

ISOLATION AND EXPANSION OF CIRCULATING TUMOR-REACTIVE LYMPHOCYTES FOR ADOPTIVE CELL THERAPY

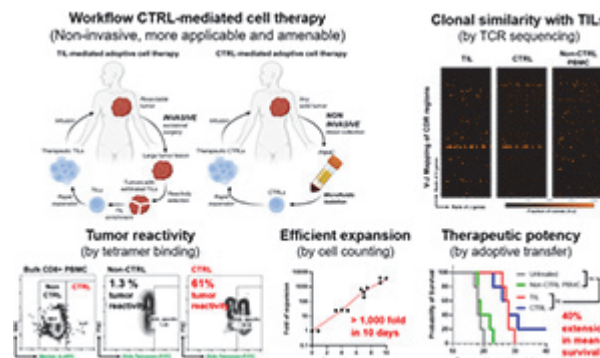
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Background The autologous transplantation of tumor-infiltrating lymphocytes (TILs) expanded from resected tumors has become a promising therapeutic modality in the clinic. The clinical outcome is extremely encouraging so far – long-term complete responses have been observed in subsets of melanoma patients. Despite positive results in the clinic, the use of tumor-infiltrating lymphocytes (TILs) to treat solid tumors is limited by the use of fresh, large, viable tumor fractions from invasive resectable surgery, which is not often feasible in patients with unresectable tumors or recurrent metastases. Recent studies on peripheral T cell dynamics have revealed a string result – a subset of peripheral lymphocytes shares clonotypes with TILs and their expansion is highly correlated with response to treatment. However, these circulating tumor-reactive lymphocytes (CTRLs) are extremely rare in peripheral T cell populations (as low as 0.002%), and their molecular signature and therapeutic potency are yet to be examined.

Methods Conventional cell sorting is infeasible to enrich CTRLs with high purity as they due to their rarity. We developed a novel approach, named microfluidic immunomagnetic cell sorting (MICS), that efficiently isolates CTRLs from blood circulation for molecular assay, rapid expansion and cellular therapy (figure 1).

Results With the high recovery and purity of MICS, we identified that the expression of CD8⁺MarkerA⁺ almost exclusively defines the CTRL population in circulation. This population has a tissue-resident-like (T_{rm}-like) phenotype and can re-enter blood circulation from primary tumors and accumulate in secondary tumors. We successfully expanded the isolated CTRLs through a feeder-based rapid expansion protocol (REP) and found CTRLs have strong therapeutic potency in multiple adoptive cell transfer models in mice. The cocktail of CTRLs and immune checkpoint blockade successfully achieved an 80% complete response (CR) rate in the mouse colon cancer model. In addition, we also confirmed that the human CD8⁺ MarkerA⁺ lymphocytes in blood circulation have higher tumor reactivity, by comparing the level of interferon-gamma (IFN- γ) secretion and clonal similarity.

Conclusions In this work, we adapted our MICS technology for the isolation of CTRLs, a rare tumor-targeting cell population in blood circulation, and deconvolute their molecular signature comprehensively. In addition, we developed the protocols to expand rare CTRLs to a therapeutic scale for the first time. The successful expansion and administration of CTRLs promise to transfer adoptive cell therapy by eliminating invasive surgery and potentially providing a more amenable therapeutic modality that is broadly applicable to all patients.



Abstract 17 Figure 1 Circulating tumor-reactive lymphocytes Figure 1. Circulating tumor-reactive lymphocytes from blood circulation as a mean for cellular therapy. CTRLs cover major TIL clonotypes, are highly tumor-reactive and expandable, and deliver potent anti-tumor efficacy in vivo. Compared to conventional TIL-mediated therapy, CTRL-mediated are non-invasive, more amenable and broadly applicable to all cancer stages

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