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Hot News

Welcome to «Hot News», a section of AIDS Reviews written by the editors and invited experts which focuses on recently reported information believed to be of both impact and higher interest to the readership.

Excerpts from my conversation with HIV-1 about virus extinction

"... Some of you may think that I am not smart virus because I make a lot of errors during my RNA-dependent DNA synthesis. But, let me tell you something, I purposefully make all those errors so I can adapt to any selective pressure you may try. I am aware that I produce many non-viable virions, but I am still able to generate escape mutants. Since I can produce ~10^{10} particles a day, it doesn't matter if the majority of them are defective. Escape is my objective. Escape from drugs and the immune system. Even when you combine several drugs to try to suppress me, I still manage to replicate. I will always have a pre-existing *quasispecies* with a selective advantage or can generate one *de novo*. By selecting mutant viruses you may reduce my replication capabilities but not my ability to replicate. And I can also recombine and hide in places that may be inaccessible to drugs! Doesn't this prove how smart I am?

Of course, all of us have an error threshold; you have one too. I probably replicate near my error threshold, as other RNA viruses do. I know that Sierra, et al. (J Virol 2000;74:8316-23) were able to extinct fit populations of foot-and-mouth disease viruses by increasing the mutation frequency by only 2 to 6-fold. I am also aware of the work of Loeb, et al. (PNAS 1999;96:1492-7) who crossed my error threshold by using mutagenic nucleoside analogs, and melted my genetic information in culture driving me into error catastrophe and extinction. They called it lethal mutagenesis. But, as Eigen recently indicated (PNAS 2002;99:13374-6), you will have to do a lot of experimental work to understand how lethal mutagenesis can operate on me. Grande-Pérez, et al. (PNAS 2002;99:12938-43) have recently showed this by using a prototype arenavirus extremely susceptible to extinction mutagenesis. For instance, they found that some regions of the genome could accept higher increments in mutation frequency than others and that the analysis of just one genomic region may lead to the wrong conclusion about the molecular mechanism of virus extinction. They also suggested that the largest increases in mutation frequency found with current assays may not predict virus extinction and may just reflect a pre-extinction population.

I realize that many of you are now going to pursue this antiviral strategy but, as Eigen has said, "this is going to be one of the greatest challenges of the 21st century". You also have to design a mutagen that is specific for me, and I anticipate you are going to encounter many problems. Foremost is that by using mutagens you might increase my ability to escape to the immune system! Are you ever going to prove that you are smarter than I am?"

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Alfa-defensins are the missed CD8+ antiviral factor

With major expectation in the audience, David Ho presented, at the 42nd ICAAC, held last September in San Diego, his new findings on HIV pathogenesis, which in parallel appeared published in *Science* during those days (Zhang et al. Science 2002;297:2234-9). Ho, et al. claim the identification of the missed soluble CD8+ antiviral factor (CAF) postulated by Jay Levy for more than one decade (Mackewicz, et al. AIDS Res Hum Retroviruses 1992;8:1039-50). Levy's group postulated that an unknown product released by CD8+ T-cells produced inhibition of HIV replication and was responsible for the non-cytotoxic activity of these cells. The activity of CAF did not involve HLA class I. They estimated its molecular weight to be lower than 20 KDa.

Five years ago, Robert Gallo's group reported the characterization of three human beta-chemokines that seemed to account for the CAF activity (Cocchi, et al. Science 1995; 270:1811-5). RANTES, MIP-1 alfa and MIP-1 beta block HIV infection of target cells through its binding to CCR5, one of the co-receptors for HIV entry. However, X4 viruses, which enter cells throughout the CXCR4 co-receptor, are

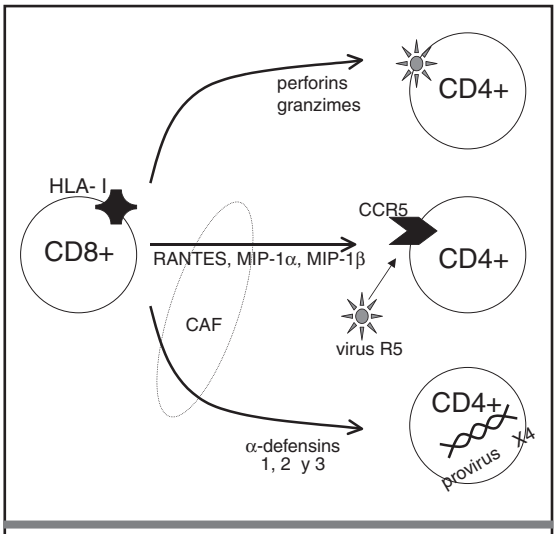

Figure 1. Anti-HIV activity of CD8+ T-cells

only partially diminished in their infectivity in the presence of beta-chemokines. Clearly, beta-chemokines were only a part of CAF, but not all: they did not account for all soluble CD8+ activities against HIV.

David Ho's team examined a small group of well-characterized long-term nonprogressors (LTNP) followed at their institution for more than a decade. They found three chemokines, known as **alfa-defensins** and released by neutrophils and activated CD8+ T lymphocytes, as the major factor responsible for the inhibition of infection caused by X4 viruses.

Alfa-defensins are short peptides of 29-30 amino acids. So far, it was believed that they were involved in the destruction of bacteria (Hill, et al. Science 1991;251:1481-5). Now, alfa-defensins are claimed to be the main factor responsible for the inhibition of infection due to X4 viruses, although they also contribute to blocking infection due to R5 viruses. Their effect seems to occur at transcriptional level and not by blocking HIV entry into the cells. The distinct mechanisms of inhibition of HIV by CD8+ T-cells are shown in the figure. Further studies are needed to confirm these findings, which may represent an important step to understanding HIV pathogenesis, and to presenting new opportunities for designing new therapeutic targets.

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No benefit of STI in chronically HIV-infected patients under successful therapy

The rationale of performing treatment interruptions in patients with undetectable viral load is to expose the immune system to HIV antigens, anticipating an enhancement of immune responses, and to relieve, at least temporarily, the toxic effects of the drugs. Patients under long-term successful therapy tend to loose immune responses to the virus. Whereas treatment interruption of acute infection was shown to contribute to 'autovaccination' (Rosenberg, et al. Nature 2001;407:523-7), recent results from Oxenius, et al. (PNAS 2002;99:13747-54) suggest no virologic or immunologic improvement for chronically HIV-infected patients. In 97 patients with chronic HIV infection enrolled in the Swiss-Spanish Intermittent Therapy Trial, after 4 cycles of STI (2 weeks off, and 8 weeks on therapy), treatment was interrupted for 12 weeks. The viral load set-point was similar to the pre-therapy set-point, while immune responses tended to be worse instead of better. Abbas and Mellors (PNAS 2002;99:13377-9) even argue that the risks associated with STI are substantial, such as virus drug resistance, symptomatic acute retroviral syndrome, reseeding of viral reservoirs, CD4 drops, higher risk for transmission, and adherence problems. Drug resistance is a major issue, since several groups have reported increased resistance during STI. Therefore, current data suggest that the only argument in favor of STI in chronically HIV-infected patients is to reduce toxicity, which has to be carefully weighed against the above-mentioned risks, including the selection of drug resistance.

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