Memory phenotype CD8⁺ T cells are superior to naive CD8⁺ T cells in separating graft anti-tumor activity from GVHD after bone marrow transplantation: Application To DLI

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Abstract

We compared the graft anti-tumor effect and GVHD activities of naturally occurring naive and memory phenotype subsets of C57BL/6 (H-2^b) CD8⁺ T cells after bone marrow transplantation into BALB/c (H-2^d) mice. The tumor used for the study was the BCL_1 lymphoma, a spontaneously arising non-transfected cell line. We found that naive CD8⁺ T cells ($CD62L^{hi}CD44^{lo}$) express higher levels of gut homing molecules $\alpha_4\beta_7$, CCR9 and CD103 compared to memory subsets comprised of both effector ($CD62L^{lo}CD44^{hi}$) and central memory cells ($CD62L^{hi}CD44^{hi}$). The proliferation of the naive cells was ten-fold higher than memory phenotype cells against BALB/c stimulators and memory cells secreted significantly more IFNγ in the MLR. All BALB/c hosts without tumor cells that were given donor memory CD8⁺ T cells along with T cell depleted bone marrow cells (TCD BM) survived over 100 days of transplantation without significant weight loss compared to TCDBM controls. However, 25% of the mice given naive CD8⁺ T cells and TCD BM died due to GVHD and had significantly greater weight loss compared to TCD BM controls or to hosts given memory CD8⁺ T cells and TCD BM. BALB/c hosts given 500 BCL_1 and TCD BM all died of lymphoma within 28 days of transplantation. Hosts given BCL_1 cells, TCD BM and either memory or naive cells cleared the tumor by day 28 but weight loss and survival was significantly improved in the memory versus naive cell groups despite non significant differences in the GVHD scores in the liver and gut at day 100. *Ex vivo* imaging of mice receiving BCL_1 tumor cells, TCD BM, and CD8⁺ T cells from luciferase transgenic donors showed increased accumulation of naive phenotype CD8⁺ T cells in the liver and the gut compared to memory phenotype cells after 6 days of transplantation. We compared the memory and naive CD8⁺ T cells in a model of donor lymphocyte infusion (DLI) in which BALB/c mice with progressive growth of BCL_1 tumor after TCD BM transplantation were given infusion of the CD8⁺ T cells. Both naive and memory cells are effective in clearing the tumor, and converting the hosts from mixed to complete chimeras. Differences in GVHD are observed. In conclusion, CD8⁺ memory phenotype T cells are a desirable subset that mediates potent anti-tumor activity without severe GVHD, and can be used in a DLI model.

Introduction

In a MHC mismatch model of BMT, donor CD8⁺ T cells mediate anti-tumor effect against BCL_1 lymphoma. (Bone Marrow Transplant 2007, 40: 487; Transplantation 1995, 60: 355). However, these cells also induce lethal GVHD.

Unprimed $CD62L^-$ memory T cells were unable to induce GVHD, whereas, BCL_1 tumor primed $CD62L^-$ memory T cells inhibited the lymphoma growth. (Blood 2004, 103:1534).

It is not clear whether unprimed memory phenotype CD8⁺ T cells can mediate Graft versus Lymphoma effect without inducing lethal GVHD.

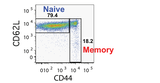
Donor lymphocyte infusions are used to treat lymphoma or leukemia relapse in patients after allogeneic bone marrow transplantation, however, these donor lymphocytes also induce lethal GVHD.

Therefore, we addressed the use of naive and memory phenotype CD8⁺ T cells as donor lymphocyte infusions for potential GVL effect sparing lethal GVHD.

