IL-4-Producing CD8$^+$ T Cells with a CD62L $^{++}$ (bright) Phenotype Accumulate in a Subgroup of Older Adults and Are Associated with the Maintenance of Intact Humoral Immunity in Old Age

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IL-4-Producing CD8⁺ T Cells with a CD62L⁺⁺(bright) Phenotype Accumulate in a Subgroup of Older Adults and Are Associated with the Maintenance of Intact Humoral Immunity in Old Age

Susanne Schwaiger, Anna Maria Wolf, Peter Robatscher, Brigitte Jenewein, and Beatrix Grubeck-Loebenstein

An increased production of proinflammatory cytokines occurs in a high percentage of elderly persons and is associated with an impaired humoral immune response. However, high IL-4 production has also been observed in old age. We now demonstrate an IL-4-producing subpopulation of CD8⁺ T cells in a subgroup of healthy older adults. This T cell subset is substantial in size and has a characteristic phenotype expressing CD45RO, CD28, CD62L, and CD25. IL-4-producing CD8⁺ T cells produce large amounts of IL-2 but not IFN-γ or perforin, and these cells do not have a regulatory suppressive effect on other T cells. In vivo IL-4-producing CD8⁺ T cells can be stably detected over a year. When put into culture they also have a stable cytokine production pattern but fail to produce perforin even in the presence of IL-12. This special T cell type does not occur in persons under the age of 40, but is present in 36% of the persons >60 years of age. In this age group, IL-4-producing CD8⁺ T cells are more frequent in persons who are still capable of raising a humoral immune response following immunization than in others who fail to produce protective Abs after vaccination. Our results suggest that CD8⁺ T cells with a CD62L⁺⁺(bright) phenotype accumulate in a subgroup of older adults. Due to their phenotype that enables them to migrate into lymphoid tissues and to their capacity to produce IL-4, these cells may counterbalance the overproduction of proinflammatory cytokines in old age. The Journal of Immunology, 2003, 170: 613–619.
Uppsala, Sweden). For intracellular cytokine staining PBMCs were stored in liquid nitrogen until used. Some experiments were done with freshly isolated PBMCs or whole blood.

**Influenza vaccination and Ab titers**

Twenty-four volunteers (12 females and 12 males >60 years of age) from the previously described cohort were vaccinated against influenza with a commercially available trivalent split vaccine (Vaxigrip; Aventis Pasteur, Lyon, France). Ab responses to the vaccine hemagglutinin components were determined prior to as well as 4 wk after vaccination by standard hemagglutination inhibition assay as described previously (18). According to our previous definition criterion of “humoral nonresponders” (19), five persons (two females, three males; mean age 81; age range 70–90 years) who did not have influenza-specific Abs before vaccination and who failed to raise a protective humoral immune response to all three influenza strains present in the vaccine were chosen as well as four elderly persons (two females, two males; mean age 75; age range 70–80 years) who did not have influenza-specific Abs before vaccination, but did have titers of ≥1:40 to all three influenza strains 4 wk after vaccination and thus corresponded to our previous definition of “humoral responders.” The number of CD8+ IL-4-producing cells was then compared in the two person groups. The remaining persons vaccinated against influenza did not fulfill the stringent criteria of humoral responders or nonresponders. This result was either due to high prevaccination Ab titers or to a varying response to the three influenza strains present in the vaccine. Results were additionally compared in persons (n = 3) with a 4-fold increase in titer to all three influenza strains following vaccination, and with other persons (n = 7) who did not fulfill this requirement.

