COMPETING FINANCIAL INTERESTS
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A sweet surprise for HIV broadly neutralizing antibodies

Johannes P M Langedijk & Hanneke Schuitemaker

The production of cross-reactive neutralizing antibodies is the ultimate goal in HIV vaccine development, but no immunogen other than HIV itself has been able to elicit this type of humoral immunity. In natural HIV infections, these antibodies take several years to develop. A new study sheds light on what may be causing this delay in neutralizing antibody development (pages 1688–1692).

The HIV-1 envelope spike, composed of gp120 and gp41 trimers, is extremely variable, which challenges the design of a vaccine that needs to protect against the majority of, if not all, circulating HIV-1 strains. The only conserved protein surfaces on the envelope spike that can be targeted by broadly neutralizing antibodies are the relatively recessed receptor-binding site and a transiently exposed hydrophobic membrane-proximal external region (MPER) at the base of the spike's stem. The remaining surface of the spike is highly variable, hidden by conformational masking or shielded by carbohydrates that make up more than half of the molecular weight of the envelope molecule. Interestingly, these carbohydrates, which are usually considered immunologically silent self antigens that shield the protein surface, are in fact a major component of the epitope of a recently discovered new class of very potent and broadly neutralizing antibodies against HIV[1,2]. These antibodies recognize the high-mannose component of two specific, closely spaced carbohydrates in combination with a small patch of protein surface and can be grouped into antibodies that mainly bind the glycan at position 160 of the envelope molecule and those that bind the glycan at position 332 (refs. 3,4). Notably, these glycan-based epitopes seem to be even more commonly recognized by antibodies in HIV-infected people than the established targets CD4bs and MPER.

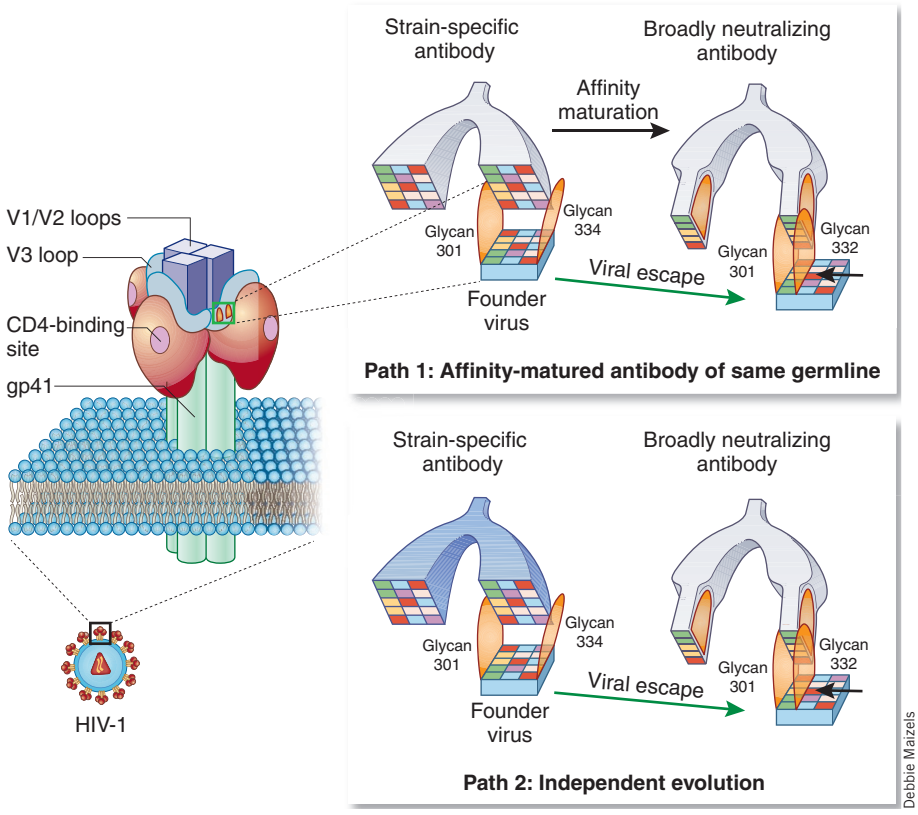

Figure 1 A new pathway for evolution of HIV-1 broadly neutralizing antibodies. Broadly neutralizing antibodies can take several years to develop after natural infection by HIV. This may be due to the time-consuming process of affinity maturation (path 1) or the necessity to generate completely new antibodies (path 2) as a result of the initial absence of an epitope on the founder virus. The data of Moore *et al.*[9] imply that the emergence of a glycan at position 332 in the HIV-1 envelope spike, which allows the virus to escape the initial antibody response, creates a new epitope for a broadly neutralizing antibody. This knowledge may subsequently be applied to develop heterologous prime–boost regimens in vaccination strategies against HIV. The left images in paths 1 and 2 show the variable epitope, consisting of a large protein surface with many different amino acids (indicated as different colors), and the images on the right show the glycan canyon that is created by the glycan shift from position 334 to 332, resulting in a conserved epitope with a small protein surface fenced by two conserved high-mannose glycans in orange. Complementary antibodies are shown in the context of the different HIV-1 epitopes.

