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Post-thymic regulation of CD5 levels in human memory T cells is inversely associated with the strength of responsiveness to interleukin-15

Dietmar Herndler-Brandstetter [a,*], Stefan Brunner [a], Daniela Weiskopf [a], Ruth van Rijn [a], Katja Landgraf [a], Christian Dejaco [b], Christina Duftner [c], Michael Schirmer [d], Frank Kloss [e], Robert Gassner [e], Günter Lepperdinger [a], Beatrix Grubeck-Loebenstein [a]

[a] Institute for Biomedical Aging Research, Austrian Academy of Sciences, Innsbruck, Austria
[b] Department of Rheumatology, Medical University Graz, Graz, Austria
[c] Department of Internal Medicine, Kufstein Hospital, Kufstein, Austria
[d] Department of Internal Medicine, Medical University Innsbruck, Innsbruck, Austria
[e] Department of Cranio-Maxillofacial and Oral Surgery, Medical University Innsbruck, Innsbruck, Austria

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ABSTRACT

Immunologic memory is a critical feature of the adaptive immune system to fight recurrent infections. However, the mechanisms that shape the composition and function of the human memory T-cell pool remain incompletely understood. We here demonstrate that post-thymic human T-cell differentiation was associated with the downregulation, but not loss, of the inhibitory molecule CD5. The sensitivity of human $CD8^+$ and $CD4^+$ memory T cells to interleukin (IL)–15 was inversely associated with the level of CD5 expression. CD5 expression was downregulated by IL-15–mediated signaling *in vitro* and $CD5^{lo}$ memory T cells accumulated in the bone marrow. Persistent antigenic stimulation, as in the case of cytomegalovirus infection and rheumatoid arthritis (RA), was also associated with an increased number of $CD5^{lo}$ memory T cells. In conclusion, CD5 may be a useful marker to identify memory T-cell subsets with distinct responsiveness to the homeostatic cytokine IL-15.

1. Introduction

The ability to develop and maintain highly functional memory T cells after infection or immunization is a hallmark of the adaptive immune response. However, the human memory T-cell pool is heterogeneous, and comprises distinct populations that can be distinguished based on homing markers and effector functions [1]. Cytokines have been shown to be essential for the long-term maintenance of functional $CD8^+$ and $CD4^+$ memory T cells [2,3]. Yet, cytokine-induced signaling can modulate phenotypic and functional characteristics of memory T cells [4–7]. In addition, chronic viral infections and autoimmune diseases have been shown to induce distinct phenotypic and functional changes within the memory T-cell pool [8,9]. Thus, antigens and cytokines dynamically shape the memory T-cell pool throughout life [10].

So far, the role of the transmembrane glycoprotein CD5 in the process of memory T-cell differentiation and maintenance has not been addressed. CD5 surface expression is tightly regulated during T-cell development, with low levels expressed on immature, double negative $CD4^-CD8^-$ thymocytes, followed by an approximately sixfold increase in CD5 at the double positive $CD4^+CD8^+$ stage and a further three- to fivefold increase in CD5 expression on mature, single positive $CD4^+$ and $CD8^+$ thymocytes [11]. All mature T lymphocytes and a subset of B cells, B-1a cells, express CD5 [11,12]. Data from $CD5^{-/-}$ mice indicate that CD5 acts as a negative regulator of cellular activation by being recruited into lipid rafts and dephosphorylating signaling molecules [13–16]. Recently, it has been demonstrated in mice that the level of CD5 on naive T cells does not correlate only with the strength of TCR-mediated signaling but also with the strength of responsiveness to cytokines, such as interleukin (IL)–15 [17]. Furthermore, the level of the inhibitory molecule CD5 on naive T cells could be downregulated by cytokines, such as IL-7 and IL-21, which rendered the cytokine-primed naive T cells more responsive to antigenic stimulation [18].

In this study we demonstrate that the expression of the inhibitory molecule CD5 is decreased during human memory T-cell differentiation and is associated with the strength of responsiveness to IL-15. In addition, we show which environmental cues may be involved in regulating CD5 expression on post-thymic human memory T cells.

