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Human Bone Marrow Hosts Polyfunctional Memory CD4+ and CD8+ T Cells with Close Contact to IL-15–Producing Cells

Dietmar Herndler-Brandstetter,* Katja Landgraf,* Brigitte Jenewein,* Alexandar Tzankov,† Regina Brunauer,* Stefan Brunner,* Walther Parson,‡ Frank Kloss,§ Robert Gassner,§ Günter Lepperdinger,* and Beatrix Grubeck-Loebenstein*

Recently, a key role in memory T cell homing and survival has been attributed to the bone marrow (BM) in mice. In the human BM, the repertoire, function, and survival niches of CD4+ and CD8+ T cells have not yet been elucidated. In this study, we demonstrate that CD4+ and CD8+ effector memory T cells accumulate in the human BM and are in a heightened activation state as revealed by CD69 expression. BM-resident memory T cells produce more IFN-γ and are frequently polyfunctional. Immunofluorescence analysis revealed that CD4+ and CD8+ T cells are in the immediate vicinity of IL-15–producing BM cells, suggesting a close interaction between these two cell types and a regulatory role of IL-15 on T cells. Accordingly, IL-15 induced an identical pattern of CD69 expression in peripheral blood CD4+ and CD8+ T cell subsets. Moreover, the IL-15-inducible molecules Bel-xL, MIP-1α, MIP-1β, andCCR5 were upregulated in the human BM. In summary, our results indicate that the human BM microenvironment, in particular IL-15–producing cells, is important for the maintenance of a polyfunctional memory CD4+ and CD8+ T cell pool. The Journal of Immunology, 2011, 186: 6965–6971.

Immunological memory is a key component of the adaptive immune system, providing long-lasting immunity against recurrent infections. In response to viral or bacterial infection, Ag-specific T cells preferentially migrate to nonlymphoid tissues, where they reside as long-lived effector memory cells (1). In mice, it has recently been shown that a major proportion of Ag-specific memory CD4+ T cells relocates to the bone marrow (BM) within 3–8 wk after generation and remains there for a prolonged period of time at a high frequency in distinct survival niches (2). In the mouse, the BM has also been demonstrated to be a preferred site for the proliferative renewal of memory CD8+ T cells, depending on the presence of IL-15 (3, 4). Furthermore, BM-resident naive and memory T cells in the mouse could be efficiently activated by dendritic cells (5, 6). The human BM also contains a variety of Ag-specific memory T cells (7–9). In particular, a higher number of CMV-specific central memory CD8+ T cells and more CD8+ T cells specific for EBV lytic Ags were identified in the human BM compared with the peripheral blood (PB) (7, 8). In osteoarthritis patients, it has been shown that CD8+ effector memory T cells (TEM) with an activated phenotype and an increased cytotoxic potential accumulate in the BM (10). These CD8+ TEM also show a rapid response to recall Ags. In summary, these results indicate that the BM is important for the long-term maintenance of immunological memory and plays a role in systemic T cell-mediated immunity.

Yet, little information is available about the phenotype, function, and repertoire of CD4+ and CD8+ T cells in the BM of healthy individuals. The interaction of T cells with other cells in the human BM, in particular cytokine-producing cells, is also poorly understood. To address these issues, we collected bone biopsies from the iliac crest of healthy individuals. Our results show characteristic differences in the composition of the CD4+ and CD8+ T cell pools in the BM compared with the PB. BM CD4+ and CD8+ TEM are in a heightened activation state, and a high number of polyfunctional memory T cells reside in the human BM. We also show for the first time, to our knowledge, that BM CD4+ and CD8+ T cells are in close contact with IL-15–producing cells, suggesting a role of IL-15 in the survival of memory T cell populations in the human BM.

Materials and Methods

Sample collection and preparation

Paired blood and BM samples were obtained from systemically healthy individuals who did not receive immunomodulatory drugs or suffered from diseases known to influence the immune system, including autoimmune diseases and cancer. Informed written consent was obtained, and the study was approved by the Ethics Committee of Innsbruck Medical University. Bone from the iliac crest was harvested at the Department of Cranio-Maxillofacial and Oral Surgery at Innsbruck Medical University for bone molding/recontouring prior to insertion into other areas of the body, in

*Institute for Biomedical Aging Research, Austrian Academy of Sciences, 6020 Innsbruck, Austria; †Institute of Pathology, University Hospital Basel, CH-4031 Basel, Switzerland; ‡Institute of Legal Medicine, Innsbruck Medical University, 6020 Innsbruck, Austria; and †Department of Cranio-Maxillofacial and Oral Surgery, Innsbruck Medical University, 6020 Innsbruck, Austria

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Abbreviations used in this article: BM, bone marrow; BMMC, bone marrow mono-nuclear cell; PB, peripheral blood; TEM, effector memory T cell; TEMRA, effector memory RA T cell.

