CD8+ T-Cell Subpopulations in Human Abdominal Aortic Aneurysm Lesion

To the Editor:

We read with great interest the article by Duftner et al reporting the prevalence of peripheral interferon-γ (IFN-γ)–producing CD4+/CD28+ and CD8+CD28+ T cells in patients with small abdominal aortic aneurysm (AAA). Along with the recent description that Th1-type immune responses predominate in human end-stage AAA lesion,1,2 their observation further supports preference toward polarized type 1 T-cell responses in aneurysm disease. The potential involvement of Th1 cells in the pathogenesis of the disorder is also suggested by the convincing demonstration that absence of CD4+ T cells or targeted deletion of IFN-γ prevents the induction of experimental AAA in a calcium chloride–induced mouse model.3,4 AAA formation being reconstituted by administration of IFN-γ into CD4+ mice or infusion of competent splenocytes from wild-type mice into IFN-γ–mice.

In their study, Duftner et al further established that both circulating CD4+CD28+ and CD8+CD28+ T cells are highly differentiated cells that display extensive CD45RO to CD45RA reverision and produce large amounts of IFN-γ and perforin. Surprisingly, low percentages of CD8+CD28+ T cells were identified in AAA tissue sections using immunohistochemistry compared with flow cytometric analysis of peripheral blood mononuclear cells. In a series of our own, we examined the surface phenotype of infiltrating T lymphocytes freshly isolated from aneurysmal aortic wall for comparison with their circulating counterparts using flow cytometry. As shown in the Table, ex vivo immunophenotyping confirmed reduced proportions of CD8+CD28+ T cells in the aneurysmal aortic wall compared with control peripheral blood. In view of the regulatory properties of CD8+CD28+ T cells,5,6 their decrease in human AAA wall might suggest their potential implication in the regulation of aortic wall immune responses. This underscores the need for future studies to assess the presence of and delineate the role played by various regulatory T-cell subsets in aneurysm disease. Besides, a population of CD8+ T cells lacking the costimulatory molecule CD27 was detected in human AAA lesion compared with control peripheral blood (Table). Focusing on the distribution of CD8+ T-cell subsets in AAA specimens, we observed for the first time local expansion of CD8+CD27- cells compared with CD8+CD28+ cells (Table). Furthermore, the proportion of infiltrating CD45RO T cells was higher among the CD8+CD27- subset (median percentage of positive cells 70%; minimum value 57, maximum value 86) than the CD8+CD28+ subset (median percentage of positive cells 44%; minimum value 43; maximum value 45). Although preliminary, our data suggest the presence of both intermediate and late differentiated CD8+ T-cell subsets in human end-stage AAA lesion. Moreover, because CD27 is a determinant for the accumulation of CD8+ effector T cells at tissue sites,7,8 our findings highlight the possibility that lesional CD8+CD27- T cells could participate in the regulation of the expansion and maintenance of CD8+ effector T-cell subpopulations in the aortic wall. Further experimental studies are needed to reveal the exact role of the differentiation process in aortic wall immune responses and to clarify the functional relevance of distinct subsets of CD8+ T cells with differing functional and migratory properties.

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In Response:

We read with great interest the letter by Galle et al reporting a decreased prevalence of CD3+CD45RO+CD8+CD28+ in abdominal aortic aneurysm (AAA) tissue specimens compared with the peripheral blood of the same AAA patients (as shown in the Table of their letter). This group focuses on the memory cell type, and their findings parallel our data of low percentages of CD8+CD28+ T cells in AAA tissue specimens.1 Because they focus on the CD45RO+ cell population, they exclude late differentiated CD28- and CD27- T cells of the CD45RA+ phenotype1,2 and thus obtain

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<th>CD8+ T-Cell Subsets in Human Abdominal Aortic Aneurysm</th>
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<tr>
<td><strong>Peripheral Cells</strong> (median per-</td>
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<tr>
<td>CD8+CD27- cells</td>
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<tr>
<td>(16.72–44.60)</td>
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<tr>
<td>CD8+CD28+ cells</td>
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Mononuclear cells were purified from peripheral blood and aneurysmal aortic wall obtained from patients undergoing elective open abdominal aortic aneurysm repair (n=3). Immediately after the isolation procedure, cells were stained with fluorescein isothiocyanate (FITC)-, phycoerythrin (PE)-, peridin chlorophyll–a protein (PerCP)-, and allophycocyanin (APC)- conjugated monoclonal antibodies (mAbs) against CD45, CD3, CD27, and CD28 antigens, and the corresponding isotype-matched irrelevant mAbs. Flow cytometric analysis of surface phenotype is shown after gating on CD45+CD3+ cells. Results are expressed as median percentage of positive cells; values within brackets represent the corresponding minimum and maximum values.

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lower percentages of CD28+ T cells than we did. Besides, Galle et al describe the local expansion of CD3+CD45RO-CD8+CD27- T cells in AAA tissue specimens and peripheral blood.

CD28 and CD27 are costimulatory receptors consecutively involved in the regulation of T-cell activation and the generation of antigen-primed cells. Expression of CD28 and CD27 is particularly useful in distinguishing between subsets of differentiated CD8+ T cells. Based on CD28 and CD27 expression, CD8+ T cells can be separated into 3 distinct populations: CD28+CD27-“early”; CD28-CD27+“intermediate”; and CD28-CD27-“late-differentiated” cells. Although CD45RA is associated with the definition of naive T-cell responses, it is re-expressed on late-differentiated CD8+ T cells.2–3 Interestingly, Galle et al describe in their letter the local expansion of both CD8+CD27+ and CD8+CD27- T cells. Because CD8+CD28- occur earlier in the differentiation process, their data suggest that CD8+CD27+ cells display a CD45RO+ phenotype even more than CD8+CD28- cells. However, these differentiation states have been established for circulating CD8+ T cells, and it remains elusive so far whether this concept of T-cell differentiation also holds true for the sites of inflammation. Further phenotypic studies are necessary to address these questions.

The function of CD3+CD45RO-CD8+CD27- T cells remains undefined. Galle et al propose that CD8+ T cells lacking CD28 expression function as suppressor cells in the aortic wall. The fact that others had observed a correlation between the frequency of CD8+CD28- T cells and low-response rates to influenza vaccination as well as long-term allograft survival supports the concept of CD8+CD28- as suppressor T cells.4–7 Whether this also holds true for CD8+CD27- T cells in aortic aneurysms has to be validated. Because circulating CD8+CD27- T cells from AAA patients revealed high production of perforin and interferon-γ,1 it cannot be excluded that CD8+CD27- T cells comprise both proinflammatory and suppressor cells.

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