2. Subjects and methods

2.1. Peripheral blood and bone marrow samples

Peripheral blood samples were obtained from healthy volunteers. All participants had given their informed written consent, and the study was approved by the Ethics Committee of the Medical

* Corresponding author.
E-mail address: dietmar.herndler-brandstetter@oeaw.ac.at (D. Herndler-Brandstetter).

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University Innsbruck. Cytomegalovirus (CMV) seropositivity was determined by enzyme-linked immunosorbent assay (ELISA) using ENZYGNOST (Dade Behring, Vienna, Austria). Peripheral blood mononuclear cells (PBMC) were isolated by Ficoll-Hypaque density gradient centrifugation (Amersham Biosciences).

Paired blood and bone marrow (BM) samples were obtained from individuals who had given informed written consent and the study was approved by the Ethics Committee of the Medical University Innsbruck. Bone from the iliac crest, which otherwise would have been discarded based on necessary bone molding/recontouring before insertion into other areas of the body, in particular facial regions was harvested at the Department of Cranio-Maxillofacial and Oral Surgery at the Medical University, Innsbruck. Exclusively bone biopsies from systemically healthy individuals who did not receive immunomodulatory drugs or who had diseases known to influence the immune system, including autoimmune diseases and cancer, were used. The bone biopsy samples were washed with complete MEM (Invitrogen, Lofer, Austria), fragmented, and treated with highly purified collagenase (Worthington, Lakewood, NJ; 20 U/ml) for 1 h at 37°C. Thereafter, collagenase-treated cells were centrifuged and BM mononuclear cells (BMMC) were purified by density gradient centrifugation (Ficoll-Hypaque; Amersham Biosciences, Vienna, Austria).

Peripheral blood samples were obtained from 10 individuals who fulfilled the American College of Rheumatology (ACR) classification criteria for RA [19]. Median disease duration was 18 years (range 5–25 years), and 80% of the patients were positive for rheumatoid factor. The RA patients had moderate clinical disease activity (median disease activity score (DAS)-28 4.3; range 1.7–6.6) and were treated with methotrexate ($n = 5$), other conventional disease-modifying antirheumatic drugs (DMARDs) ($n = 3$), or tumor necrosis factor (TNF)–α blocking agents ($n = 2$). The study was approved by the Ethics Committee of the Medical University Graz.

2.2. Flow cytometry and cell culture experiments

Immunofluorescence surface staining was performed by adding a panel of directly conjugated mAbs to freshly prepared PBMC and BMMC. The antibodies used were CD3 (PE-Cy7 and APC-Cy7), CD4 (PerCP), CD5 (PE and APC), CD28 (APC), CD45RA (APC), CD62L (APC-Cy7), CD69 (PE), CD122 (PE), CD132 (PE), and TCR$\alpha\beta$ (PE) (all BD Pharmingen, San Diego, CA), CD8 (PerCP) (BioLegend, San Diego, CA), and CCR7 (FITC) (R&D Systems, Minneapolis, MN). The labeled cells were measured by a FACSCanto II (BD Biosciences, San Diego, CA), and the data were analyzed using FACSDiva software (BD Biosciences, San Diego, CA).

Cell culture experiments were performed with RPMI 1640 (Invitrogen, Lofer, Austria) supplemented with 10% FCS (Sigma-Aldrich, Vienna, Austria) and 1% kanamycin sulfate (Invitrogen, Lofer, Austria). To analyze the responsiveness of memory T-cell subsets to IL-15, peripheral blood T cells were stimulated with IL-15 (50 ng/ml; Sigma-Aldrich, Vienna, Austria) for 4 days and CD69 was measured on $CD8^+$ and $CD4^+$ memory T-cell subsets. The gating of memory T cells was performed by excluding $CCR7^+CD45RA^+$ naive T cells. Low expression of CD5 was defined by gating on the lower third of CD5-expressing T cells and the gating was confirmed by additional CD45RA and CD28 staining. Thus, $CD5^{lo}$ T cells had a $CD45RA^{+/-}CD28^-$ phenotype. To determine the regulation of CD5 expression, peripheral blood $CD8^+$ and $CD4^+$ T cells were labeled with the fluorescent dye carboxyfluorescein diacetate succinimidyl ester (CFSE) as described previously [20] and stimulated with IL-15, 50 ng/ml for 7 days in the presence of irradiated autologous PBMC.

