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 (β2m). In addition, we found that HLA-E levels are often underestimated, because a fraction of HLA-E is surface-expressed as a tightly β2m-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 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 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 multifaceted 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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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, 12). The second (B), hypothesized here on the basis of the previously observed HLA-E cross-reactivity with DT9, envisages a compound multifaceted effect. Because HLA-E requires peptides donated from the signal sequence of HLA-C for its stable assembly with β2m, 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.

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