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particular facial regions. A biopsy of substantia spongiosa osseum, which would otherwise have been discarded, was used to isolate BM mononuclear cells (BMMC). The bone biopsies were washed once with complete MEM (MEM with Glutamax supplemented with 20% FCS, 100 U/mL penicillin, and 100 μg/mL streptomycin; Invitrogen). Bone biopsies were fragmented and treated with sterile-filtered, chromatographically purified collagenase (CLSPA; Worthington; 20 U/mL in complete MEM) for 1 h at 37°C, 20% O₂, 5% CO₂. Thereafter, collagenase-treated cells were centrifuged, and BMMC were purified by density-gradient centrifugation (Ficoll-Hypaque). Preparation of PBMC was also performed by density-gradient centrifugation.

**Immunohistochemical and immunofluorescent analysis of BM biopsies**

Formalin-fixed, paraffin-embedded 4-μm BM sections were deparaffinized in xylene, followed by hydration in ethanol. For the staining of BM sections with IL-15, slides were blocked with 3% skim milk in TBS/Tween for 20 min at room temperature. IL-15 Ab (3 μg/mL; ab55276; Abcam) was incubated over night at 4°C. After washing, anti-mouse ALP Ab (1:300; Dako) was incubated for 1 h at 4°C. Detection was performed by using BICP/NBT (PLUS) Alkaline Phosphatase (Moss) together with Levamisole (Dako) to block endogenous phosphatases. Thereafter, the slides were boiled in 0.01 M citrate buffer (pH 6) for 16 min in the microwave for epitope retrieval and allowed to cool for about 1 h at room temperature. Then the slides were blocked with 3% milk in TBS/Tween for 20 min. BM slides were incubated overnight at 4°C with a rabbit anti-CD3ε (1:80; RM-9107; Thermo Scientific), mouse anti-CD8 (1:150; M7103; Dako), and a mouse anti-CD20 (1:50; MS-340-S1; Thermo Scientific). Following washing steps with TBS/0.1% Tween, the BM sections were incubated for 1 h at 4°C with a biotinylated swine anti-rabbit Ab (1:300; E0431; Dako) and a goat anti-mouse Alexa Fluor 546 Ab (1:300; A11018; Molecular Probes). Following washing steps with TBS/0.1% Tween, the BM sections were incubated for 30 min at 4°C with a streptavidine-Alexa Fluor 488 Ab (1:500; S11233; Molecular Probes). Stained slides were analyzed using confocal microscopy with a μ-Radiance confocal scanning system (Bio-Rad). The composition of the CD4+ and CD8+ T cell pools in the BM and PB. The numbers indicate the percentage of TN (CD45RA+CCR7+, central memory (CD45RA-CCR7+), and TEMRA (CD45RA+CCR7+), and TEM (CD45RA-CCR7+), and TCM (CD45RA+CCR7+), T EM (CD45RA-CCR7+), and T EM (CD45RA+CCR7+), and TEM (CD45RA-CCR7+), and TEM (CD45RA+CCR7+), and TEM (CD45RA-CCR7+). B. Composition of the human CD4+ T cell pool in paired BM and PB samples. The lines represent mean values. C. The density plots show the proportion of human CD8+ T cell subsets in the BM and PB. The numbers indicate the percentage of naive (TN; CD45RA-CCR7+), central memory (TCM; CD45RA-CCR7+), TEMRA (CD45RA-CCR7+), and TEM (CD45RA-CCR7+). D. Composition of the human CD8+ T cell pool in paired BM and PB samples. The lines represent mean values. Statistical analysis was performed using paired t test. *p < 0.05, **p < 0.01, ***p < 0.001.

**Flow cytometric analysis**

Immunofluorescence surface staining was performed by adding a panel of directly conjugated mAbs to freshly prepared PBMC and BMMC. The Abs used were: CCR5 (PE), CD3 (PE-Cy7 and allophycocyanin-Cy7), CD4 (PerCP), CD45RA (allophycocyanin), CD25 (allophycocyanin), CD69 (FITC and PE), CD122 (PE), CD127 (PE), CD132 (PE), CD137 (4-1BB, PE) (all BD Pharmingen), CD8 (PerCP; BioLegend), and CCR7 (FITC; R&D Systems). The labeled cells were measured by a FACScantio II (BD Biosciences), and data were analyzed using FACSdiva software (BD Biosciences).

