

EDITORIAL

The Autoimmunity Taught by HIV

Since the Eighties, when the Acquired Immunodeficiency Syndrome was first described, many signs of autoimmune dysfunction were observed in HIV-positive subjects, such as the B cell dysfunction, exemplified by the hyperproduction of antibodies and by the generation of anti-cell antibodies [1-3]. These anomalies were first associated to HIV-vs-host activity but subsequent investigations showed that some anti-cell antibodies could be interpreted as host-vs-HIV responses. Indeed, it was observed that some broadly neutralizing human antibodies elicited during the HIV infection also recognized cardiolipin and other phospholipids [4]. The finding led to suppose that these types of antibodies were restricted by mechanisms of host tolerance [5] or that HIV escaped host immunity taking advantage of molecular mimicry between host and self-antigens [6]. Notably, the studies concerning the follow-up of HIV patients receiving three broadly neutralizing antibodies, confirmed that only one of them showed a low level of *in vivo* autoreactivity, although no signs of autoimmune-related adverse events were observed in the study [7].

This issue of *Autoimmunity* focuses on some autoimmune-like humoral responses commonly observed in the course of HIV infection, including some anti-cell molecules (anti-CD4, anti-HLA, anti-CCR5). The mechanisms underlying their generation and the implications for host immunity and on their possible outfalls in antiviral therapy will also be considered.

Anti-cell antibodies usually develop when a breakage in the boundary between immunity and tolerance occurs. The review by Holl *et al.* describes the mechanisms that usually control auto-reactivity and tolerance during B cell ontogenesis and prevent the generation of B cell clones expressing rare antibody specificities. Anti-CD4 antibodies were often observed in the course of HIV infection, as a result of the interaction between viral envelope, cell membrane and its cellular receptors, such as CD4 and CCR5 [8]. Depending on their interaction with gp120-CD4 complex, these antibodies may direct the infection in two opposite directions, either contributing to HIV spread and to depletion of T helper lymphocytes, or preventing HIV entry and the progressive disruption of host immunity. Breda *et al.* makes an overview of the antiviral potential role of anti-CD4 antibodies in subjects who are naturally resistant to HIV, and their promising applications in anti-HIV therapy. Allo-immunization has been used in clinics and has already shown its protective potential to HIV infection [9, 10]. Smith and Dalgleish address the mechanisms of molecular mimicry fostering the generation of anti-HLA antibodies and their possible modes of protection from HIV. CCR5 is the major coreceptor enabling HIV infection in human mucosa, and is a key molecular target for development of HIV entry inhibitors, such as small drugs or monoclonal antibodies [11, 12]. Natural anti-CCR5 antibodies have been described in HIV-exposed uninfected people and in Long-Term-Non Progressing seropositive patients, supporting their role in protecting the host from HIV infection [13, 14]. Russo *et al.* review the issue of anti-CCR5 antibodies, their biological functions and the mechanisms involved in their generation, either natural and therapeutic. Recombinant DNA technologies and protein engineering offer many ways to improve antibodies originated in response to natural stimuli or to immunization, changing their affinity or their biological properties. Frigerio *et al.* summarizes the advances in molecular technologies which can be helpful in reshaping antibodies, in producing versatile tools for investigation and innovative “bullets” for HIV targeting.

REFERENCES

- [1] De Milito A, Nilsson A, Titanji K, *et al.* Mechanisms of hypergammaglobulinemia and impaired antigen-specific humoral immunity in HIV-1 infection. *Blood* 2004; 103: 2180-6.
- [2] Friedli F, Rieben R, Wegmuller E, Moerenhout M, Nydegger UE. Normal levels of allo- but increased levels of potentially autoreactive antibodies against ABO histo-blood group antigens in AIDS patients. *Clin Immunol Immunopathol* 1996; 80: 96-100.
- [3] Hunziker L, Recher M, Macpherson AJ, *et al.* Hypergammaglobulinemia and autoantibody induction mechanisms in viral infections. *Nat Immunol* 2003; 4: 343-9.

- [4] Haynes BF, Fleming J, St Clair EW, *et al.* Cardiolipin polyspecific autoreactivity in two broadly neutralizing HIV-1 antibodies. *Science* 2005; 308: 1906-8.
- [5] Haynes BF, Moody MA, Verkoczy L, Kelsoe G, Alam SM. Antibody polyspecificity and neutralization of HIV-1: a hypothesis. *Hum Antibodies* 2005; 14: 59-67.
- [6] Scherer EM, Zwick MB, Teyton L, Burton DR. Difficulties in eliciting broadly neutralizing anti-HIV antibodies are not explained by cardiolipin autoreactivity. *AIDS* 2007; 21: 2131-9.
- [7] Vcelar B, Stiegler G, Wolf HM, *et al.* Reassessment of autoreactivity of the broadly neutralizing HIV antibodies 4E10 and 2F5 and retrospective analysis of clinical safety data. *AIDS* 2007; 21: 2161-70.
- [8] Beretta A, Furci L, Burastero S, *et al.* HIV-1-specific immunity in persistently seronegative individuals at high risk for HIV infection. *Immunol Lett* 1996; 51: 39-43.
- [9] Spruth M, Stoiber H, Kacani L, Schonitzer D, Dierich MP. Neutralization of HIV type 1 by alloimmune sera derived from polytransfused patients. *AIDS Res Hum Retroviruses* 1999; 15: 533-43.
- [10] Wang Y, Underwood J, Vaughan R, *et al.* Allo-immunization elicits CCR5 antibodies, SDF-1 chemokines, and CD8-suppressor factors that inhibit transmission of R5 and X4 HIV-1 in women. *Clin Exp Immunol* 2002; 129: 493-501.
- [11] Corbeau P, Reynes J. CCR5 antagonism in HIV infection: ways, effects, and side effects. *AIDS* 2009; 23: 1931-43.
- [12] Olson WC, Jacobson JM. CCR5 monoclonal antibodies for HIV-1 therapy. *Curr Opin HIV AIDS* 2009; 4: 104-11.
- [13] Barassi C, Lazzarin A, Lopalco L. CCR5-specific mucosal IgA in saliva and genital fluids of HIV-exposed seronegative subjects. *Blood* 2004; 104: 2205-6.
- [14] Pastori C, Weiser B, Barassi C, *et al.* Long lasting CCR5 internalization by antibodies in a subset of Long Term Non Progressors: a possible protective effect against disease progression. *Blood* 2006; 107: 4825-33.

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