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 (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).

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 (6).

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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References and Notes


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