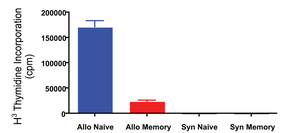
Experiments and Results

Characterization of naive and memory phenotype CD8⁺ T cells

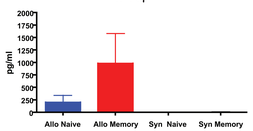
Naive CD8⁺ T cells express high levels of gut homing molecules



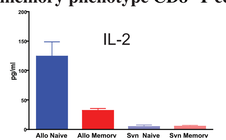
Naive CD8⁺ T cells proliferate more than memory phenotype CD8⁺ T cells in MLR



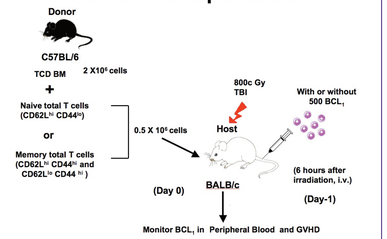
Memory phenotype CD8⁺ T cells produce more IFNγ than naive CD8⁺ T cells



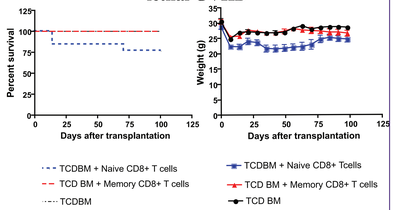
Naive CD8⁺ T cells produce more IL-2 than memory phenotype CD8⁺ T cells



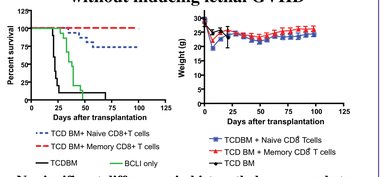
Experimental design for bone marrow transplantation



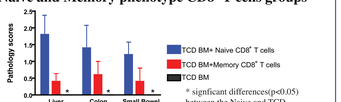
Memory phenotype CD8⁺ T cells do not induce lethal GVHD



Memory phenotype CD8⁺ T cells mediate GVL without inducing lethal GVHD

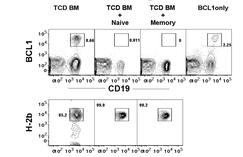


No significant differences in histopathology scores between Naive and Memory phenotype CD8⁺ T cells groups

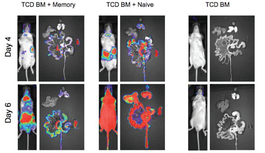


* signficant differences(p<0.05) between the Naive and TCD BM group

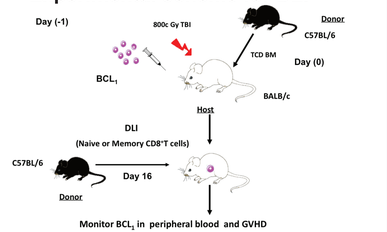
Naive and memory phenotype CD8⁺ T cells equally clear BCL_1 lymphoma



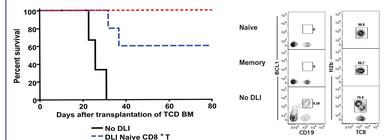
Naive phenotype CD8⁺ T cells accumulate more in the gut than memory phenotype CD8⁺ T cells



Experimental scheme for DLI



Memory phenotype CD8⁺ T cells as DLI clear BCL_1 lymphoma cells without inducing lethal GVHD



Conclusions

Memory phenotype CD8⁺ T cells proliferate significantly lower than naive CD8⁺ T cells in MLR.

They produce higher levels of IFNγ and lower levels of IL-2 than naive CD8 ⁺ T cells cells.

Memory phenotype CD8⁺ T cells do not induce lethal GVHD.

Memory phenotype CD8⁺ T cells mediate Graft versus Lymphoma effect against BCL_1 lymphoma cells.

Memory phenotype CD8⁺ T cells show decreased accumulation in the gut compared to naive CD8⁺ T cells.

As donor lymphocyte infusions, memory phenotype CD8⁺ T cells clear BCL_1 lymphoma without inducing lethal GVHD.

This work was supported by a grant from the **Leukemia and Lymphoma Society.**

There are no relevant conflicts of interest to disclose.