**Intracellular cytokine staining**

The production of cytokines by memory CD4+ and CD8+ T cells in the BM and PB was assessed by stimulating the cells for 15 h with 30 ng/ml PMA and 500 ng/ml ionomycin in the presence of 10 μg/ml brefeldin A (all Sigma-Aldrich). Cells were permeabilized using the Cytotox/Cytoperm kit (BD Pharmingen), and intracellular staining of IFN-γ (FITC), TNF-α (PE), IL-2 (PE-Cy7), IL-4 (PE), and MIP-1β (CCL4) (all BD Pharmingen) was performed.

**Isolation of RNA and quantitative RT-PCR**

RNA was isolated from purified PBMC and BMMC using the RNeasy Plus mini kit (Qiagen). First-strand cDNA synthesis was performed using a Reverse Transcription system (Promega). Quantitative RT-PCR experiments were performed using the Lightcycler 480 System (Roche Diagnostics, 2× SYBR Green 1 Master (Roche Diagnostics), and GAPDH and β-actin as housekeeping genes for relative quantification of candidate genes as described previously (11). Sequence-specific oligonucleotide primers were designed using Primer3 software (12) and synthesized by MWG Biotech (Ebersberg, Germany). The primers used were: IL15: 5'-TTTTGGGCTGTTTCAGTGC-3' and 5'-TTACTTTGCAACTGGGGT-3'; β2m: 5'-CAGAAACCCGCGGTGA3' and 5'-TTCTGGATCCTGACATCCCA-3'; Mipa: 5'-AAATTCATGTGAATCTGGC-3' and 5'-TGCTCAGACATGCGGCT-3'; Mipβ: 5'-AAAGCTCTGGGTGACGTCTCC-3' and 5'-ACAGGGTTTGGCCTGG-3'.

**TCR Vβ CDR3 spectratype analysis**

TCR Vβ transcripts of PBMC and BMMC were amplified by PCR using a HotStarTaq Master Mix Kit (Qiagen) and primers (MWG Biotech) specific for each of the human Vβ families and a specific primer for the C region of the β-chain (labeled with fluorescein) as previously described (13, 14). An aliquot of the PCR product was diluted in 20 μl formamide and 1.2 fmol internal lane standard GeneScan-500 LIZ (Applied Biosystems). The samples were denatured at 90°C for 2 min and loaded on
a CE 3100 Genetic Analyzer (Applied Biosystems). Each sample was injected for 5 s at 15 kV and electrophoresed for 24 min at 10 kV using a 36-cm capillary and POP6 (Applied Biosystems). Analysis of the raw data was performed applying the GeneScan 3.7 analysis software package (Applied Biosystems) using the Local Southern method for fragment size estimation. The frequency of polyclonal, oligoclonal, and monoclonal profiles within the 24 Vβ regions from paired BM and PB T cells from five donors was quantified based on deviations from the Gaussian distribution as described previously (14).

**Results**

**CD4**<sup>+</sup> and CD8<sup>+</sup> TEM with an enhanced activation state accumulate in the human BM

We first analyzed the composition of the human CD4<sup>+</sup> and CD8<sup>+</sup> T cell pool in the BM and PB. We used the two surface molecules CD45RA and CCR7 to characterize the different human T cell subpopulations. Within the CD4<sup>+</sup> T cell compartment, the number of CD45RA<sup>+</sup>CCR7<sup>+</sup> naive CD4<sup>+</sup> T cells was decreased, whereas the number of CD45RA<sup>−</sup>CCR7<sup>−</sup> CD4<sup>+</sup> TEM was increased in the BM compared with the PB (Fig. 1A, 1B). Similarly, within the CD8<sup>+</sup> T cell pool, the percentage of naive cells was decreased and the percentage of TEM was increased in the BM compared with the PB (Fig. 1C, 1D). These results indicate that CD4<sup>+</sup> and CD8<sup>+</sup> T cells with an effector memory phenotype accumulate in the human BM.

