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A recent AIDS vaccine trial of more than 16,000 volunteers in Thailand showed that the vaccine reduced the risk of HIV infection by more than 30%. Although this outcome is far from ideal, it certainly provides a hope for further improvement. While the efforts of developing a perfect vaccine should continue, our efforts should also be focused on improving the traditional antiviral drug therapies for HIV infection. The current antiviral drug therapies are limited by their side effects and viral resistance. One promising alternative strategy is gene therapy. Although most of the gene therapy against HIV employ viral vectors, the safety concern of using live viral vectors remains an unsolved issue. Thus, non-viral vectors have emerged as an alternative for their superiority in terms of safety, immunogenicity, and ease of use. Despite such advantages, however, non-viral anti-HIV gene therapy has not been able to produce efficient and selective delivery of the transgene to HIV-infected target cells, such as T lymphocytes. To overcome the difficulty, scientists developed a unique non-viral method, called D-RECS (drug or gene delivery system responding to cellular signals) [1]. D-RECS utilizes polymer-based vehicles with a specific substrate peptide sequence of a target intracellular signal, which permits highly selective expression of transgenes to target cells. The D-RECS concept was applied to counteract the virus infection, specifically HIV and coxsackievirus B1 (CVB1).

The paper by Asai et al. in this issue [2] describes the use of a synthetic gene regulator, CPCHIVtat (cationic polymer possessing a cleavage site for HIV-1 protease), which releases DNA in response to the activity of HIV-1 protease. The key feature of this gene delivery system is the use of a cationic copolymer with an HIV-Tat peptide-linked substrate sequence for HIV protease as a trigger of intracellular DNA release and subsequent expression. HIV protease is a hallmark of HIV infection, because it is expressed specifically in activated HIV-infected cells. A protein transduction domain (PTD) peptide such as HIV-Tat can be used to transport a wide variety of molecules with different sizes and biological properties. It is also known that simultaneous active targeting of cell surface molecules, e.g., with a specific antibody and PTD peptide, results in a decrease of the targeting specificity [3]. Since CPCHIVtat-polyplex was able to discriminate between normal and infected states by using intracellular information, namely by active HIV-1 protease, it is expected to show increased specificity.

As shown on the cover of this issue, a synthetic gene regulator named CPCHIVtat forms a stable polyplex with plasmid DNA. As a result, expression of the transgene is suppressed in the polyplex. In HIV-infected Jurkat cells, however, HIV-1 protease cleaves the cationic portion of the pendant peptide at the substrate peptide sequence, leading to the release of the plasmid DNA from the polyplex and subsequent expression of the transgene. In uninfected cells that lack HIV-1 protease, the transgene is not released from the polyplex, and therefore is not expressed. The authors confirmed that reporter gene expression required HIV-1 protease both in a cell-free system and in living cells with low-toxicity [2]. Moreover, the authors also showed that this methodology was effective for another virus-specific protease, CVB1 2A protease. It appears that the D-RECS system should be suitable for delivering a wide range of genes, including genes encoding apoptosis-promoting proteins, negative regulators of programmed cell death, suicide genes, and fluorescent/luminescent genes for molecular imaging. Indeed, the D-RECS methodology could be a versatile strategy to achieve cell-specific gene expression.

While the results are very promising, it is still premature to predict whether the D-RECS approach that works well in cell culture system can be translated into in vivo systems, but the concept is certainly new and brings a lot of hope. The question now is whether we can expect that the D-RECS therapy can prevent or cure HIV infection in the near future. The article by Asai et al. in this issue provides a highly hopeful answer, which is “yes, we can.”

References


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