models. (A) Representative images showed CM in 848-bearing mice. (B) Differential immune-related gene expression between 4T1 and 848 tumor tissues. (C–D) Generation and phenotyping of mouse CIK cells.(E) CIK cells exhibited higher cytotoxicity against 848 than 4T1 cells in vitro. (F–G) Flow cytometry and Western blot analyses revealed enhanced apoptosis in CIK-treated groups. (H) ATP assays confirmed reduced cell viability after CIK cell treatment.

Post-surgical CIK cell therapy suppresses cutaneous metastasis in CMBC-like mice and is enhanced by TLR7 stimulation

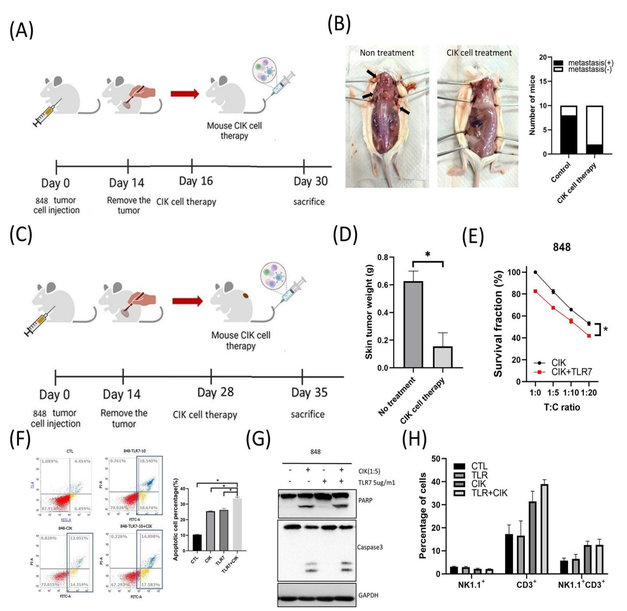


Figure 4. Evaluation of CIK cell therapy in the 848 murine CMBC model. (A–B) Experimental design and representative images showing reduced metastasis after CIK cell therapy. (C–D) Tumor growth and weight were significantly decreased following CIK treatment. (E) In vitro cytotoxicity assay showing enhanced tumor cell killing by CIK + TLR7 agonist. (F–G) Flow cytometry and Western blot analyses revealed increased apoptosis after combined treatment. (H) Flow cytometric analysis of immune cell subsets in CIK-treated mice.

Conclusions

CIK cell therapy demonstrates robust preclinical efficacy against CMBC and effectively reshapes the tumor immune microenvironment. These findings provide a strong rationale for the further development of CIK-based immunotherapy, potentially in combination with innate immune modulators for patients with CMBC.