We further demonstrate that CD4<sup>+</sup> and CD8<sup>+</sup> T cells in the human BM were in a heightened activation state compared with T cells in the PB, as indicated by the expression of the activation molecule CD69 (Fig. 2A, 2D). Analysis of the expression of CD69 on individual T cell subsets in the BM revealed that a high proportion of CD4<sup>+</sup> and CD8<sup>+</sup> TEM expressed CD69, though only a small percentage of central memory CD4<sup>+</sup> and CD8<sup>+</sup> T cells expressed CD69, and its expression was absent in naive T cells (Fig. 2B, 2E). In the PB, CD4<sup>+</sup> and CD8<sup>+</sup> T cell subsets did not contain CD69-expressing cells, with the exception of a few positive cells within the CD8<sup>+</sup> effector memory RA T cell (TEMRA) subset (Fig. 2B, 2E). The IL-2Rα (CD25) was also upregulated on CD8<sup>+</sup> T cells in the BM compared with the PB (Fig. 2F). In addition, the costimulatory molecule 4-1BB (CD137), which is upregulated upon T cell activation (15), was increased in BM-resident CD4<sup>+</sup> and CD8<sup>+</sup> T cells (Fig. 2C, 2F). In summary, our results indicate that CD4<sup>+</sup> and CD8<sup>+</sup> TEM are in a heightened activation state in the human BM.

**BM-resident T cells have a relatively diverse but distinct TCR repertoire**

We next performed TCR Vβ CDR3 spectratype analysis and compared the clonal composition of T cells in the BM and PB. The TCR repertoire of BM T cells was relatively diverse but distinct...
from that of PB T cells (Fig. 3A). The black rectangles highlight some deviations in the clonal architecture between BM and PB T cells. However, by classifying the TCR CDR3 length profiles as monoclonal, oligoclonal, and polyclonal, no significant differences were observed between T cells in the BM and PB (Fig. 3B). In particular, the frequency of monoclonal expansions did not differ between T cells in the BM and PB (p = 0.23), indicating that the accumulation of CD69-expressing T cells in the BM was not due to excessive Ag-driven T cell activation and clonal expansion.

**BM-resident memory CD4+ and CD8+ T cells produce more IFN-γ and are frequently polyfunctional**

To assess the function of BM-resident memory T cells, we stimulated the cells with PMA and ionomycin in the presence of brefeldin A and analyzed the cytokine expression profile of CD4+ and CD8+ T cells in the BM and the PB. Our results demonstrate that a higher number of IFN-γ-producing CD4+ and CD8+ T cells was identified in the BM compared with the PB (Fig. 4A). In contrast, the number of IL-4-producing memory CD4+ and CD8+ T cells was relatively low and did not differ between BM and PB (Fig. 4B). Importantly, the number of memory CD4+ and CD8+ T cells, which produced IFN-γ, TNF-α, and IL-2 simultaneously, was more frequent in the BM compared with the PB (Fig. 4C). Thus, our results suggest that the BM microenvironment increases the frequency of IFN-γ-producing T cells and plays a key role in the maintenance of polyfunctional memory CD4+ and CD8+ T cells.

**BM-resident CD4+ and CD8+ T cells are in close contact with IL-15–producing cells**

The proliferative renewal of memory T cells is essential for maintaining long-term immunity and has been shown to depend on cytokines such as IL-15 (16, 17). Our results show that II15 was upregulated 6-fold in human BMMC compared with PBMC (Fig. 5A), indicating that IL-15 may play an important role within the BM microenvironment. To investigate whether T cells are in contact with IL-15–producing cells in the BM, we performed double staining of CD3 and IL-15 in human BM sections. IL-15 was expressed by a variety of BM cells, and we could show that a proportion of BM-resident T cells was in close vicinity to IL-15 (Fig. 5B). Interestingly, we observed up to three T cells that were in close contact with one IL-15+ cell in the BM (Fig. 5B, left panel). In general, 11.8% of T cells in the BM were in contact with IL-15–producing cells (Fig. 5C). We could also demonstrate that CD3+CD8+ presumably CD4+ T cells (Fig. 5D) and CD8+ T cells were in close contact with IL-15–producing cells in the human BM (Fig. 5E). In contrast, we did not observe B cells that were in contact with IL-15+ cells in the human BM (Supplemental Fig. 1A). In addition, only 1.5% of CD8+ T cells were in contact with B cells (Supplemental Fig. 1B), indicating that the contact between T cells and IL-15+ cells was not a random chance. Taken together, our results suggest a role for IL-15 in the accumulation and/or survival of memory CD4+ and CD8+ T cells in the human BM.