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The higher than initially expected prevalence of broadly neutralizing antibodies in HIV-infected individuals[5–7] has sparked optimism of the possibility of making a vaccine that can elicit them. However, the time it takes for HIV-infected people to develop these antibodies (which can be up to years[8]) poses a big hurdle to HIV vaccine development. The article by Moore *et al.*[9] in this issue of *Nature Medicine* may shed some light into why the process of developing broadly neutralizing antibodies takes so long. The authors describe an HIV evolutionary pathway in which viral escape from a first antibody response that is directed against an epitope in the viral envelope C3 region is mediated through a shift of an envelope glycan from position 334 to position 332 (**Fig. 1**). This creates a new epitope that subsequently elicits the production of broadly neutralizing antibodies by the host immune response. Therefore, the escape viral variant with the relocated glycan, not the founder virus, is responsible for eliciting a broadly neutralizing antibody response.

The new data of Moore *et al.*[9] can be better understood in the context of the cocrystal structure of PGT128, a glycan-dependent broadly neutralizing antibody against HIV-1, in complex with the HIV-1 envelope gp120 outer domain[4]. This structure indicates that recognition of the HIV-1 envelope by PGT128 requires two closely spaced glycans at positions 301 and 332 at the base of the third variable domain (V3) in gp120, which form a glycan canyon that can be penetrated by the long CDR3 region of this antibody[4] (**Fig. 1**). The HIV-1 escape mutation described by Moore *et al.*[9] shifts an N-linked glycan from position 334 to position 332. This reshapes the epitope from one that binds an HIV strain-specific antibody with a relatively large footprint on the variable protein surface of the spike into one with a glycan canyon with enough non-selfness for immune recognition and a smaller protein surface, thus creating a new conserved viral epitope (**Fig. 1**). Interestingly, Moore *et al.*[9] discovered that there is a similar evolutionary path for the creation of the highly conserved glycan 160–based epitope of HIV-1. They found that the appearance of virus variants with the 332 glycan later in infection is common among HIV-1 clade C viruses, although not all patients can mount a broadly neutralizing immune response to that epitope. This implies that there are still unknown factors that influence whether broadly neutralizing antibodies will develop or not.

The identification of this HIV evolutionary pathway that drives the breadth of the host humoral immune response may provide new clues for the development of vaccine regimens. Although it is not known whether the first type-specific antibodies and the subsequent broadly neutralizing antibodies in the HIV-infected patients studied by Moore *et al.*[9] were from the same germ line, the pathway that they describe may indicate that affinity maturation of the first type-specific antibody is driven by the HIV-1 escape variant, affecting the broadly neutralizing antibody specificity. Their results could also imply that heterologous prime–boost regimens using different HIV envelope epitopes may be required to elicit broadly neutralizing humoral immunity. The absence of the 332 glycan in a substantial proportion of HIV-1 clade C founder viruses may suggest that a vaccine containing only this epitope will have insufficient efficacy. Therefore, the inclusion of other HIV-1 epitopes, for instance, an epitope that includes the glycan at position 160, should be considered, because this epitope is relatively conserved among founder viruses. Finally, similar evolutionary studies on virus–host interactions in HIV-infected individuals who developed different broadly neutralizing antibody specificities will be required to obtain a more complete picture of potential heterologous prime–boost vaccine regimens that may be used to elicit protective broadly neutralizing antibodies.

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A sirtuin link between metabolism and heart disease

Keith A Webster

The sirtuins (SIRTs) have gained preeminence for their roles in the response to caloric restriction and the regulation of aging and lifespan. A new study now identifies gene promoters that bind the transcription factor AP1 as targets for silencing by SIRT6, providing possible links between SIRT6 deficiency and dysregulation of insulin-like growth factor signaling, hypertrophic cardiomyopathy and heart failure (pages 1643–1650).

The SIRTs are a family of class III histone deacetylases (HDACs), distinguished from other HDAC classes by their requirement for nicotinamide adenine dinucleotide (NAD) in the deacetylation reaction. SIRTs can catalyze deacetylation of histone and nonhistone lysines. The requirement for NAD constitutes an ancient and evolutionarily conserved mechanism that may link the expression of SIRT-regulated genes with metabolism and nutritional state[1].

SIRTs were first discovered in yeast, in which an extra copy of *SIR2* was shown to extend lifespan by 50%, whereas its deletion shortened lifespan[1]. In worms (*Caenorhabditis elegans*) and flies (*Drosophila melanogaster*) the respective SIR2 homologs seemed to similarly regulate lifespan, and in worms this regulation was found to be mediated by DAF-16, a homolog of human Forkhead (FOXO) transcription factors that regulate stress-related genes, apoptotic factors, antioxidants and metabolism[2,3]. Regulation of glucose homeostasis is a recurring theme linking SIRTs with caloric restriction, aging and lifespan throughout evolution. Daf2, an insulin-like receptor that regulates PI3K, also regulates DAF-16 and is downregulated by Sir2 or caloric restriction[4].

Compelling evidence now implicates each of the mammalian nuclear SIRTs 1, 6 and 7 in the regulation of aging, with links to metabolism, caloric restriction and, especially in the case of SIRT6, glucose homeostasis and the insulin

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