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Can antigenic studies of HIV Env spikes using human monoclonal antibodies inform the design of an HIV vaccine?

The antigenicity of HIV Env trimers is a chemical property that originates in small regions of the Env protein known as epitopes that are able to bind to small binding sites, known as paratopes, found in the binding pockets of antibodies (Ab) raised against Env. Each Ab binding pocket made up of 60-70 hypervariable residues always harbours several overlapping or non-overlapping paratopes of about 10-20 residues that can bind to related or unrelated epitopes. This means that every Ab , as well as every B cell receptor (BCR), which is an Ab possessing a tail that anchors it in the B cell membrane is always polyspecific for numerous epitopes but never monospecific for a single epitope. It must be appreciated that the chemical environment is not the same when an epitope recognizes a free Ab molecule or a BCR receptor embedded in a lipid membrane. This means that the antigenic epitope bound to a free Ab is unlikely to be identical with what is usually assumed to be the same epitope when it acts as an immunogen bound to a BCR. It used to be believed that an epitope was defined both by its antigeniciy and by its ability to elicit the antibody it recognizes, which made the existence of the epitope depend on the biological properties of a particular immune system (IS). This belief is still prevalent with many vaccinologists although it is at odds with the fact that antigenic and immunogenic properties of a protein antigen can be located in different parts of the molecule. This is one of the reasons why an Env epitope binding to a polyspecific, neutralizing Ab is usually not able to induce similar neutralizing Abs when it is used for immunizing humans. It is often overlooked that the advantages of Mabs for dissecting immune responses have led to an analytical bias which emphasizes immune responses to single epitopes although it is well-known that protective immune responses are always polyclonal. Env antigenic sites such as the CD4 binding site or the VIV2 site always consist of several overlapping epitopes that induce a collective immune response which cannot be elicited by a single epitope. Several other difficulties that impede the use of antigenic information on Env for the so-called design of HIV vaccines will be discussed. These include 1) the considerable plasticity of Env during the infection process which leads to considerable conformational changes, 2) paratopes consist of residues located on highly flexible loops while epitopes are frequently located in mobile regions of antigens, 3) the dynamic binding process of an epitope to a paratope involves major induced fit phenomena, 4) the structure of bound sites can differ considerably from that of unbound sites which makes it difficult to know exactly the structure of immunogens bound to BCRs, 5) structural vaccinologists only concentrate their attention on recognition processes between single epitope-paratope pairs and tend to overlook the fact that the biological properties of individual ISs determine whether protected Abs will be produced. Structure-based reverse vaccinology can only improve the binding capacity (i.e. the antigenicity) of single epitopes and cannot "design" vaccine immunogens. It is the host Ab gene repertoire and the presence of helper and suppressor T cells and of numerous immunological regulatory mechanisms in the IS that determine if candidate Env immunogens have the potential to become an effective HIV vaccine.

Biography

Marc H V Van Regenmortel is currently an Emeritus Research Director at the CNRS (French National Research Center) in the School of Biotechnology of the University of Strasbourg, France. He was for 22 years Director of the Immunochemistry Laboratory at the CNRS Molecular Biology Institute in Strasbourg and previously was a professor at several Universities in South Africa and France. He served (1984-1990) as Vice Chairman and Chairman of the Virology Division of the International Union of Microbiological Societies (IUMS) and was Secretary General of IUMS from 1990 to 1999. He was also for six years (1996-2002) President of the International Committee on Taxonomy of Viruses. He supervised the research work of 30 PhD students and has published 400 research and review papers as well as 17 books in the fields of Virology and Immunochemistry. In 2009 he co-edited with Brian Mahy of the CDC in Atlanta, the third edition of the Encyclopedia of Virology in 5 volumes published by Elsevier. He is currently Editor-in-Chief of Archives of Virology, Journal of Molecular Recognition and Journal of AIDS & Clinical Research; An Associate Editor of Advances in Virus Research, Frontiers in Immunotherapies and Vaccines, Journal of Immunological Methods, ISRN Immunology, Bionomina and Expert Reviews of Proteomics.

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