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The quest for highly specific anti-HIV neutralizing monoclonal antibodies: The Holy Grail of reductionist structure-based vaccinology

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Abstract

The concept of antibody specificity has been difficult to define (1, 2). The dissection of immune responses with monoclonal antibodies (mAbs) has fostered the illusion that an Ab molecule can be specific for a multiepitopic protein or virus although an Ab can in fact only possess a limited specificity for a single epitope of an antigen. An immunoglobulin (Ig) such as an IgG molecule possesses two identical binding regions of about 60 hypervariable residues that harbor numerous paratopes of 10-15 residues able to bind to various epitopes; The presence of multiple paratopes in every Ig means that antibodies are always polyspecific and able to cross react with many different antigens, a situation which is responsible for the degeneracy of the immune system (3,4). The specificity of a polyclonal antiserum directed to a protein arises from the binding activity of the numerous different Abs present in the serum that recognize different epitopes in the protein and the resultant collective specificity is always higher than the specificity of a single mAb directed to the protein antigen. Although each polyspecific Ab in the antiserum cross reacts with numerous epitopes not necessarily present in the antigen , these cross reactive epitopes are different for each individual Ab , with the result that the collective cross reactive potential of the antiserum is diluted out and the individual cross reactivities of the different Abs are masked (5 ,6) .The cross reactivity of a single mAb is not masked in this manner which could make it appear to be less specific than the antiserum. The ability of the immune system to specifically recognize virtually any antigen is not due to the existence of innumerable antibodies, recognizing a unique epitope present only in that antigen, but is due to the combinatorial effect of polyspecific antibodies recognizing different epitopes on the same antigen molecule.

All attempts to develop HIV vaccines by structure-based reverse vaccinology (7) using the structure of individual epitope-paratope pairs have failed so far (6, 8). This is due to the impossibility of reducing the neutralizing anti-viral immune response to the reactivity of a single mAb. There is no reason to expect that a single epitope, reverse-engineered to fit one mAb, would possess the immunogenic capacity of inducing a neutralizing polyclonal antibody response. Such an unwarranted expectation is based on a confusion between antigenicity which is a chemical property of antigens and immunogenicity which is a biological property dependent on many features of the immune system that are independent of the antigen. Furthermore, by focusing vaccine design on single epitope - paratope pairs, the neutralizing synergy that usually occurs with polyclonal antibody responses will be missed .One synergy mechanism is that binding to a first antibody alters the conformation of the antigen, making new epitopes accessible to other Abs.

Passive immunization to achieve HIV immunoprophylaxis by gene therapy, using antibody- encoding genes derived from broadly neutralizing mAbs is a novel strategy that is currently receiving considerable attention (9, 10). For the reasons mentioned above, it seems likely that successful vector immunoprophylaxis in a human population would require the combined transfer of genes from numerous neutralizing mAbs, a requirement that will complicate considerably the design of human clinical trials and the application of this vaccination approach.

(1) Day, E (1990) Advanced Immunochemistry, 2nd edition, John Wiley, New York (2) Eisen, HN, Chakraborty, AK (2010) Proc Natl Acad Sci USA 107: 22373-22380 (3) Wucherpfennig, KW et al (2007) Semin Immunol 19: 216-224 (4) Van Regenmortel MHV (2012) Arch Virol 157: 1-20 (5) Richards FF et al (1975) Science 187: 130-137 (6) Van Regenmortel MHV (2012) Frontiers Immunol doi: 10.3389/ fimmu.2012.00194 (7) Van Regenmortel MHV (2011) Vaccine 29: 7875 (8) Van Regenmortel MHV (2011) J Mol Recognit 24: 741-753 (9) West AP et al (2012) J Virol 86: 195-202 (10) Balazs, AB, West, AP (2013) Nat Immunol 14: 1-5

Biography

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