2.3. Statistical analysis

Differences between groups were evaluated using two-tailed Student's t test. A value of $p < 0.05$ was considered statistically significant.

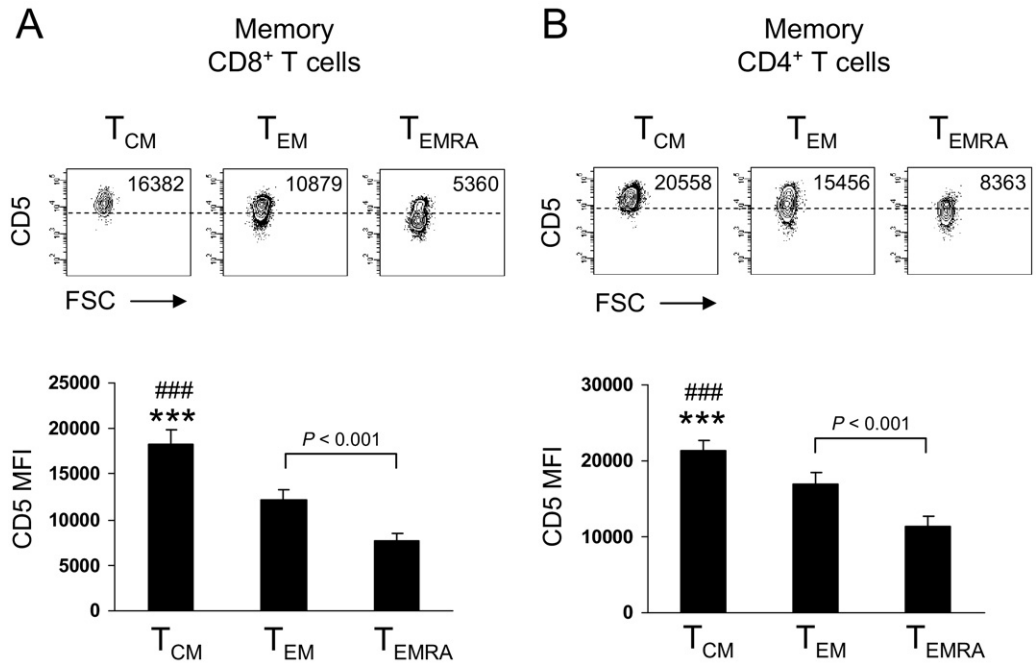

Fig. 1. CD5 is downregulated during peripheral human $CD8^+$ and $CD4^+$ memory T-cell differentiation. (A) Density plots show expression of CD5 on human $CD8^+$ memory T-cell subsets. Memory subsets were classified as central-memory (T_{CM}; $CD45RA^-CCR7^+$), effector-memory (T_{EM}; $CD45RA^-CCR7^-$), and effector-memory $CD45RA^+$ (T_{EMRA}; $CD45RA^+CCR7^-$). Numbers indicate CD5 mean fluorescence intensity (MFI). Data are representative of 12 experiments. Bar graph shows CD5 MFI on human $CD8^+$ memory T-cell subsets ($n = 12$). Statistical analysis was performed using Student's t test. $^{***}p < 0.001$, T_{CM} vs T_{EM} and $^{###}p < 0.001$ T_{CM} vs T_{EMRA}. (B) Density plots show the expression of CD5 on human $CD4^+$ memory T-cell subsets. Memory subsets were classified as described above. Numbers indicate CD5 MFI. Data are representative of eight experiments. Bar graph shows CD5 MFI on human $CD4^+$ memory T-cell subsets ($n = 8$). Statistical analysis was performed using Student's t test. $^{***}p < 0.001$, T_{CM} vs T_{EM} and $^{###}p < 0.001$ T_{CM} vs T_{EMRA}.