IL-15 mimics the CD69 expression pattern observed in ex vivo-isolated BM-resident CD4+ and CD8+ T cell subsets

As IL-15 is well known to induce T cell activation and proliferation, we wondered which memory T cell subsets were most susceptible to IL-15–mediated stimulation. Our results demonstrate that CD69 expression induced by IL-15 in PB CD4+ T cell subsets was indistinguishable from the CD69 expression pattern in untreated BM-resident CD4+ T cell subsets (Fig. 6A). Similarly,
**FIGURE 6.** The CD69 expression pattern in CD4+ and CD8+ T cell subsets in the BM is mimicked by IL-15 in vitro. A, The bar graph shows the percentage of CD69 expression in untreated CD4+ T cell subsets from the BM (black bars; n = 6) and CD4+ T cell subsets from PB, which were stimulated with IL-15 for 4 d (n = 16). B, The bar graph shows the percentage of CD69 expression in untreated CD8+ T cell subsets from the BM (black bars; n = 8) and CD8+ T cell subsets from PB, which were stimulated with IL-15 for four days (n = 16). Mean values ± SEM are shown. C, The histograms show the expression of the IL-15–signaling chains CD122 and CD132 on CD4+ TEM and TEMRA in the BM (black) and PB (gray). Data are representative of two experiments. D, The histograms show the expression of CD122 and CD132 on CD8+ TEM and TEMRA in the BM (black) and PB (gray). Data are representative of two experiments.

**FIGURE 7.** IL-15–responsive molecules are upregulated in the human BM. To assess the impact of IL-15 in the human BM, we analyzed key molecules that are known to be upregulated by IL-15 (18–20). Our results demonstrate that the antiapoptotic molecule Bclxl and the chemokines Mip1α and Mip1β were upregulated in BMMC compared with PBMC (Fig. 7A). Intracellular cytokine staining revealed that MIP-1β production was much higher in CD4+ and CD8+ T cells derived from BM than from PB (Fig. 7B, 7C). Moreover, CCR5, a ligand for MIP-1α and MIP-1β, was more frequently expressed on BM-resident CD4+ and CD8+ T cells com-
pared with PB T cells (Fig. 7D, 7E), and CCR5+ T cells in the BM coexpressed the activation molecule CD69 (Fig. 7D). As CD8+ T cells are more sensitive to IL-15 (21, 22), and IL-15 has been shown to invert the CD4/CD8 ratio (23), we analyzed the proportion of CD4+ and CD8+ T cells in the human BM. Our results demonstrate that the CD4/CD8 ratio was lower in the BM compared with the PB (Fig. 7E), indicating that a high proportion of CD8+ T cells resides in the human BM. Taken together, the upregulation of IL-15–responsive molecules in the BM suggests an important role for IL-15 in the human BM.

Discussion

Although immunological memory is a critical feature of the adaptive immune system, the mechanisms, in particular the role of niches that support memory T cell survival in the absence of their cognate Ag, remain incompletely understood. It is believed that the number of memory CD4+ and CD8+ T cells is maintained by homeostatic proliferation mediated by cytokines, such as IL-7 and IL-15 (2, 16). In this study, we show that CD4+ and CD8+ TEM accumulate in the BM of healthy individuals and are in a heightened activation state, as demonstrated by high CD69 expression. The relatively diverse TCR repertoire, in particular the absence of large clonal expansions, and the lack of expression of the proliferation marker CD25 (data not shown) suggest that the heightened activation state of T cells is most likely not due to a recent Ag-driven immune response followed by an accumulation of CD69-expressing T cells in the BM. In fact, the proliferative renewal of memory T cells has been shown to depend on IL-15 signals, as IL-15−/− and IL-15Rα−/− mice exhibit a selective loss of memory phenotype CD8+ T cells (24–26). Furthermore, the BM has been identified as the preferred site for IL-15–mediated proliferation of memory T cells (3, 16). Accordingly, immunofluorescence analysis of human BM sections revealed that BM-resident CD4+ and CD8+ T cells are in immediate vicinity of IL-15–producing cells. Although we did not further characterize the nature of IL-15–producing cells in the human BM, morphological analysis suggests that IL-15+ cells may constitute a heterogeneous cell population, including dendritic cells, monocytes, as well as stromal cells. All of these cell types have been shown to express IL-15Rα and trans-present IL-15 on their surface, thereby enhancing and sustaining the biological activity of IL-15 (27–32).

