SIV envelope evolution and virus virulence
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Chapter 7

General Discussion
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The structure and function of viral genes and their interaction with cellular factors greatly influence the events during infection. Viral variation of the env in human infections is governed by both functional and epidemiological variables. It is difficult to trace due to the usually unknown infectious inoculum, and the detection of infection well past seroconversion. In order to study the human infection we have used an analogous animal model. SIV is African in origin, and in Asian non-human primates it induces AIDS, where as in its “natural host” species of African origin it is nonpathogenic. The infection in the African nonhuman primates is species specific and there are now eight separate strains of SIV which have been characterized (11,12,14). The SIV strain most closely related to human immunodeficiency virus type 2 (HIV-2) is SIVsm, the strain specific to the sooty mangabey (Cercocebus atys (8)). The experimental infection of Asian primates with SIV allows the study of the viral infection with a known strain of the virus from the moment of infection. The sequencing of large numbers of clones of the env reveals the genetic imprint made on the virus in time.

A preponderance of nonsynonymous nucleic acid changes is seen as evidence of adaptive evolution (classically known as Darwinian evolution, or the opposite form of selection to the neutral theory (13)). The high rate of amino acid change belies a biological pressure upon the proteins translated from the nucleic acid of the organism, and from there a selection from the pool of available genomes (which is very large in SIV infection). The reference to the competing models (Darwinian and neutral) is important as the evolution seen during infection of SIVsm in a new species is rapid and punctuated (20). Evolution of the env takes place at an extremely rapid rate during the initial infections but then moves towards a steady state of low variation. The two modes of variation (synonymous and nonsynonymous) are shown to vary dramatically according to the time after cross-species transmission. The decrease in variation coincides with the increase in virulence, and the markedly shortened asymptomatic period before progression to AIDS. Variation in codon usage between the variable (external), and the constant (internal) regions allows the virus to adjust at different rates in different regions to changes caused by mistakes in reverse transcription, and may be a possible mechanism of increasing amino acid variation to escape immune selection.

The clustering of env sequences according to passage and pathogenicity shows that variation found during passage takes place in a structured manner. Likelihood mapping (17,19) showed that phylogenetic reconstruction of the passage was possible because a high percentage of the env nucleic acids sequenced contained tree-like data. The use of quartet puzzling (18) to produce the phylogenies showed a correlation between the env sequences, number of passages, and increased pathogenicity.

Originally the T cell CD4 receptor was thought to be the only mediator of binding and entry of HIV and SIV. Inconclusive inhibition of binding and entry by Abs led to the belief that there must be other cellular receptors in use by these viruses, and the cloning of the first and recognition of the other “orphan” coreceptors was the beginning of the understanding of tropism during infection. What were termed coreceptors are now known to be able to support binding and infection without the use of CD4 in some cases. The genetic variation in the env and its biological significance was shown to differ with the situation in HIV-1 in humans (5), where the env follows similar patterns of variation but the biological pattern of infection
varies with the switch from CCR5 use to CXCR4 use late in infection. Switches in coreceptor use from CCR5 (macrophage tropic virus) to CXCR4 (T cell tropic virus) herald the progression to AIDS in some cases (5,7). In the SIVsm transmission there was no change in coreceptor usage throughout the passage. The variation in the env would lead one to believe that it played a role in the increased pathogenicity. The lack of variation of coreceptor usage may mean the changes seen in the env are for increased binding of the receptor, and or coreceptors used. The charted changes in the env show that in later passages some clones are found that were not seen in the earlier passages, but were present in the primary inoculum (1). Large quasispecies can dominate, or suppress, fitter variants (6) simply by occupying the available target cells. In *in vitro* studies decreasing the size of the quasispecies, or dilute passage, can bring out variants not seen earlier in infection (16). The decreasing heterogeneity of the quasispecies during passage did not obscure the earlier hidden (or minority and thus not sampled) variants. In passage three (P3S-3, P3D-1 & 3) variants known to exist in the primary inoculum were present at a percentage high enough to be found during isolation from the serum.

Viral load is a clinical marker of the health of the HIV infected, especially when under drug, or multi-drug treatment, a rise in viral load can mean the beginning of the failure of intervention as mutants arise able to replicate while under treatment. During the serial passage the virus load increased until the third passage. The virus load increased as the genetic heterogeneity of the quasispecies decreased. Population passages cause vast gains in growth rates during each large quasispecies infection (4,15). The large number of genomes present increases the chances that there is a very fit variant in the inoculum, the stochastic nature of virus growth (21) leads to a competition between the most fit variants. The increased homogeneity seen during passage may be an indicator of greater intrinsic differences seen between variants present than in HIV infection (21), which allow for the outgrowth of the major variant in spite of the complex relationship of replicative ability, host cell, and cellular stimulation.

The wild populations of primates represent an unexplored reservoir of evolving and emerging infectious diseases that can spread to man (3,9,10,14,22). This reservoir can be used to serve as an indicator of coming pathogens and provide models of natural transmission dynamics. The low frequency of seropositivity in the wild population may be due to predation effects. The seemingly nonpathogenic infection may possibly make the infected non-human primates more opportune to other pathogens, or predators, thus removing them from the population before the virus could spread to the remaining troupe members. It may be that the feral populations have already been through the selection of an “ancient infection” (2). The genetic pool of African nonhuman primates surviving today may be the descendants of ancestors who were long term nonprogressors, or had resistance genes able to ensure asymptomatic infection and survival. There is a discontinuity between the numbers of infected feral monkeys found and the nonmonogamous mating habits of these species which should lead to a higher seroprevalence. Elucidation of the transmission patterns and serosurvey of the feral species is seemingly impossible now with the large scale destruction of their territories, and decreasing population size. Any advances made in understanding the infection among the nonhuman primates, and its natural history, might help to elucidate its spread to man. Wild primate populations remain a source of emerging human virus infection.
References:


