Interpreting Antibody Responses to EIAV Proteins that Vary

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Antigenic variation is a result of changes in the protein sequence of agents which are caused by changes in the nucleic acid sequence that determine which amino acids are used to make the protein. Changes in nucleic acid sequence are caused by different mechanisms in different agents.

In lentiviruses—including equine infectious anemia virus (EIAV), caprine arthritis and encephalitis virus (CAEV), ovine progressive pneumonia virus (OPPV), feline immunodeficiency virus (FIV), human immunodeficiency virus (HIV) and others—amino acid changes occur in all the proteins the virus makes. These changes occur when a DNA copy is made from viral RNA after a cell is infected because about one in 5000 nucleotides used to make the DNA is wrong. This is not corrected because the reverse transcriptase (RNA-dependent DNA polymerase) which catalyses the reaction does not have the proof-reading capacity attributed to other DNA polymerases. Therefore, one or two random mutations occur each time a DNA copy of the approximately 8000 nucleotide viral RNA is made. During virus production, the mutated DNA copy is integrated into the infected cell's genome and then RNA and subsequently protein are made. Some of this new RNA is packaged into progeny virus which carries the mutations to newly infected cells to repeat the cycle. Since the mutations are random, amino acid changes occur in every protein that the virus makes.

Why then does the envelope protein gp90 of EIAV have more mutations when the sequence is actually determined than do other proteins like p26? The answer is selection. In this case, the selective pressures that determine which mutant viruses survive are the immune response of the host and the survivability of the mutants. Examples that affect virus survivability are that some mutations are lethal, some may infect cells better or worse, and some may replicate faster or slower. Rapid changes in gp90 are best explained by the host immune response, in particular, neutralizing antibody. Neutralizing antibody is made to gp90 of the infecting virus and prevents infection of new cells by any virus with the same gp90. Therefore, for the continued infection which occurs with EIAV, viruses which have mutations in gp90 occur which cannot be recognized by existing neutralizing antibody in the horse. Only those gp90 mutants can infect new cells.

Since neutralizing antibody does not bind to p26 which is an internal capsid protein of the virus, what is the explanation for amino acid changes in p26 which can be as high as 12%? One explanation is selection by cytotoxic T lymphocytes (CTL) which recognize and kill infected cells which present p26 epitopes bound to MHC class I molecules on their surface. Once these CTL are present, there is a selective advantage for mutant viruses which have amino acid changes in the recognized epitopes. Another explanation is selection based on mutations that affect survivability that were listed in the previous paragraph.

If antigenic variation occurs in p26, how can protein derived from a single recombinant bacterium used in the VMRD AGID and cELISA tests detect antibody in the serum of horses infected with viruses with amino acid changes in p26? First, the maximum p26 amino acid difference described is 12%, so shared epitopes remain and/or mutated epitopes cross-react. Second, other common epitopes are present and stable in p26 because mutations in these regions do not result in viable virus or competitive virus. Such common epitopes are likely located in regions of the protein required for function. In addition, there are common epitopes in functional regions of gp90. These explanations may account for the initial observation that p26 derived from a single virus strain could be used to detect serum antibody from horses infected with laboratory and field strains.