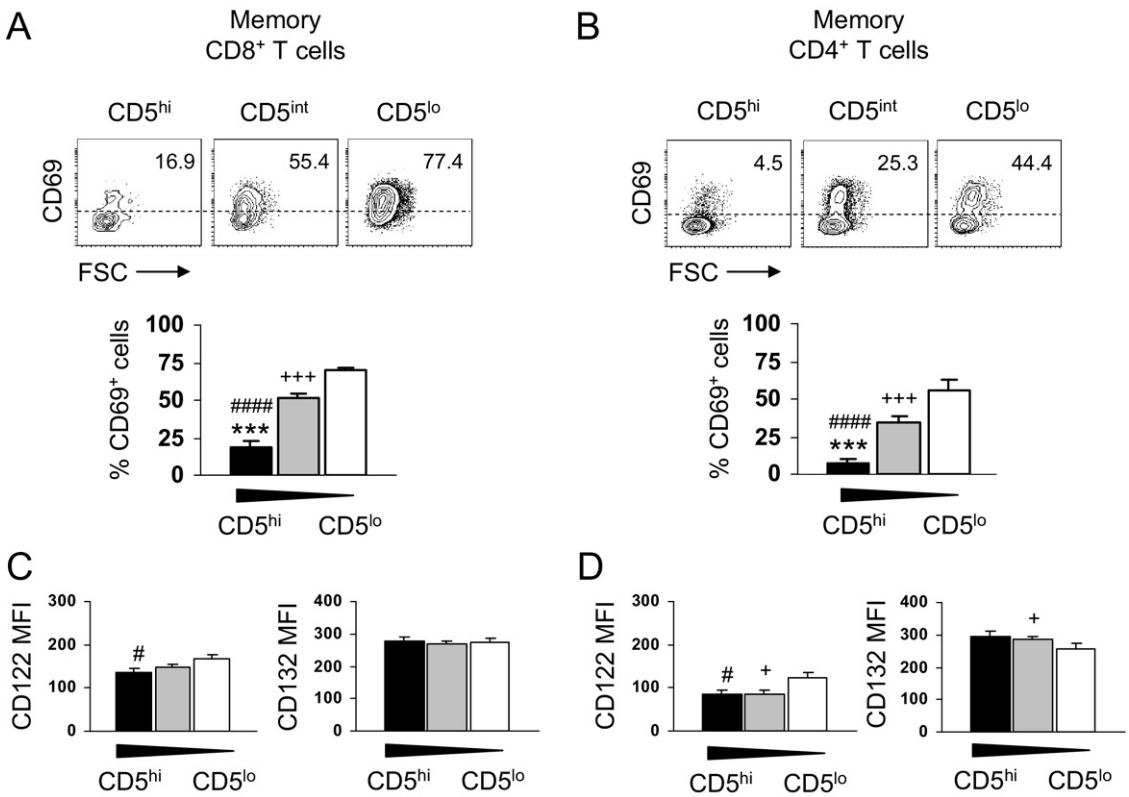

Fig. 2. Responsiveness of human CD8$^+$ and CD4$^+$ memory T-cell subsets with distinct CD5 levels to IL-15. (A) Representative density plots that show the expression of the activation molecule CD69 upon IL-15–mediated stimulation of CD8$^+$ memory T cells with distinct CD5 level. Bar graph shows percentage of CD69-expressing CD8$^+$ memory T cells with high (filled bars), intermediate (gray bars), and low (open bars) expression of CD5 after stimulation with IL-15, 50 ng/ml for 4 days. Statistical analysis was performed using paired Student's *t* test ($n = 11$). (B) Representative density plots that show the expression of CD69 upon IL-15–mediated stimulation of CD4$^+$ memory T cells with distinct CD5 level. Bar graph shows percentage of CD69-expressing CD4$^+$ memory T cells with high (CCR7$^+$CD45RA$^-$; filled bars), intermediate (CCR7$^-$CD45RA$^-$; gray bars), and low (CCR7$^-$CD45RA$^+$; open bars) expression of CD5 after stimulation with IL-15, 50 ng/ml for 4 days. Statistical analysis was performed using paired Student's *t* test ($n = 11$). $^{***}p < 0.001$, CD5^{hi} vs CD5^{int}; $^{\#\#\#}p < 0.001$, CD5^{hi} vs CD5^{lo} and $+++p < 0.001$, CD5^{int} vs CD5^{lo}. (C) Flow-cytometric analysis of CD122 MFI and CD132 MFI in CD8$^+$ memory T cells with high (filled bars), intermediate (gray bars), and low (open bars) expression of CD5 ($n = 8$). (D) Flow-cytometric analysis of CD122 MFI and CD132 MFI in CD4$^+$ memory T cells with high (filled bars), intermediate (gray bars) and low (open bars) expression of CD5 ($n = 8$). Statistical analysis was performed using Student's *t* test. $^*p < 0.05$, CD5^{hi} vs CD5^{int}; $^{\#}p < 0.05$, CD5^{hi} vs CD5^{lo} and $+p < 0.05$, CD5^{int} vs CD5^{lo}.

