T-Cell Receptor $\gamma\delta$ Bearing Cells in Normal Human Skin

To the Editor:

I have read with great interest the article by Bos et al [1] in which it was demonstrated that although gamma/delta T cells reside in the skin, they are not enriched in the skin [2]. Of particular interest was the finding of occasional cells bearing the phenotype CD1+ TCR (T-cell receptor) gamma/delta positive. But I disagree with their interpretation that these cells represent Langerhans' cells with TcR.

As mentioned by the authors, Langerhans' cells with T-cell receptors are unlikely, given the lack of CD3 on Langerhans' cells and the coordinate expression of TCR with CD3. Expression of TCR requires gene rearrangement. Although TCR genes may be rearranged in B-cells, rearrangement of TCR genes in Langerhans' cells has not been demonstrated. It is thought that the necessary enzymes for gene rearrangement are unique to lymphoid differentiation. Furthermore, dendritic morphology is not useful in determining cell lineage, as evidenced by the murine thy-1^+ dendritic T cell.

It must be remembered that CD1 is also a marker of immature thymocytes. Given the evidence that gamma/delta receptor rearrangements precede alpha/beta rearrangements, it may be expected that gamma/delta cells are less mature [3]. Thus, the finding of rare T cells bearing CD1 along with gamma/delta should not be surprising. It would be predicted that such cells would also be CD2+CD3+. This interpretation supports the hypothesis that extra-thymic T-cell differentiation may take place in the skin [4].

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REPLY

The letter of Dr. Kalish refers to a possible artefact that we have noted while quantitating the distribution of T cells expressing TCR $\alpha\beta$ or TCR $\gamma\delta$ in normal human skin [1]. First, we observed in tissue sections extremely rare, highly dendritic cells that stained with anti-TCR $\gamma\delta$ monoclonal antibody and in adjacent sections with CD1a antibody. Because we felt that we had observed the possible presence of TCR $\gamma\delta$ in Langerhans cells (LC), a subsequent search was carried out in LC enriched cell suspensions [2]. In cytospin preparations of these suspensions over 10% of human LC reacted with a number of different anti-TCR $\gamma\delta$ monoclonal antibodies. It should be stressed that this reactivity was exclusively found in the cytoplasm and not on the cell surface.

Our observations raised the possibility that in human skin LC might express TCR $\gamma\delta$ in the cytoplasm. We are aware that this is a highly disputable conclusion and have therefore observed the greatest caution in interpreting these results. Arguments against TCR $\gamma\delta$ expression in LC are obvious and have our greatest attention. They are, in the first place, the lack of CD3 expression both in the cytoplasm and at the cell surface. In a more general sense, there is no evidence for lineage relationships between LC and T cells. The option raised by Kalish, that the observed cells might represent immature T lymphocytes possibly differentiating at this extra-thymic site in the epidermis, does not seem very attractive to us either. If these cells are immature T cells, they should express cytoplasmic CD3 components. In thymic T-cell differentiation, cytoplasmic CD3 expression occurs prior to TCR expression. Also, the dendritic morphology of these cells suggests a relationship to LC rather than to T cells. A comment directly relating to Kalish's remark: "TCR $\gamma\delta^+$ cells cannot be considered less mature than TCR $\alpha\beta^+$ cells." It is established by now that the TCR $\gamma\delta^+$ and TCR $\alpha\beta^+$ lineages are independent [3]. There is no evidence for differentiation of TCR $\alpha\beta$ expressing cells from TCR $\gamma\delta$ expressing precursors.

In short, we want to leave the discussion at the statement also found in the paper; namely, that the option that human LC would contain molecules homologous or identical to TCR $\gamma\delta$ clearly needs further investigation. We cannot exclude that all the confusion stems from a fortuitous cross-reaction of antibodies. We regret that this discussion tends to distract those who are interested in TCR $\gamma\delta^+$ cells from what we really reported. Our publication concerns primarily the relative contribution of TCR $\alpha\beta^+$ and TCR $\gamma\delta^+$ cells to the T-cell population in normal human skin. We have confirmed our previous finding that the majority of T cells in normal human skin is localized perivascularly: less than 5% of T cells are present in the epidermis [4]. We have also reported that only a minority of epidermal T cells express TCR $\gamma\delta$, which poses a great discrepancy with the situation in murine epidermis, where TCR $\gamma\delta^+$ cells are more abundant in absolute numbers and constitute the great majority of T cells (>95%) [5].

Taken together, our findings do not support the hypothesis that TCR $\gamma\delta$ cells play a major role in epithelia surveillance in normal human skin. Also, their very low relative numbers do not give much ground to the idea that the epidermis serves as a major site of extra-thymic differentiation of this lineage.

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