**Flow cytometry**

Surface staining was performed by adding a panel of directly conjugated titrated Abs (FITC, PerCP, PE, APC) against CD8, CD3, CD45RO, CD62L, CD69, CD28, CD27, CD25 (all BD PharMingen, San Jose, CA) to PBMCs or to 10^6 µl of whole blood. After an incubation period of 20 min at room temperature in the dark, PBMCs were washed and fixed with 2% formaldehyde until analysis on a FACS Calibur (BD PharMingen). When doing whole blood stainings, erythrocytes were lysed after the staining step by adding 500 µl of FACS Lysing solution (BD PharMingen). After washing, cells were fixed with 2% formaldehyde until analysis on a FACS Calibur (BD PharMingen). Data were analyzed with CellQuest Pro software (BD PharMingen). CCR7 was stained by a multistep procedure using purified mouse anti-CCR7 IgM Ab followed by biotinylated rat anti-mouse IgM and streptavidin-APC conjugate (all BD PharMingen). For measuring intracellular cytokines, PBMCs were defrosted and suspended in RPMI 1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS (Sigma-Aldrich, St. Louis, MO) at a concentration of 2×10^6/ml. Cells were stimulated with 10 ng/ml PMA and 0.5 µg/ml ionomycin (both Sigma-Aldrich) in the presence of 1 µg/ml GolgiPlug (BD PharMingen) for 4 h at 37°C. After this stimulation period, cells were washed with FACS buffer (PBS containing 0.02% BSA) and stained with titrated directly conjugated anti-CD3, CD8, CD45RO, CD28, CD27, CD25 (all BD PharMingen, San Jose, CA) to PBMCs or to 150 µl of whole blood. For measuring IL-4 and streptavidin-APC conjugate (all BD PharMingen). Data were analyzed with CellQuestPro software (BD PharMingen). For measuring intracellular cytokines, PBMCs were defrosted and suspended in RPMI 1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS (Sigma-Aldrich, St. Louis, MO) at a concentration of 2×10^6/ml. Cells were stimulated with 10 ng/ml PMA and 0.5 µg/ml ionomycin (both Sigma-Aldrich) in the presence of 1 µg/ml GolgiPlug (BD PharMingen) for 4 h at 37°C. After this stimulation period, cells were washed with FACS buffer (PBS containing 0.02% BSA) and stained with titrated directly conjugated anti-CD3, CD8, CD45RO, CD28, CD27, CD25 (all BD PharMingen) for 30 min at 4°C in the dark. After washing, permeabilization of cells with Cytofix/Cytoperm (BD PharMingen) solution was performed. Permeabilized cells were stained for intracellular cytokines, for the activation marker CD69, or for perforin by adding titrated Abs recognizing IL-4, IFN-γ, IL-2, perforin, and CD69. Finally cells were washed and stored in 2% formaldehyde until analysis. For properly setting the cut off, isotype control and unstained control samples were used. CD62L is proteolytically cleaved from the cell surface by metalloproteinases even after mild stimulation (20, 21) and can therefore not be stained together with intracellular cytokines without special pretreatment. To overcome this problem, the hydroxamic acid derivative GM6001 (Calbiochem, Darmstadt, Germany) was used for blocking stimulation-induced shedding of CD62L from the cell surface. Cells were pretreated with fluorescence-conjugated Ab against CD62L for 15 min at room temperature before stimulation as described (22). After washing, GM6001 was added at a concentration of 100 µM to the culture medium. This procedure completely prevented FACS-induced shedding of CD62L from the cell surface.

**Purification of T cells and IL-4 secretion assay**

CD8+ T cells were purified by a positive selection procedure using CD8+-labeled MicroBeads and the MACS system (Miltenyi Biotec, Bergisch Gladbach, Germany). CD8+ T cells were labeled with MultiSort MicroBeads and positively selected in a MACS column. Subsequently the selected cells were incubated with the MultiSort Release Reagent (Miltenyi Biotec), which enzymatically removes the MicroBeads from the cells. A purity of ≥96% could be obtained. The CD8+ fraction obtained was used for further enrichment or isolation of the cell populations described below.

For the enrichment of live IL-4-producing CD8+ cells, a commercially available IL-4 Secretion Assay, Cell Enrichment and Detection Kit (Miltenyi Biotec) was used. Purified CD8+ T cells were stimulated with 10 ng/ml PMA and 0.5 µg/ml ionomycin for 4 h. Subsequently the assay was performed according to the manufacturer’s instructions. A fraction with a 5-fold enrichment of IL-4-producing CD8+ cells could be obtained. For the isolation of CD8-CD25+ cells, the purified CD8+ fraction was separated over a MACS column for a second time using anti-CD25-labeled MicroBeads. The purity of the positively selected cells was >96%, as determined by FACS analysis.

**Cell culture**

CD8+ cell populations that had been enriched for IL-4-producing cells by the IL-4 secretion assay were seeded at a density of 5×10^6 cells/well in 24-well plates in medium supplemented with 20 ng/ml rIL-2 (Novartis, Basel, Switzerland) and plate-bound OKT3 (Orthoclone, Transplant, Vienna, Austria), 10 ng/ml rIL-4 (Chemicon, Temecula, CA) or 10 ng/ml rIL-12 (Chemicon). Cytokines and media were replaced every 2 days. After 1 wk of culture, the cells were restimulated with PMA and ionomycin for 4 h, and intracellular cytokine and perforin staining was performed as described previously.

