References


To the editor:

HIV Env reduction postreceptor binding: a new target for AIDS treatment?

Markovic et al. confirmed recently a role for an oxido-reductase activity, presumed to be that of protein disulfide isomerase (PDI), in the events that follow HIV envelope (Env) binding to cellular receptors. PDI action is thought to enable structural rearrangement of Env that precedes virus-cell fusion. A role for PDI was first reported in the seminal study by Ryser et al in 1994, who observed that the presence of PDI inhibitors during HIV interaction with lymphoid cells impaired infection. We confirmed their study in 2001 and, additionally, addressed the step at which blockade occurs by showing that PDI co-clustered with CD4-enriched regions of the lymphocyte surface is required for HIV/cell fusion.3 At this stage, the precise mechanism of PDI involvement—reorganization of the Env disulfide network to enable the conformation changes required for fusion or alteration of thiol/disulfide content of other cell surface antigens involved in fusion—was unclear. Recently, in concomitantly accepted manuscripts, we4 and Ryser et al5 provided biochemical evidence that reduction of gp120 disulfide bonds by PDI during interaction with the lymphocyte surface was required for fusion. We concluded that 2 disulfide bonds were cleaved in the process.6 Markovic et al7 reported that reduction occurs within a multimeric CD4/CXCR4/Env/PDI complex induced by Env binding to the cell surface, which enables gp41 to reach the fusogenic 6-helix bundle conformation.

The data are significant, as they indicate a new area for anti-HIV intervention through development of thiol-interchange inhibitors such as the experimental anti-tumor sulfonylurea analogs6 and bactracin. Important steps in the process, however, remain unclear: the identification of which disulfides are cleaved and the precise stage in viral entry where cleavage occurs. The latter point is one of debate, as Env reduction has been observed following either CD41,3,5 or CXCR4 interaction.4 The capacity of the soluble forms of recombinant CD4 to promote Env binding to CXCR4 is more consistent with the PDI-independence of the Env-CXCR4 interaction.

That Env needs conversion by PDI in order to reach its fusogenic conformation highlights the role of cell surface catalysts in the generation of the fusion synapse and shows that the presence of the requisite receptors is not sufficient. In addition to Env, oxido-reduction of CD4 has been observed during HIV/cell fusion.3 Originally suggested as a requirement for fusion, we suggest, in the light of the data reported above, that CD4 redox change is a consequence of Env reduction and not an independent mechanism. Plausibly, the D2 domain, which does not play an active function in Env binding, acts in a donor/acceptor capacity to enable the gp120 reduction.

In addition to drug development, and as noted in a commentary here by Kornbluth,8 partially reduced Env may constitute a vaccine candidate capable of eliciting neutralizing antibodies directed against epitopes masked on the native antigen. Encouragingly, if the required antibodies could be induced, the half-life of the fusion intermediate at the cell surface appears sufficient4 to enable antibody binding to occur.

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References

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