IL-15 is an important mediator of T cell activation and survival, particularly targeting TEM and effector CD8+ T cells (21, 22, 33–36). Concordantly, more CD8+ than CD4+ T cells were activated in the BM (36% versus 15%; p < 0.001). The CD69-expressing T cells in the human BM displayed a TEM and TEMRA phenotype, and these cells highly expressed the IL-15–signaling chains CD122 and CD132. As CD69 inhibits the expression of the sphingosine 1-phosphate receptor type 1 and lymphocyte egress from lymphoid organs (37–39), the high expression of CD69 may be a mechanism to prevent TEM egress from the BM. Whereas 24.3 ± 2.7% of CD3+ T cells in the human BM expressed CD69, 11.8% of CD3+ T cells were in close contact with IL-15–producing cells. As ~2-fold more BM T cells express CD69 than are in contact with IL-15+ cells, this may indicate that the interaction between T cells and IL-15+ cells is transient and TEM compete for interaction with IL-15+ cells in the human BM.

In addition to CD69, an increased frequency of CD25-expressing CD8+ T cells was observed in the BM compared with the PB. In contrast, the percentage of CD4+ T cells that expressed CD25 was similar between the BM and PB and may most likely not reflect activation but rather identify CD25hi regulatory T cells. Taken together, our results suggest that CD4+ and CD8+ TEM are maintained in the BM in survival niches defined by IL-15–producing cells, which induce and/or maintain CD69 expression in TEM and thereby mediate their retention in the BM.

In addition to our results showing that T cells are in close contact with IL-15–producing cells in the BM, there is appealing evidence that IL-15 plays a central role in the BM. First, a characteristic feature of the BM is a decreased CD4/CD8 ratio, with 2.3 in the PB and 1.3 in the BM. As the administration of IL-15 has been shown to rapidly invert the CD4/CD8 T cell ratio throughout the body in rhesus macaques (23), IL-15 may thus explain the accumulation of CD8+ T cells in the human BM.

Second, IL-15–sensitive molecules, such as Bcl-xL, MIP-1α, MIP-1β, CCR5, and 4-1BB, were upregulated in the human BM (15, 18–20). Importantly, IL-15 not only mediates T cell activation but also contributes to the long-term survival of memory T cells, in particular by upregulating the antiapoptotic molecule Bcl-xL (18, 40). Accordingly, a high expression of Bcl-xL correlates with T cell fitness defined by enhanced survival and cytokine responsiveness (41). IL-15 has also been shown to upregulate chemokines, such as MIP-1α and MIP-1β, as well as their corresponding ligand CCR5 (21, 42). The increased expression of MIP-1α and MIP-1β in the human BM may therefore explain the accumulation of CCR5-expressing CD4+ and CD8+ T cells and highlight an additional mechanism of memory T cell recruitment to the BM. Additionally, CCR5 surface levels have been positively correlated with IL-2 production (43), which, together with the increased expression of IFN-γ in BM memory T cells, may explain the high number of polyfunctional (IFN-γ/IL-2/TNF-α+) memory CD4+ and CD8+ T cells in the human BM. A high percentage of IFN-γ–producing CD4+ TEM was also identified in the BM of mice (2) and may be triggered by the BM microenvironment, in particular IL-15 (44, 45). Polyfunctional T cells have been shown to be functionally superior to single cytokine-producing T cells and are good correlates of protective antiviral immunity (46–48). As the TCR repertoire in the human BM is relatively diverse, a broad variety of Ags can be recognized by BM memory T cells (7–9).

Another molecule that is upregulated by IL-15–mediated signaling is 4-1BB (CD137), a member of the TNFR family (15). 4-1BB is important for recall responses, and fewer memory CD8+ T cells have been recovered from the BM of 4-1BBL–deficient mice (49, 50). The increased expression of 4-1BB on BM T cells may therefore reflect recent encounter of IL-15 and 4-1BB/4-1BBL interactions may contribute to the survival of memory T cells in the BM (51).

Taken together, our results indicate that a diverse repertoire of polyfunctional memory CD4+ and CD8+ T cells resides in the human BM and is maintained by close contact with IL-15–producing cells. BM-resident memory T cells may thus represent an important line of defense to assure a rapid immune response against recurrent infections and may be useful for the rapid generation of T cells with enhanced functionality for adoptive immunotherapy.

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Disclosures

The authors have no financial conflicts of interest.