**Mixed lymphocyte reaction**

For MLR cultures, PBMCs from two donors with a “type 2” IL-4-producing pattern (Fig. 1) were incubated with irradiated (30 Gy) allogeneic PBMCs (both at 1×10^6/well) in a total volume of 200 µl of RPMI/10% FCS. Increasing numbers of purified CD8+ CD25- T cells obtained from the donors whose PBMCs served as responder cells to the cultures. After 1 wk, the cells were pulsed with 1 µCi [3H]thymidine (ICN Pharmaceuticals, Costa Mesa, CA) for the last 8 h of culture and then harvested onto glass fiber filters (Wallac, Turku, Finland). [3H]Thymidine incorporation was quantified on a liquid scintillation counter. The results are expressed as cpm as mean of triplicate determinations.

![FIGURE 1. CD8+ T cells produce IL-4 in a subgroup of older adults. PBMCs from 74 persons age 20–90 years were analyzed for the intracellular production of IL-4 in CD8+ and in CD8- cells gated on all CD3+ cells after stimulation with PMA and ionomycin. a, Different patterns of IL-4 production were observed: Type 1, IL-4 production in CD8+ CD3+ cells >1.5% of CD3+ cells, no IL-4 detectable in CD8- CD3+ cells; Type 2, IL-4 production in CD8+ as well as in CD8 CD3+ cells >1.5% of CD3+ cells; Type 3, IL-4 production in both CD8+ and CD8- CD3+ cells <1.5% of CD3+ cells. Representative FACS profiles are shown. The percentages of IL-4-producing cells are indicated in the quadrants. Total CD8+ cells are considered as 100%. b, Age distribution of the different IL-4 production patterns (n = 21, 20, and 33 in the three age groups, respectively; the total number of persons in one age group is always considered as 100%).](http://www.jimmunol.org/Download)
Statistical analysis

For the comparison of the percentages of IL-4-producing CD8\(^+\) T cells between humoral responders and nonresponders to influenza vaccination, a Student’s \(t\) test for unpaired data was performed. A Pearson’s regression analysis was performed to analyze the relationship between the percentage of IL-4-producing CD8\(^+\) T cells after stimulation with PMA and ionomycin and the percentage of CD45RO\(^+\)CD62L\(^-\)/CD8\(^+\) T cells within unstimulated PBMCs.

Results

CD8\(^+\) T cells produce IL-4 in a subgroup of older adults

T cells from young persons of up to 40 years of age had a homogeneous IL-4 production pattern on stimulation with PMA and ionomycin. These cells produced IL-4 within the CD8\(^-\)CD3\(^+\) population, whereas CD8\(^+\)CD3\(^+\) cells hardly contained IL-4. This IL-4 production pattern (type 1 production pattern; Fig. 1a) was also found in 65% of the persons between the ages of 41 and 60 years and in 33% of the 61–90-year-old cohort (Fig. 1b). In contrast, IL-4 production by CD8\(^+\) T cells was observed in older persons. CD8\(^+\) as well as CD8\(^+\)CD3\(^+\) cells produced IL-4 (type 2 production pattern; Fig. 1a) in 15% of the persons between the ages of 41 and 60 years and in 36% of elderly persons between 61 and 90 years of age (Fig. 1b). The remaining persons (20% in the 41–60 years and 30% in the 61–90 years age group) produced very little IL-4 (<1.5% of the CD3\(^+\) cells) in both CD8\(^+\) and CD8\(^-\)CD3\(^+\) cells. This IL-4 production pattern is referred to as type 3. IL-4-producing cells reached an average percentage of 11 ± 3% (range 7–16% of all CD8\(^+\) T cells in persons with a type 2 IL-4 production pattern). CD8\(^+\) T cells from persons with a type 2 cytokine production pattern also produced IL-5, whereas IL-5 production by CD8\(^+\) T cells was never observed in persons with a type 1 or a type 3 cytokine production pattern. There was no statistical difference in the production of IFN-\(\gamma\) by CD8\(^+\) T cells among the groups. To characterize CD8\(^+\) IL-4-producing T cells in more detail the following experiments were performed.

IL-4-producing CD8\(^+\) T cells do not produce IFN-\(\gamma\)

Cytokine double-stained experiments were performed to find out whether IL-4-producing CD8\(^+\)CD3\(^+\) T cells also produced other cytokines (Fig. 2). Most IL-4-producing CD8\(^+\) cells coexpressed IL-2 at high intensity, but a smaller subpopulation of IL-4\(^+\) cells did not produce IL-2. IFN-\(\gamma\) was never detectable in IL-4-producing CD8\(^+\) cells. IL-10 was not produced by CD8\(^+\) T cells under the described conditions.

IL-4-producing CD8\(^+\) T cells can be stably detected in vivo and in vitro

To find out whether the occurrence of IL-4-producing CD8\(^+\) T cells was a consistent feature in a subgroup of older adults, we analyzed the IL-4 production of persons with a type 2 cytokine production pattern twice at a year’s interval. Intracellular IL-4 production did not change, suggesting that the IL-4-producing CD8\(^+\) T cell population was stable in vivo (Fig. 3a). To analyze the stability of IL-4-producing CD8\(^+\) cells in vitro, we enriched CD8\(^+\)IL-4\(^+\) cells from PBMCs (5 ± 2% to 28 ± 3% enrichment) and cultured the obtained population for 1 wk in the presence of different stimuli. Cells were stimulated with IL-4, IL-12, or with plate-bound OKT3 in combination with IL-2. After 1 wk in culture, the cells were restimulated with PMA and ionomycin and the production of IL-4 and IFN-\(\gamma\) was analyzed. Under all culture conditions tested, a polarized IL-4 production pattern by CD8\(^+\) cells was maintained (Fig. 3b). The percentage of IL-4-producing cells was similar after culture with IL-4 or the combination of OKT3 and IL-2 (26%), but was slightly decreased in the presence

![FIGURE 2](http://www.jimmunol.org/Downloadedfrom)  
**FIGURE 2.** IL-4-producing CD8\(^+\) T cells do not produce IFN-\(\gamma\); intracellular cytokine production in a gated CD8\(^+\)CD3\(^+\) population is presented. PBMCs from an elderly person (72 years of age) were stimulated with PMA and ionomycin. The figure represents one of ten similar experiments in which cells from persons between 47 and 82 years of age were used. The percentage of cells in each quadrant is indicated. CD3\(^+\)CD8\(^+\) cells are considered as 100%.
of IL-12. No perforin was produced under any of the culture conditions tested (not shown).

IL-4-producing CD8+ T cells are CD45RO+CD62L+ (bright)

IL-4-producing CD4+ memory T cells have been described to express CD62L (22). This led us to hypothesize that IL-4-producing CD8+ cells might have a similar phenotype. We therefore analyzed the production of IL-4, IFN-γ, and IL-2 in CD8+CD45RO+ as well as in CD62L+CD45RO+CD8+ cells (Fig. 4, a and b). IL-4 was only produced by CD8+CD45RO+ cells, whereas IFN-γ was produced by CD8+CD45RO+ as well as CD45RO− cells. IL-2 was produced primarily by CD45RO− cells. Fig. 4b depicts the cytokine production of CD62L cells in the CD8+CD45RO+ gate. The results demonstrate that IL-4 was produced exclusively by CD62L+ (bright) cells. In contrast IFN-γ was produced mostly by CD62L− cells. Only a few IFN-γ-producing cells expressed CD62L at low intensity (CD62L−/dim). IL-2 was produced by CD62L+ , CD62L−, and CD62L− cells. We also analyzed the relationship between the percentage of unstimulated CD45RO−CD62L+ cells and of PMA/IONOMycin-stimulated IL-4-producing cells within the CD8+ gate. A Pearson’s regression analysis showed a direct correlation between the expression of CD62L on unstimulated CD45RO−CD8+ and the production of IL-4 by stimulated CD8+ T cells (Fig. 4c). CD62L mediates the rolling and attachment of lymphocytes on high endothelial venules, but for firm arrest and extravasation at these sites the chemokine receptor CCR7 is needed (23, 24). We therefore studied the expression of CCR7 on CD8+CD45RO−CD62L+ T cells. Fig. 4d shows that the whole CD62L+ population within the CD8+CD45RO+ gate, which contains almost 100% of the IL-4-producing CD8+ cells expressed CCR7. CD8+CD45RO−CD62L+ had not been recently activated, as they did not express the early activation marker CD69.

