Differential Expression of Lymphocyte Function-Associated Antigen 1 (LFA-1) on Epidermotropic and Non-Epidermotropic T-Cell Clones

To the Editor:
The article “Differential Expression of Lymphocyte Function-Associated Antigen 1 (LFA-1) on Epidermotropic and Non-Epidermotropic T-Cell Clones” by Shiohara and co-workers [1] states that “the presence of high levels of LFA-1 on T cells is absolutely necessary for their epidermotropic migration.”

However, two parts of the results speak against this statement. First, there is one clone (82F12) that expresses high levels of LFA-1 without being epidermotropic. Second, even in those clones that have phorbol ester induced expression of LFA-1, there is no change from a non-epidermotropic to an epidermotropic state. Thus it is more likely that LFA-1 is not the molecule primarily involved in this experimental epidermotropism. Interestingly, there is also no information concerning the expression of ICAM-1, the ligand of LFA-1 on the epidermis of the foot-pads which would allow the use of this receptor ligand pair in epidermotropism. This could have been simply tested by staining with monoclonal antibodies against murine ICAM-1.

It rather seems likely that other receptor ligand pairs are relevant for the observation of the authors because normal epidermis expresses a wide variety of ligands belonging to various adhesion molecule families that would permit the entrance of T cells into the epidermis [2].

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REPLY
Dr. Sterry’s comments regarding our recent paper [1] appear to contain a misapprehension of our observations and statement. Although he did not mention the important findings of our previous study in his comments, we have clearly demonstrated that in vivo administration of monoclonal antibody (MoAb) to LFA-1 specifically blocks epidermotropic migration of cutaneous GVHD-producing T cells and the subsequent destruction of the epidermis [2].

In addition, there is increasing experimental and clinical evidence to indicate that the receptor-ligand type interaction between LFA-1 on lymphocytes and ICAM-1 on keratinocytes serves a crucial role in adhesions of lymphocytes to epidermal keratinocytes [3,4]. Our findings that a close correlation between the density of LFA-1 on T cells and the epidermotropic nature was observed in six clones of seven clones tested, together with the previous findings mentioned above, support the notion that the presence of high levels of LFA-1 on T cells is necessary for their epidermotropic migration. We do not state, however, that LFA-1/ICAM-1 interaction can be the only mechanism to explain the epidermotropism of certain T cells, because clone 82F12, despite high levels of LFA-1 expression, is non-epidermotropic. Thus, we are, of course, in agreement with the notion that adhesion molecules other than LFA-1 are also involved in epidermotropism of the T cells. However, his statement that adhesion molecules expressed by normal epidermis are involved in epidermotropism of T cells seems unlikely. It does not make sense for the epidermis to normally express adhesion molecules that would allow the entry of leukocytes with ease. In order to protect the integrity of the epidermis from various unfavorable stimuli such as infection and trauma, this type of adhesion molecule should not be constitutively expressed, but be induced upon such stimuli on the keratinocytes.

As mentioned briefly in the paper, it becomes clear that qualitative, rather than quantitative, changes in LFA-1 expression are important for the regulation of LFA-1- and ICAM-1-mediated leukocyte adhesion [3,5]. Therefore, it is likely that up-regulation of LFA-1 with no increase in the avidity is not sufficient to trigger the epidermotropic migration.

Because the mouse homologue of human ICAM-1 had not been identified at that time, and MoAb to human ICAM-1 such as RR1/1 did not cross-react to murine ICAM-1, it has remained to be determined whether ICAM-1 expression on keratinocytes is necessary for the epidermotropic migration of the T cells. Because a recent publication [6] showed that the murine lymphocyte activation antigen MALA-2 is indistinguishable from human ICAM-1 in function, cellular distribution, and molecular properties, studies with the use of a rat MoAb to MALA-2 may provide direct evidence that LFA-1/ICAM-1 interaction is primarily involved in the epidermotropic migration of T cells.

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