3. Results and discussion

3.1. CD5 is downregulated during post-thymic CD8$^+$ and CD4$^+$ memory T-cell differentiation in human beings

By using flow-cytometric analysis, we could demonstrate that CD5 was highly expressed on central-memory CD8$^+$ T cells, whereas its expression was downregulated in CD45RA$^-$CCR7$^-$ and CD45RA$^+$CCR7$^-$ effector-memory CD8$^+$ T cells (Fig. 1A). Similarly, when using CD45RA and CD28 to characterize memory T-cell subsets, CD45RA$^+$CD28$^-$ effector-memory T cells displayed the lowest level of CD5 expression (Figs. S1A and S1B). However, the expression of CD3 and TCR$\alpha\beta$ were not downregulated during CD8$^+$ memory T-cell differentiation (Fig. S1A). In CD4$^+$ T cells, the expression of CD5 was also downregulated during post-thymic memory T-cell differentiation (Fig. 1B and Figs. S1C and S1D), whereas the expression of CD3 and TCR$\alpha\beta$ was not (Fig. S1C). These results indicate that the expression of CD5 is not only regulated during thymic development [11], but highlight a role for CD5 during post-thymic CD8$^+$ and CD4$^+$ memory T-cell differentiation in human beings.

3.2. Expression level of CD5 on human CD8$^+$ and CD4$^+$ memory T cells is inversely associated with the strength of responsiveness to IL-15

CD5 has been shown to act as a negative regulator of cellular activation by dephosphorylating signaling molecules [13,15,16] and to modulate cytokine responsiveness of naive CD8$^+$ T cells [17]. We thus analyzed whether memory T cells with distinct CD5 levels differ in their responsiveness to IL-15, which is known to be an important cytokine for memory T-cell survival and proliferative renewal [2,21]. Although memory T-cell subsets did not express CD69 in the absence of IL-15 (data not shown), IL-15 led to the upregulation of the activation molecule CD69 on CD8$^+$ and CD4$^+$ memory T cells and was inversely associated with the level of CD5 (Figs. 2A, 2B). One explanation for the hyper-responsiveness of CD5^{lo} CD8$^+$ and CD4$^+$ memory T cells to IL-15 could be that these cells have a higher number of cytokine receptors. However, this is unlikely, because there were no marked differences in the expression of the signaling chains CD122 (IL-2Rβ) and CD132 (γ_c) between memory T cells with different levels of CD5 (Figs. 2C, 2D). Interestingly, a high expression of monosialotetrahexosylganglioside (GM) 1–containing lipid rafts was associated with a high responsiveness to IL-2 and IL-15 in naive CD8$^+$ T cells and was directly correlated with the expression of CD5 [17]. Accordingly, a recent study in human subjects demonstrated that central-memory CD4 T cells expressed a high membrane lipid order (GM1^{lo}), whereas effector-memory CD4 T cells expressed an intermediate membrane lipid order (GM1^{int}) [22]. This indicates that the GM1 content directly correlates with the responsiveness to IL-15 in memory T-cell subsets but inversely correlates with the level of CD5.