CD8+ T cells express costimulatory receptors and have a CD25+ -activated phenotype but do not produce perforin

For further phenotypic characterization of the CD8+CD3− IL-4-producing population, the expression of CD28, CD27, and CD25 was analyzed. IL-4-producing CD8+ cells were CD28+ and had a variable expression of CD27, as about two-thirds of the population was CD27+, whereas one-third was not (Fig. 5). IL-4-producing CD8+ cells were also CD25+, CD8+ IL-4-producing cells expressed CD25 following PMA stimulation, and unstimulated CD8+CD45RO−CD62L+ cells also contained a CD25+ population that corresponded in size to the CD8+ IL-4-producing cell. Isolated CD8+CD25+ cells also characteristically had a high production of IL-4 and IL-2, but hardly contained IFN-γ following stimulation with PMA and Ionomycin (data not shown). To find out whether the IL-4-producing CD8+ T cell population had cytolytic capacity, we analyzed the expression of perforin after stimulation with PMA. IL-4-producing CD8+ cells did not express perforin. In contrast, IFN-γ-producing CD8+ T cells were frequently CD28+ and CD27− but never CD25+, and a high percentage of IFN-γ-producing CD8+ T cells produced perforin.

CD8+CD25+ cells do not show suppressor activity in an MLR

The expression of CD25 on IL-4-producing CD8+ cells raises the question whether these cells might have regulatory effects as described for CD4+CD25+ cells (25, 26). CD8+CD25+ cells were therefore separated by MACS technology and tested for a possible suppressive effect on the proliferation of autologous PBMCs on allogeneic stimulation in an MLR experiment. Increasing numbers of CD8+ CD25+ T cells had no inhibitory effect on the proliferation of PBMCs in an MLR (Fig. 6) suggesting that CD8+CD25+ T cells were not suppressor cells.

CD8+ IL-4-producing T cells are more frequent in humoral responders than in nonresponders to influenza vaccination

We also analyzed whether the occurrence of IL-4-producing CD8+ cells was related to an effective humoral immune response following immunization. Because influenza vaccination is frequently performed in elderly persons and does not lead to Ab production in 30–50% of this cohort (27, 28), we used this type of immunization as a model situation. The percentage of IL-4-producing CD8+ cells was compared in persons who did or did not produce influenza-specific Abs following vaccination. The strategy of defining subgroups of elderly persons according to their humoral immune

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**FIGURE 4.** IL-4 is produced by CD8+CD45RO− cells that express lymph node homing receptors. The production of IL-4, IFN-γ, and IL-2 in CD8+CD45RO− (a) and in CD8+CD45RO−CD62L− (b) cells is shown. PBMCs from an elderly person (70 years of age) were stimulated with PMA and Ionomycin. Three- and four-color flow cytometry was performed, respectively. To avoid the shedding of CD62L during activation, the hydroxamic acid derivative GM6001 was added to the cultures in a concentration of 100 μM. The figure depicts one of six similar experiments in which cells from persons between 60 and 76 years of age were used. c. The relationship between the percentage of IL-4-producing cells and the percentage of CD45RO−CD62L− cells gated on all CD8+ T cells in different persons. Unstimulated PBMCs were used for the analysis of CD45RO− and CD62L−. PMA/Ionomycin-stimulated cells were used for the analysis of IL-4. A Pearson’s regression analysis showed a direct correlation (β = 0.5x − 1.18; R² = 0.77; p < 0.001). d. The surface expression of CD62L in relation to the surface expression of CCR7 and CD69 gated on all CD8+CD45RO− T cells is shown. The figure represents one of four similar experiments. FACS stainings were done with unstimulated whole blood.
response has been used previously by our group (19). The percentage of IL-4-producing CD8⁺ cells was significantly higher in persons who did produce protective Ab titers following vaccination than in persons who failed to produce protective Ab titers (Fig. 7), suggesting that IL-4 production by CD8⁺ cells was a feature associated with intact humoral immunity in old age. Identical results were obtained when results were compared in persons with a 4-fold increase in titer to all three influenza strains following vaccination and others who failed to fulfill this requirement (difference between groups p < 0.05).

