Background The immunogenic nature of melanoma has been exploited for the development of adoptive transfer of ex-vivo expanded tumor infiltrating lymphocytes (TIL). This adoptive cell transfer therapy has overall response rates of around 50%. Multiple factors may determine the quality of the TIL product including components of the tumor microenvironment. B-cells are frequently found in melanoma metastasis, and display signs of antigen experience. Recently, B-cell tumor infiltration has been associated with improved clinical responses to immune checkpoint inhibitors, but their role in TIL therapy remains unexplored. Considering the potential role of B cells, we aim to develop strategies to enhance the quality of TIL products through B-cell stimulation during ex-vivo TIL expansion.

Methods We stimulated melanoma infiltrating B-cells using human recombinant CD40L on the first day of ex-vivo TIL expansion. Thirteen samples were expanded from melanoma tumor single cell suspensions, in high dose IL-2 alone (standard protocol), or in high dose IL-2 plus CD40L. After up to four weeks of expansion, the TIL phenotype was analyzed by flow cytometry.

Results The expansion success rate from the frozen tumor digests was 69% (95% CI: 38.6–90.9%) in the CD40L treatment condition compared to 23% with the standard protocol. Also, TILs cultured in the presence of CD40L expanded to higher numbers than with the standard protocol (P = 0.02). Interestingly, most of the samples expanded with CD40L had a significant increase in the percentage of CD4+ T cells (P = 0.03), but not to the detriment of the absolute number of CD8+ T cells. Treatment with CD40L increased the percentage of effector memory-like T cells (P = 0.03) and of CD39-CD69- T cells (P < 0.05), which were recently associated with response to TIL therapy.

Conclusions This preliminary work demonstrates that the stimulation with CD40L at the initiation of TIL culture leads to enhanced TIL expansion and an increase in CD4+ T cells with an effector memory-like and stem-like phenotype. Our group and others have previously described cases of patients who had tumor regression after receiving TIL therapy that were predominantly CD4+ T cells, suggesting that expansion of the CD4+ TIL repertoire may enhance TIL therapy.

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