



Opinion

Structure-Based Reverse Vaccinology Did not Succeed in Developing an Effective Vaccine Against HIV-1 Because the Binding of Viral Epitopes with Antibodies Did Not Induce a Protective Immunogenicity in the Epitopes

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Terms like immunogen and immunogenicity may suggest that epitopes are able to generate immune responses, although they only trigger in the host a series of reactions with B-cell receptors that eventually leads the Immune System (IS) to produce a variety of protective antibodies. Much of HIV vaccine research concentrates on elucidating the structure of the HIV epitopes present on the glycoprotein spikes of the virion because these epitopes are potential vaccine immunogens that can induce protective antibodies against viral infection. The approach known as Structure-Based Reverse Vaccinology (SBRV) analyses the 3D structure of HIV epitopes bound to antibodies since investigators know that if the epitope did bind strongly to an antibody, it would also be able to induce neutralising antibodies when used as a vaccine [1]. In bacteriology, Reverse Vaccinology (RV) refers to the strategy of predicting all the potential vaccine immunogens that a bacterium is able to express, which can be tested empirically. In virology, the reverse engineering approach was unsuccessful [2] because the viral antigens, which recognized monoclonal antibodies better, did not acquire the immunogenic ability of eliciting protective antibodies [3]. Vaccinologists were unable to develop an HIV-1 vaccine by rational design because their attempts were based on a number of erroneous assumptions and a confusion between immunogenicity and antigenicity, since an antigenic epitope that binds with a neutralising antibody is not necessarily able to induce a protective immune response [1]. It is indeed always imperative to verify empirically that a potential vaccine

candidate possesses an adequate protective immunogenicity [4] since rational vaccine design based only on antigenicity will not reveal which immunogens would be able to lead to a protective immune response [5]. The natural immune response in HIV-1 infected individuals also does not clear the infection, which indicates that a vaccine must achieve something that the IS is not able to do when it encounters the virus. An additional impediment is that HIV can integrate into the host genome which then conceals the virus from immune recognition while the virus also exhibits a pronounced antigenic variability that progressively destroys the IS. The antigenic structures visualised in epitope-paratope complexes are always very different from the structures of the binding sites in the free molecules before they have been altered by mutual adaptation and induced fit; however, for achieving protective immunogenicity the binding sites of viral antibodies must previously have been altered during their interaction with complementary epitopes which endows the paratopes with an induced protective immunogenicity that is essential for vaccinal efficacy [6].

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