Discussion
Our results demonstrate that IL-4-producing CD8⁺ T cells occur in a subgroup of healthy older adults. At a percentage up to 16% of CD8⁺ T cells in some persons, they represent a substantial subpopulation. The cells occur in 15% of the persons 41–60 years of age and in 36% in the age group from 61 to 90 years. They are never detected in healthy young adults. IL-4-producing CD8⁺ cells express CD62L at high intensity. Thus they are able to migrate to secondary lymphoid organs (29, 30), where they might provide help to CD4⁺ T cells or B cells (10, 31, 32). They might also affect the phenotype and cytokine production profile of dendritic cells and change the polarization of naïve T cells as a consequence (33). Whether CD8⁺ IL-4-producing T cells were unable to confer protective cellular immunity in response to challenge with their specific Ag (34–36), an increased IL-4 production in secondary lymphatic tissues should still be of advantage in old age.

Old age is characteristically associated with an overproduction of type 1 cytokines (37, 38), and high serum neopterin concentrations suggest an increased whole body load of IFN-γ (39, 40). High IFN-γ does not only trigger chronic inflammatory processes that seem to support the development of age-related diseases such as Alzheimer’s disease (41) and atherosclerosis (42), but may also be responsible for the insufficient efficacy of vaccines to induce Ab production in elderly persons (19, 43, 44). In this context, our finding that elderly persons who produced protective Ab titers following influenza vaccination had increased numbers of IL-4-producing CD8⁺ T cells than did those elderly persons who could not raise a sufficient humoral immune response seems of special interest (Fig. 7). It suggests that IL-4-producing CD8⁺ T cells do indeed have a beneficial effect because they may stimulate humoral immunity and thus counteract one of the detrimental effects of increased IFN-γ production in old age.

IL-4-producing CD8⁺ T cells that occur in healthy older adults are strictly polarized, cannot be triggered to produce IFN-γ, and do not produce perforin. This suggests that this CD8⁺ T cell subpopulation is unable to kill. It may still play a regulatory role. Despite expressing CD25, CD8⁺ IL-4-producing T cells are not regulatory suppressor cells. In contrast to CD4⁺ CD25⁺ regulatory cells that do not produce IL-2 (45), the CD8⁺ IL-4-producing cell type described in this study expresses IL-2 at high intensity (Fig. 2). In addition its capacity to suppress other cells was tested in an MLR. Regulatory CD4⁺ CD25⁺ suppressor T cells inhibit the activation and proliferation of other T cells on TCR-mediated or
allogeneic stimulation (25, 26). In contrast to no inhibitory effect of purified CD8^+CD25^+ was observed (Fig. 6).

It is presently not clear why CD8^+ IL-4-producing T cells express CD25. Repeated antigenic reactivation may be a possible explanation. The association of certain T cell differentiation stages with different viral infections has recently been demonstrated (46).

The accumulation of CD8^+CD25^+ T cells has for instance been suggested to concur with CMV infection (46, 47). Whether the increase in CD8^+CD28^+IFN-γ-producing T cells characteristically observed in healthy elderly persons (48, 49) is also a symptom of underlying latent CMV infection is still a matter of debate (50, 51). It seems, however, tempting to speculate that the accumulation of IL-4-producing CD8^+CD45RO^+CD62L^+ T cells in a subgroup of persons >40 years of age is the result of latent or past infections with so far unidentified pathogens. This would explain why an only relatively small percentage of persons from a certain age onward is affected. A recent report demonstrates that immunization of mice with heat killed but not live *Listeria monocytogenes* primed CD8^+ T cell populations with a CD62L^+ phenotype that were substantial in size, but did not provide full protection from subsequent *L. monocytogenes* infection (36). This also suggests that vaccinations with inactivated or attenuated microorganisms might have induced the accumulation of memory CD8^+ T cells in older adults. Experiments to determine the specificity and exact activation requirements as well as a clonotypic analysis of CD8^+ IL-4-producing cells are presently underway in our laboratory.

The concept that infections or even vaccinations may affect the aging of the immune system differently in different persons is not only tempting from an academic point of view, but could also have practical consequences. If CMV, for instance, drives the accumulation of IL-4-producing T cells showing B cell helper function and reduced cytolytic activity in healthy elderly persons (48, 49) is also a symptom of pulmonary cavities.

References