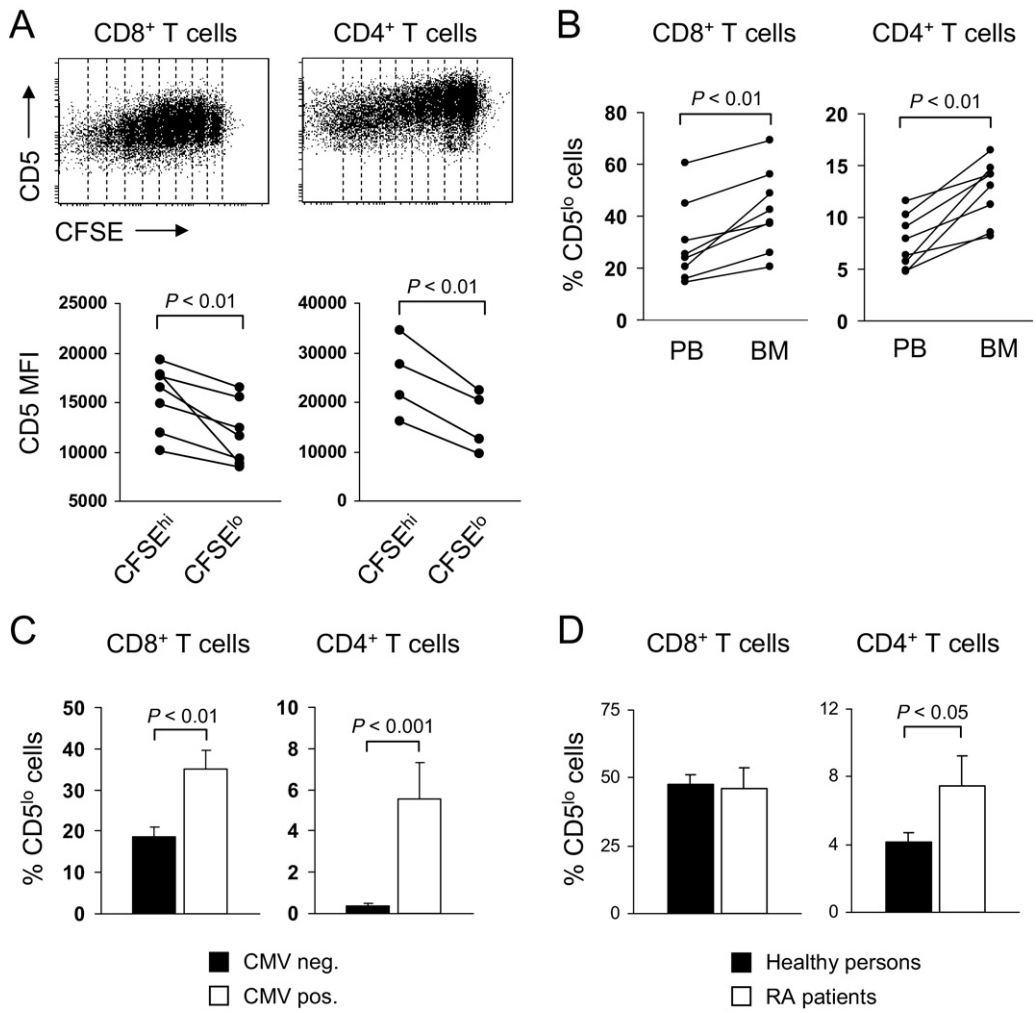

Fig. 3. Impact of environmental cues, persistent CMV infection, and RA on the frequency of $CD5^{lo}$ T cells. (A) Regulation of CD5 surface expression by IL-15–mediated proliferation in $CD8^+$ and $CD4^+$ T cells. Histograms show expression of CD5 in CFSE-labeled $CD8^+$ and $CD4^+$ T cells stimulated with IL-15, 50 ng/ml for 7 days in the presence of irradiated PBMC. One representative experiment is shown. Graphs show CD5 MFI in $CFSE^{hi}$ (not divided) and $CFSE^{lo}$ $CD8^+$ and $CD4^+$ T cells (four or more cell divisions) stimulated with IL-15 for 7 days. Statistical analysis was performed using paired Student's *t* test. (B) Graphs show percentage of $CD5^{lo}$ cells within the $CD8^+$ and $CD4^+$ T-cell pool in PB and bone marrow (BM) of healthy individuals (definition and phenotype of $CD5^{lo}$ T cells is explained in *Subjects and methods* section). (C) Left bar graph shows percentage of $CD5^{lo}$ cells within the $CD8^+$ T-cell pool in CMV seronegative persons ($n = 26$; mean age ± SEM: 41 ± 4 years) and seropositive persons ($n = 15$; 41 ± 5 years). Right bar graph shows percentage of $CD5^{lo}$ cells within the $CD4^+$ T-cell pool in CMV seronegative persons ($n = 23$; mean age ± SEM: 38 ± 4 years) and seropositive persons ($n = 13$; 41 ± 5 years). (D) Left bar graph shows percentage of $CD5^{lo}$ cells within the $CD8^+$ T-cell pool in healthy persons ($n = 38$; mean age ± SEM: 72 ± 1 years) and RA patients ($n = 10$; 71 ± 3 years). Right bar graph shows percentage of $CD5^{lo}$ cells within the $CD4^+$ T-cell pool in healthy persons ($n = 28$; mean age ± SEM: 71 ± 1 years) and RA patients ($n = 10$; 71 ± 3 years). Healthy persons and RA patients were all CMV seropositive. Statistical analysis was performed using Student's *t* test.

