Tricking the Immune System into Making the Antibodies We Want

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Generation of broadly neutralizing (bN) antibodies against the HIV envelope glycoprotein (Env) of HIV following immunization is one of the goals in HIV vaccine research, since such antibodies have been shown to offer protection in experimental HIV/SHIV models. Shortly after HIV infection, a rapid production of narrow neutralizing (nN) antibodies is induced by Env, while bN antibodies appear only in some individuals and several years post-infection. Similarly, attempts to elicit bN antibodies by vaccination often result in the production of non-, or narrow neutralizing antibodies, but not bN antibodies.

The urge to understand the mechanism behind the production of nN over bN antibodies following immunization with Env prompted Dr. Andrew McGuire of the Stamatatos Lab in the Vaccine and Infectious Disease Division (VIDD) to investigate the matter. In a paper published last December in *Science*, Dr. McGuire led us through the story of the generation of neutralizing antibodies against HIV. "This study sheds some light onto why previous HIV vaccine efforts are skewing the immune response towards making non-protective antibody responses", commented Dr. McGuire.

The researchers studied the interactions of Env with B cell receptors, the progenitors of antibodies. The B cell receptors are antibody precursors expressed on the surface of naïve B cells. When a B cell receptor recognizes a foreign antigen the B cell becomes activated, internalizes the antigen, and begins to divide and mutate the B cell receptor gene. This process occurs many times and the end result is a number of daughter B cells that secrete soluble version of the B cell receptors (aka mature or mutated antibodies) that bind the initial antigen better than the original precursor (germline). Even though bN and nN antibodies target the same Env regions, the study found that germline bN antibodies recognized Env poorly, while nN antibodies were really good at it. Furthermore, naïve B cell progenitors of bN antibodies, in contrast to progenitors of nN antibodies, are not stimulated by recombinant Env proteins and do not internalize them.

In a previously published paper, Dr. McGuire and coworkers showed that disruption of three Env glycosylation sites resulted in an increased binding and activation of B cells producing bN antibodies. Although the mutated form (glycan deleted) of Env was able to activate B cells producing

bN antibodies, it preferentially activated those producing nN antibodies. Following up on these findings, the investigators showed that further deletion of the variable loops V1, V2 and V3 (ΔV1-3) of the glycan-deleted protein reduces the binding affinity of nN antibodies recognizing the CD4 binding site of Env and the capacity to activate B cells producing such antibodies. In a mixed culture of B cells producing nN, bN and non-Env specific antibodies, the glycan deleted form of Env lacking the variable loops stimulated exclusively B cells producing bN antibodies at low concentrations and preferentially at high concentrations.

One of the mechanisms that controls antibody production in germinal centers is a negative feedback loop mediated by high affinity antibodies that bind to and mask antigen blocking the activation and proliferation of B cells expressing low affinity B-cell receptors (BCRs). Since the affinity of bN antibodies (and the BCRs expressed on B cell secreting such antibodies) for the modified form of Env is high as compared to that of nN antibodies, bN antibodies should have an advantage when such protein is used as an immunogen. Indeed, the presence of nN antibodies decreased the activation of bN antibody producing B cells in vitro when the glycan deleted form was used as immunogen, but this inhibitory effect was reduced when the variable loops of the protein were deleted as well.

In sum, a series of Env modifications favored the generation of bN antibodies. "We hope that the novel immunogen described in the study will perform better than those used in the past, but we'll have to get it into people to find out." said Dr. McGuire. "In the current study, we focused on one epitope region of Env (the CD4 binding site), but there are many others, and the techniques developed in this study can be used to compare the activation of B cell progenitors of broad and narrow neutralizing antibodies targeting other regions of Env, or even be applied to vaccine design against other pathogens." Needless to say, the results published in this study open the path to a novel approach and to previously unexplored possibilities for vaccine research.

McGuire AT, Dreyer AM, Carbonetti S, Lippy A, Glenn J, Scheid JF, Mouquet H, Stamatatos L. 2014. Antigen modification regulates competition of broad and narrow neutralizing HIV antibodies. Science, 346(6215):1380-3.

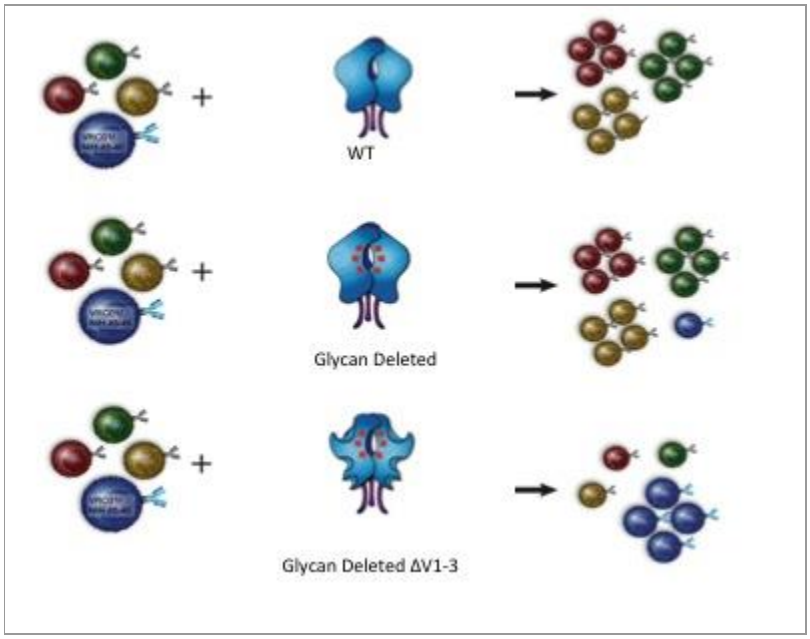

Image provided by Dr. Andrew McGuire

The figure summarizes the study. The blue colored B cells are the targets that should be stimulated to produce bN antibodies. Wildtype Env (top) stimulates everything but the target B cells. The glycan deleted Env stimulates the blue B cells but preferentially activates the other B cell types (middle). When the variable regions are removed as well, the target B cells are preferentially stimulated.