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Cover Story

Selective endothelial targeting of stealthed adenovirus

Viruses have considerable potential as customizable nano-particle drugs capable of expressing a wide variety of therapeutic proteins to address several important diseases. However, the use of viruses to treat systemic disease, such as cancer, can be frustrated by poor targeting of virus particles, limiting the amount of infectious viruses available to express therapeutic genes at the intended site of action. In fact, this problem has been universal to all drug delivery particles. The so-called targeted delivery has not been as successful as the drug delivery scientists have anticipated.

The most important consideration for delivery of viruses via the blood stream is to 'detarget' their normal pathways of infection. Generally there are many sites of possible irrelevant infection in the body, acting as 'sinks' that deplete the circulating virus pool. Attempting to retarget virus without addressing important sinks, such as liver clearance and erythrocyte binding, is unlikely to be successful. Currently, the most effective way of delaying the clearance from the blood circulation and improving biodistribution is surface modification of virus particles with biocompatible polymers, e.g., poly(ethylene glycol), as frequently done to other drug delivery particles to make them stealth.

In the study by Bachtarzi et al. published in this issue [1], the authors have used poly[N-(2-hydroxypropyl)methacrylamide]-coated 'stealth' adenovirus vectors to physically detarget their natural tropisms for the native adenovirus receptor (coxsackievirus/adenovirus receptor, CAR), integrins and factor X binding epithelial cells. Covalent linkage of protein G onto the polymer coat allows versatile attachment of antibodies, for example recognizing E-selectin, a marker of endothelial inflammation. Inflamed or diseased endothelium is an interesting but challenging target for viral vectors. In principle, it should be possible to pursue a range of therapeutic

options from repairing damaged endothelium in cardiovascular disease to destroying it in the case of tumor feeding arteries. The reality, however, has been far different from the theory. Indeed, this has been the main hurdle in achieving the targeted drug delivery. It is time to rethink the strategies on targeted drug delivery. The studies present here are unique in that the strategy does not use a stealth virus to simply prolong the blood circulation, but to ablate natural tropism. It clearly shows the proof of concept that a 'stealth' virus without natural tropism can be selectively targeted to new receptors in vitro and in vivo. The approach of 'detarget' and 'redirect' to the right target is exactly what we need for improving the efficacy of current targeted drug delivery systems. The work presented here by Leonard Seymour's group provides a simple platform for expressing a range of agents within inflamed endothelial cells, enabling diverse approaches to therapy.

Reference

- [1] H. Bachtarzi, M. Stevenson, L.W. Seymour, K.D. Fisher, Targeting adenovirus gene delivery to activated tumour-associated vasculature via endothelial selectins, *J. Control. Release* 150 (2011) 196–203.

Kinam Park
Purdue University,
Departments of Biomedical Engineering and Pharmaceutics,
West Lafayette, IN, USA
Tel.: +1 765 494 7759; fax: +1 765 496 1912.
E-mail address: kpark@purdue.edu.