Research Highlight

Making T cells functional: a new solution for the athymic BMT recipients

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Thymus has long been known to be the site of T cell development and is required for the generation of a T cell repertoire^[1]. However, the adult bone marrow transplant (BMT) or the elderly patients suffer from a loss of thymic function resulting in low T cell production, susceptibility to infection and tumour, and a poor survival for a diversity of diseases^[2]. Increasing thymic function and/or extrathymic T-cell development can thus play an important role in patients with limited thymic function. The development and maturation of T cells involve a complex variety of interactions with nonlymphoid cell products and receptors. Generally, T cell progenitors originate in the bone marrow and, through a series of defined and coordinated developmental stages, enter the thymus, differentiate, undergo selection, and eventually mature into functional T cells (Figure 1A). Numbers of studies have indicated that T cells can develop outside the thymus^[3, 4]. However, it is controversial in disparate model systems and unclear if these cells are fully functional. The potential for extrathymic development to restore T cell immunity after BMT is poorly defined.

van den Brink and colleagues used

a mouse model of BMT to determine if extrathymic T cell development could produce functional T cells in euthymic and athymic recipients^[5]. They found that mice with impaired thymic function after BMT produced fully functional T cells, demonstrating that mesenteric lymph nodes (MLNs) can support T cell development and reconstitution in the absence of thymic function (Figure 1B). Although the spleen, peripheral lymph nodes (PLNs), and BM support early lineage-negative or double positive (DP) cell progenitors after BMT^[6], the development of extrathymic T cells were only identified in gut-associated tissues, such as MLNs, Peyer's patches, intraepithelial sites, and lamina propria. By flow cytometry analysis, the MLN DP cells expressing cell-surface markers were at levels equivalent to thymic DP cells. Compared with the young BMT recipients, significantly few thymic DP cells were found in the aged BMT recipients. However, MLNs and Peyer's patches had a capacity to support DP cells to restore the T cell pool in these aged BMT recipients. Importantly, extrathymic T cell development was found to yield a broad repertoire of TCR $\alpha\beta^+$, CD4 $^+$, CD8 $\alpha\beta^+$ and other T cells in euthymic and athymic BMT mice^[5].

Furthermore, adoptive transfer of T cell precursors (preTs) used therapeutically and generated *ex vivo* into the BMT recipients significantly increased the numbers of thymopoiesis and circulating T cell, and protection against bacterial infection^[7]. By using luciferase+preTs

for *in vivo* bioluminescence imaging to analyze the kinetics and sites of preT engraftment after transplant, van den Brink and colleagues found that MLNs supported the development of preT-derived DP cell in the first 3 weeks. And preT-derived T cells in euthymic and athymic BMT recipients were naïve T lineage cells rather than the activated T cells, which might be unable to respond to immune challenges. Moreover, BMT+preT in athymic recipients significantly enhanced splenic CD4 $^+$, CD8 $\alpha\beta^+$, and CD8 $\alpha\alpha^+$ T cells, as well as resulting in a broader pool of T cells than BMT alone in MLNs, Peyer's patches, and PLNs. After *in vivo* infection with the lymphocytic choriomeningitis virus (LCMV), which induces a potent CD8 $^+$ T cell response, nude BMT+preT recipients produced much more CD4 $^+$ T cells and CD8 $^+$ T cells than nude BMT alone controls. As expected, nude recipients of BMT with or without preT had lower viral burden than no BMT, suggesting that extrathymic T cell development after BMT generates fully functional T cells from BM and preT origin.

Interestingly, though MLNs support the extrathymic development of T cells after BMT and patients with limited thymic function could still produce functional T cells, the authors did not detect a significant enhancement of antiviral immunity in nude BMT recipients compared with WT controls. This might be caused by athymic recipients tended to produce less TNF- α and IFN- γ than WT controls. And the number of functional

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Figure 1. Thymic and extrathymic T cell development. (A) The stages of T cell maturation from prethymic (PreT) to the mature single positive (SP) cells. The expression of CD4 and CD8 surface molecules separates the CD4⁺CD8⁺ double positive (DP) and SP cells from the CD4⁺CD8⁻ double negative (DN) cells. The surface expression of CD44 and CD25 characterizes the four major DN cell populations: CD44⁺CD25⁻ (DN1), CD44⁺CD25⁺ (DN2), CD44⁻CD25⁺ (DN3), and CD44⁻CD25⁻ (DN4) cells. PreT arrive at the thymus and develop to the earlythymic progenitor (ETP) cell stage, a subpopulation of the heterogeneous DN1 subset that retains the potential to generate dendritic cells (DCs), natural killer (NK) cells, and macrophages (MΦ). (B) Extrathymic development of aged or nude murine T cells after bone marrow transplantation.

T cells in athymic recipients was lower than that in euthymic recipients after BMT. However, athymic BMT recipients that received anti-*LCMV*-specific preTs had much lower viral burden than nude recipients of WT preTs. Thus, by using genetically engineered preT cells with pathogen or tumour specificity, the aged BMT patients will obtain a broad pool of T cells and function-enhanced T cell populations. The findings by van den Brink and colleagues may become an alternatively therapeutic strategy for the athymic BMT recipients in sometime.

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