From curse to cure: HIV for gene therapy?

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Retroviruses have long been considered the best choice for gene therapy because they have an efficient and predictable mechanism for integrating their genetic material into the host cell genome. However, there is a problem: Many of the targets for gene therapy are noncycling or postmitotic cells and, unfortunately, all retroviral vectors used in clinical trials thus far are oncoretroviruses, which require mitosis of the host cells for viral integration. The human immunodeficiency virus, HIV, on the other hand, is a member of the lentivirus class of retroviruses that can infect nondividing cells[1,2]. One of the natural targets of HIV in vivo is terminally differentiated cells of the macrophage lineage; thus, lentiviral vectors may have distinct advantages for gene therapy.

Now, Naldini et al.[3] have shown that injection of an HIV-derived retroviral vector into adult rat brains leads to stable introduction of a marker gene into nondividing astrocytes, neurons, and oligodendrocytes. Although HIV vectors have been described before by several other groups, Naldini et al. obtained much higher titers of HIV vector stocks by substituting the endogenous HIV envelope protein with the vesticular stomatitus virus G (VSV-G) protein *in trans*. This both broadens the host range of the vector and allows the viral stocks to be concentrated by ultracentrifugation. Potential applications for retroviral vectors that can infect nondividing cells include introducing therapeutic genes into postmitotic cells such as differentiated muscle, neurons, or epithelial cells. In contrast to its ability to infect metabolically active, terminally differentiated cells, HIV cannot productively infect quiescent cells[4,5]. Even so, a recent report has suggested that HIV might be more efficient than oncoretroviruses in transferring genes into hematopoietic stem cells[6].

But is HIV for human gene therapy a good idea? HIV is a major human pathogen responsible for the current AIDS epidemic, and any intentional introduction of HIV into people, even as a vector, needs to be approached with extreme caution. The major concern is the generation of replication-competent virus as a result of vector preparation. Homologous and/or nonhomologous recombination between viral genes and retroviral vectors that give rise to replication-competent retroviruses does occasionally occur. For this reason, the use of the authentic HIV envelope to package the vector would be unacceptable because the consequences of reconstituting wild-type HIV are too severe. On the other hand, although the use of envelope proteins from a heterologous virus would virtually eliminate this risk, it would also raise the possibility of generating something worse by nonhomologous recombination. Recombinants of HIV and the envelope of another virus have not been observed in a laboratory setting, but they would be more likely in the large scale-ups required for clinical trials, and sensitive assays for their detection would be required. The use of the VSV-G envelope is of special concern because of its ability to generate pseudoviroids that have encapsidated other RNAs[7]. These problems are compounded by the manner in which the virus stocks are generated. Because of the toxicity of various viral proteins, Naldini et al.[3] had to produce their high-titer virus stocks by transient transfection. This would not be suitable for clinical grade material because transient transfection increases the rate of recombination, and more importantly, because the material could not be rigorously tested for contaminant viruses. The alternative would be the use of an inducible system, such as one recently described for an HIV vector that uses a Tet-repressible promoter[8], although the titers of the first-generation packaging cell line are still low.

However, there are several ways to exploit our understanding of HIV infection of nondividing cells without resorting to an HIV vector itself. Although other lentiviruses have not been characterized as well as HIV, it is likely that some or all of them also infect nondividing cells. Therefore, with the proper envelope to ensure entry into human cells, it might be possible to use vectors based on visna virus, feline immunodeficiency virus, bovine immunodeficiency virus, equine infectious anemia virus, or caprine arthritis-encephalitis virus as gene therapy vehicles in humans. (The simian immunodeficiency virus is not a good choice because it is genetically indistinguishable from an attenuated human pathogen, HIV-2.) On the other hand, the development of other lentiviral vectors is not straightforward, because significant differences in genome organization between HIV and the animal lentiviruses will make it difficult to directly transpose what has been learned from the HIV vectors to other lentiviruses.

The third class of retroviruses are the spumaviruses. These viruses are nonpathogenic, and appear to be able to infect nondividing cells at a low efficiency that is slightly better than their oncoretrovirus cousins[9,10]. A separate, but technically difficult, approach to the problem of making safe retroviral vectors for gene therapy would be to improve the efficiency by which spumaviruses or oncoretroviruses infect nondividing cells by incorporating genetic components of HIV that allow it to infect nondividing cells. The viral components that allow HIV to infect nondividing cells is an area of active research, and several have already been identified[11]. Although simple exchanges of parts of HIV onto another oncoretrovirus have not yet been successful in allowing an oncoretrovirus to infect nondividing cells (G. Stivahtis, and M. Emerman, unpublished data), similar exchanges with the spumaviruses have not yet been attempted. In any case, although HIV is not likely to gain widespread use in gene therapy, it certainly can direct us down some promising avenues.

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Figure 1. HIV infection in a nondividing cell shown by double immunostaining of HIV (brown) and terminally differentiated brain macrophage/microglial cell (blue). Photo courtesy of Dr. Rosemary Vazeux.

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