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The battle against HIV has long been hampered by the inability to develop an effective vaccine. Dennis Burton and colleagues now describe a new approach for tackling this pathogen — they have found that immunizing cows with an immunogen that mimics the HIV envelope glycoprotein (Env) rapidly elicits broadly neutralizing antibodies against HIV.

To date, scientists have been unable to generate broadly neutralizing antibodies to HIV by vaccinating humans. Part of the problem has been that the Env of HIV is highly diverse and also covered by a dense ‘glycan shield’. Broadly neutralizing antibodies that have been isolated from individuals who are chronically infected with HIV contain complementarity-determining region 3 (CDR3) loops in their heavy chains that are much longer than normal. However, most vertebrate species produce antibodies containing heavy chain CDR3 loops that are restricted to 12–16 amino acids, which makes it difficult to generate broadly neutralizing antibodies in these species following immunization against HIV. By contrast, cows produce antibodies with heavy chain CDR3 loops that are on average ~26 amino acids in length and, moreover, cows have an ‘ultralong’ subset of antibodies that can have heavy chain CDR3 loops of more than 70 amino acids in length.

The authors hypothesized that these unusual features of cow antibodies may improve the ease of generating broadly neutralizing antibodies against HIV in these animals. They immunized four cows with BG505 SOSIP (an immunogen that mimics the HIV Env) and found that the animals rapidly developed potent broad neutralizing activity in their serum. In one of the cows, priming and a single boost with BG505 SOSIP led to the development of serum that neutralized 20% of HIV clades (117 isolates were tested in total) by 42 days, and by 381 days serum from this cow neutralized 96% of HIV isolates. By comparison, it has been found to take at least 5 years for broadly neutralizing antibodies to develop in HIV-infected humans.

The authors isolated ten broadly neutralizing monoclonal antibodies from this animal and found that all of these antibodies contained ultralong heavy chain CDR3 loops. One monoclonal antibody showed a neutralizing breadth of 72% and electron microscopy studies showed that this and another broadly neutralizing antibody bound to the CD4 binding site (CD4bs) of HIV Env. The CD4bs epitope is recessed and occluded on the native HIV Env and human neutralizing antibodies find it difficult to access. However, the long heavy chain CDR3 loops that are present in cow antibodies allow them to access this normally ‘hidden’ epitope, apparently with relative ease. The authors suggest that cows could be used to rapidly generate broadly neutralizing antibodies that could be used prophylactically or therapeutically against HIV and possibly other pathogens, such as malaria, that have evolved to evade human antibody responses.

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