3.3. CD5 is downregulated by IL-15–mediated signaling and $CD5^{lo}$ memory T cells accumulate in the human BM

We next analyzed which factors may contribute to the downregulation of CD5 on human T cells. We therefore stimulated purified, CFSE-labeled $CD8^+$ and $CD4^+$ T cells with IL-15 for 7 days. Although $CD8^+$ and $CD4^+$ T cells did not proliferate in the absence of IL-15 (data not shown), CD5 was progressively downregulated in proliferating $CD8^+$ and $CD4^+$ T cells stimulated with IL-15 (Fig. 3A). Comparison of CD5 levels between $CD8^+$ T cells that have not proliferated ($CFSE^{hi}$) and cells that have undergone four or more cell divisions ($CFSE^{lo}$) demonstrated that IL-15–mediated signaling decreased the CD5 mean fluorescence intensity (MFI) by 21% (Fig. 3A). Similarly, CD5 was downregulated in proliferating $CD4^+$ T cells stimulated with IL-15 and IL-15–mediated signaling decreased the CD5 MFI by 36% (Fig. 3A). The BM has been shown to be a preferred site for IL-15–mediated proliferation of memory T cells [23] and a higher expression of IL-15 was identified in BMMC compared with PBMC [24]. (Moreover, $CD4^+$ and $CD8^+$ T cells were in close contact with IL-15–producing cells in the human BM [24]. We therefore determined the expression of CD5 on memory T cells in the human BM. Our results demonstrate that a higher number of $CD5^{lo}$ $CD8^+$ and $CD4^+$ memory T cells accumulated in the human BM compared with peripheral blood (Fig. 3B). Thus, our results highlight a so far unappreciated role for IL-15–mediated signaling in modulating the expression of the inhibitory molecule CD5, which is associated with the strength of responsiveness to IL-15. Intriguingly, as memory T-cell homeostasis is critically dependent on IL-15–dependent signaling [2], increased sensitivity of $CD5^{lo}$ memory T cells to IL-15 may explain the selective survival and/or expansion of $CD5^{lo}$ memory T cells in the human BM.

3.4. Persistent CMV infection and RA drive the accumulation of $CD5^{lo}$ memory T cells

We next examined whether persistent infection with CMV, which is known to drive the accumulation of highly differentiated T cells [25,26], may alter the frequency of $CD5^{lo}$ memory T cells in human beings. Indeed, the number of $CD5^{lo}$ $CD8^+$ and $CD4^+$ memory T cells was increased in CMV seropositive compared with CMV seronegative persons (Fig. 3C). In addition, a higher percentage of

$CD5^{lo}$ $CD4^+$ memory T cells was identified in the peripheral blood of patients with RA compared with age- and CMV-matched healthy individuals (Fig. 3D). Thus, our results indicate that persistent infection with CMV and pro-inflammatory autoimmune diseases, such as RA, characteristically shape the functional composition of the human memory T-cell pool by driving the accumulation of $CD5^{lo}$ memory T cells. The lower expression level of CD5 on these highly differentiated memory T cells is also associated with an increased responsiveness to the homeostatic cytokine IL-15, which may represent a survival advantage and may drive their accumulation in the BM. In the case of RA, IL-15 is increased in the synovium and BM [27,28] and may decrease the activation threshold of highly differentiated, IL-15–sensitive $CD5^{lo}$ memory T cells, thereby contributing to increased T-cell activation and inflammation [28].

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.humimm.2011.03.028.

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