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Expansion and characterization of tumor-infiltrating lymphocytes from human sarcoma

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Background

Adoptive Cell Transfer (ACT) using Tumor Infiltrating Lymphocytes (TIL) has previously been shown at our institution and others to be an effective treatment for metastatic melanoma, resulting in a 38% response rate [1]. We applied this therapy to other solid tumors that have demonstrated a positive correlation between immune infiltrates and patient outcome [2]. Specifically in sarcoma, intra-tumoral CD4+ and CD8+ T cells have been detected, but their potential for *ex vivo* expansion is still relatively unexplored [3]. In this study, we investigated the feasibility of expanding TIL from surgically resected sarcoma specimens and analyzed the phenotype of these lymphocytes.

Methods

Four different subtypes of sarcoma were surgically resected from patients accrued under an IRB approved research protocol (MCC50064). A portion of the tumor specimens was digested and immediately phenotyped by flow cytometry. The remaining tumor was minced and plated as fragments for the isolation of TIL, which were expanded *in vitro* for six weeks using high dose IL-2. Eight separate TIL cultures were established and phenotyped by flow cytometry.

Results

Analysis of enzymatically digested human sarcoma specimens showed that 64% of lymphocytic infiltrates were CD3+ cells. TIL were isolated from fragments of each of the four sarcoma specimens as eight individual cultures and propagated *in vitro*, with TIL observed in 59 out of 84 (70%) fragments. Of the expanded CD3+ TIL, on average 39% were CD8+ T cells that expressed both the co-stimulatory molecule 4-1BB (33%) and inhibitory PD-1 (41%) by flow cytometry.

Conclusions

Human sarcoma specimens yield CD3+ CD8+ TIL which can be expanded *in vitro*, supporting further investigation into the feasibility of adoptive cell transfer as a therapy for these patients. Efforts are currently focused on the scalability of this process and the functional capacity of these TIL. Additionally, the expression of 4-1BB and PD-1 on a substantial of CD3+ CD8+ TIL demonstrates the opportunity to modulate these pathways to improve both yield and function, another endeavor we are presently investigating.

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