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-2b) CD8+ T cells after bone marrow transplantation into BALB/c (H-2d) mice. The tumor used for the study was the BCL1 lymphoma, a spontaneously arising tumor transplanted into BALB/c mice. We found that naive CD8+ T cells (CD62L+CD44-) expressed higher levels of gut homing molecules α4β7, CCR9 and CD103 compared to memory subsets comprised of both effector (CD62L-CD44+) and central memory cells (CD62L+CD44+). The proliferation of the naive cells was ten-fold higher than memory phenotype cells against BALB/c tumor cells, and memory cells secreted significantly more IFNγ in the MLR.

In a MHC mismatch model of BMT, donor CD8+ T cells mediate anti-tumor effect against BCL1 lymphoma. In MHC identical mice, Transplant 2007, 40: 487; Transplantation 2005, 70: 355. However, these cells also induce lethal GVHD.

Experiments and Results

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

Characterization of naive and memory phenotype CD8+ T cells

Unprimed CD8+ T cells produce more IFNγ than naive CD8+ T cells. Unprimed memory 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 may 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.

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.

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

Memory phenotype CD8+ T cells mediate Graft versus Lymphoma effect against BCL1, 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 BCL1 lymphoma without inducing lethal GVHD.

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