Science
AAAS

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Elisa Lo Monaco *et al.*
Science **341**, 1175 (2013);
DOI: 10.1126/science.1241266

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Comment on "Influence of HLA-C Expression Level on HIV Control"

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Apps *et al.* (Reports, 5 April 2013, p. 87) found that high human leukocyte antigen C (HLA-C) expression favors HIV-1 control. However, as noted here, HLA-C was assessed with a monoclonal antibody (DT9) that cross-reacts with HLA-E. In the context of the available evidence, this is consistent with the idea that the two leukocyte antigens collaborate to keep the HIV-1 virus at bay.

A report recently published in *Science* demonstrated that the control of HIV-1 infection is positively influenced by high human leukocyte antigen C (HLA-C) expression (*1*). We note that this observation largely relies on extensive flow cytometry testing with a monoclonal antibody (mAb) named DT9, and draw attention to the original paper in which this mAb was described to primarily bind HLA-E, HLA-C being secondarily detected as a result of cross-reactivity (*2*).

The claim by Apps *et al.* for operational HLA-C specificity of mAb DT9 is based on extensive background information previously presented by the same group, particularly the lack of coexpressed HLA-E on the surface of human peripheral blood mononuclear cells (PBMCs), as assessed by a mAb named MEM-E/08 (*3*). However, this finding has subsequently been challenged by Corrah *et al.*, who have instead documented PBMC staining with another mAb to HLA-E, called 3D12 (*4*). Further adding to this controversy, and in agreement with Corrah *et al.*, we have shown that mAb MEM-E/08 reacts with poorly expressed, unstable, unfolded HLA-E molecules free of their light chain subunit (β_2m). In addition, we found that HLA-E levels are often underestimated, because a fraction of HLA-E is surface-expressed as a tightly β_2m-associated conformer poorly reactive with the available mAbs, including to some extent even the conformational mAb 3D12 (*5*). Altogether, these results favor the possibility that HLA-E substantially contributes to DT9 reactivity on the surface of many different human cells. HLA-E cross-reactivity, even marginal, may not be negligible in this setting, since HLA-C is the lowest expressed classical class I molecule [reviewed in (*6*)].

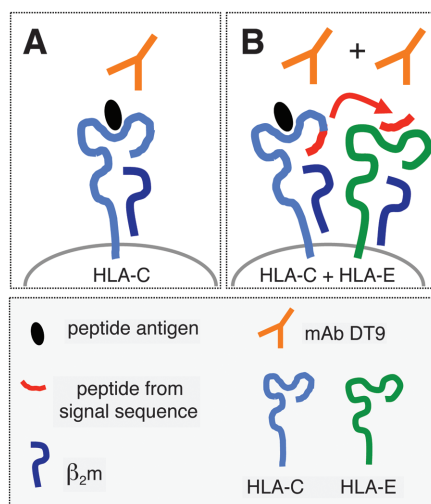On this basis, we suggest that mAb DT9 detects combined HLA-C/HLA-E expression and

Fig. 1. HLA-C and HLA-E: linked expression, reactivity with mAb DT9, and possible collaborative protection from HIV-1. Two patterns of mAb DT9 reactivity are depicted, implying different HIV-1 control models. The first (**A**), proposed by Apps *et al.*, is based on a restricted HLA-C reactivity of DT9 and is consistent with demonstrated, HLA-C–specific protective effects (*1, 11*). The second (**B**), hypothesized here on the basis of the previously observed HLA-E cross-reactivity with DT9, envisages a compound multilocus effect. Because HLA-E requires peptides donated from the signal sequence of HLA-C for its stable assembly with β_2m, we suggest that the two class I HLA molecules are coordinately expressed: The higher HLA-C is, the higher is the surface HLA-E pool. Because they are expressed in proportional amounts, HLA-E does not prevent the appreciation of differences in HLA-C expression by mAb DT9. Evidence for a protective role of HLA-E remains so far indirect.

that this combination, rather than HLA-C alone, may be considered the most accurate readout for the outcome of HIV-1 infection. Essentially all the HLA-C alleles, but only some HLA-A and HLA-B alleles, encode signal sequences potentially acting as donors of stabilizing HLA-E ligands (*7, 8*) (also see www.ebi.ac.uk/ipd/imgt/hla), providing direct insight into linked, and possibly coordinated, expression of HLA-C and HLA-E (Fig. 1). Coordination would result in HLA-E similarly contributing to DT9 binding in different HLA-C–expressing cells. Thus, HLA-E cross-reactivity would not preclude the discrimination of HLA-C–high from HLA-C–low alleles, a discrimination that is central to the HIV protection model put forward in several papers by the authors of (*1*). Protection from, and susceptibility to, HIV infection may then be interpreted in the context of a compound multilocus effect.

This alternative interpretation does not contradict, but rather complements, the original interpretation of Apps *et al.* (*1*). High HLA-C would incite cytotoxic T cell recognition, exactly as outlined by these authors, whereas high HLA-E may be instrumental in directing the lysis of virus-infected cells by certain HLA-E–restricted T cell subsets, as shown in the case of cytomegalovirus (*9*). Alternatively, or in addition, inhibitory HLA-E may engender a tolerogenic effect that paradoxically prevents the establishment of productive viral infection, as described in a macaque model of simian immunodeficiency virus vaccination (*10*).

References and Notes

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