Letters to the Editor

Can HIV p24 Be a Suitable Scaffold for Presenting Env Antigens?

Efforts to elicit protective immunity to HIV have resulted in unsatisfactory results (reviewed in reference 24). In particular, the elicitation of broadly reactive and cross-clade neutralizing antibodies (NAbs) represents an unprecedented challenge because of the intrinsic property of HIV to generate molecular and antigenic variants, escaping the immune surveillance (4).

However, cross-reactive neutralizing antibodies targeting the envelope glycoprotein can indeed arise during the natural course of HIV-1 infection (9, 11, 25, 33), and a few broadly neutralizing antibodies have been isolated from HIV-1-infected individuals. In particular, b12 and 2G12 bind to conserved epitopes in the gp120 subunit (6, 31) and 2F5 and 4E10 bind to conserved, contiguous epitopes in the gp41 subunit (18, 28). More recently, additional broadly neutralizing antibodies have been described, targeting discontinuous epitopes in trimeric structures (PG9 and PG16) (32), the CD4-binding site (HJ16, VRC01/2, and VRC03) (10, 35), or the V3 loop (1, 15, 21).

Strategies to elicit or expand such broadly reactive and cross-clade NAbs against HIV are currently pursued by several groups and are aimed at focusing the immune response on specific epitopes which can be either immunorecessive, cryptic, or transiently exposed. One of the optimal experimental strategies for this goal appears to be the selection of the minimal structural and antigenic epitopes in order to isolate them from all other confounding Env B-cell epitopes as well as from the shielding, N-linked glycans within the whole HIV envelope glycoprotein (5, 7, 20, 26, 27, 36). Such minimal epitopes can, indeed, be grafted in a constrained status onto appropriate heterologous protein scaffolds to mimic their antibody-bound conformation and possibly elicit their counterpart, broadly NAbs.

Along a similar path, the gp41 2F5-specific minimal epitope has very recently been grafted onto different protein scaffolds (19), inducing high titers of cross-reactive Abs (17). Similarly, the gp120 V3 loop has been grafted onto a cholera toxin subunit (CTB) scaffold, causing it to exhibit high-affinity binding to a large panel of broadly neutralizing monoclonal antibodies (MAbs) and induce high titers of anti-V3 antibodies with broad neutralization effects (30).

All such strategies, indeed, are based on scaffold structures which are antigenically “neutral” with respect to HIV and which aim at eliciting only anti-Env immune responses, which, if not sufficiently strong, broad, and sustained, may be insufficient for complete protection from HIV infection.

In this regard, scaffolds based on assembled HIV p24 capsid (CA) proteins would, indeed, represent an invaluable advancement. In fact, besides the presentation of relevant Env-neutralizing epitopes, it may also provide Gag epitopes for the elicitation of HIV nonneutralizing protective antibodies, which have previously been shown to be associated with a more delayed disease progression (2, 8, 12, 16, 29, 34). Furthermore, p24 is an abundant source of CD4 T-cell epitopes (3), and the induction of CD4+ T-helper-cell responses by scaffolds based on assembled HIV p24 CA proteins is highly probable.

In support of this approach, the ability of recombinant p24 capsid proteins to assemble in vitro, forming stable and soluble stand-alone nonenveloped capsomers without either cellular membranes or matrix (MA) or nucleocapsid (NC) Gag viral proteins, has recently been described (13, 22, 23). Based on such observations, the HIV p24 CA protein is potentially a highly attractive molecule to be used as a particulate protein scaffold for presenting dense repetitive arrays of minimal structural and antigenic HIV Env epitopes aimed at eliciting broadly NAbs.
Preliminary biocomputational analysis using the full Env V3 loop as proof of concept indicates that the HIV p24 CA protein has suitable acceptor sites for engrafting foreign epitopes without disrupting the formation of capsomer hexamer structures (Fig. 1) described by Ganser-Pornillos et al. (14) and that the V3 epitope does retain its antibody-bound conformation (Fig. 2).

Such observations strongly support the theoretical possibility of developing a scaffolding strategy based on p24 CA proteins displaying conformationally minimal structural and antigenic HIV Env epitopes. Unlike other strategies described to date, this strategy would provide the relevant advantage of presenting not only the Env broadly neutralizing epitopes but also the Gag epitopes for eliciting HIV nonneutralizing protective antibodies (2, 12, 34).

Studies to experimentally prove the efficacy of such a strategy are currently ongoing and are looking for a further approach to advance the efficacy of our global anti-HIV vaccine armamentarium.

REFERENCES

Luigi Buonaguro*
Maria Tagliamonte
Marina Lina Tornesello
Franco M. Buonaguro

Molecular Biology and Viral Oncogenesis Unit
Istituto Nazionale Tumori Fond. G. Pascale
80131 Naples, Italy

*Phone: 081-5903273
Fax: 081-5451276
E-mail: ircsvir@unina.it

Published ahead of print on 7 September 2011.