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Cover Story

Enhanced delivery to endothelial lysosomes by ICAM-1-targeted nanocarriers

Delivery of therapeutic agents to target sites in the body is a growing research field. The therapeutic agents are coupled to affinity molecules that recognize specific determinants expressed on the surface of the target cells that require intervention, maximizing delivery to the sites of disease. Polymer carriers under the micrometer-size range (nanocarriers) are promising vehicles for targeted drug delivery because they can incorporate therapeutics of distinct nature, and control their circulation and release rate. When nanocarriers are targeted to cellular receptors involved in endocytic transport, they also provide intracellular delivery, a requirement for a number of therapeutic goals.

Targeted drug delivery is essential for various therapeutic agents ranging from small drugs and chemicals (mostly, cancer chemotherapies), peptide and protein drugs, and oligonucleotides and genes. A variety of delivery vehicles have been developed for small and poorly soluble drugs. On the other hand, delivery of large and hydrophilic drugs, e.g., therapeutic enzymes, by targeted nanocarriers is still a relatively unexplored strategy even though it has promising applications in a wide range of pathologies, including treatment of enzyme deficiencies. In this issue, the paper by Professor Muro and her coworkers shows such an approach, exemplified in the case of delivery of α -galactosidase (α -Gal) for Fabry disease [1]. The disease is a highly debilitating lysosomal storage disorder caused by a genetic deficiency of this enzyme and, consequently, it results in aberrant accumulation of the enzyme substrate, the lipid globotriaosylceramide, within cells of the body.

Although replacement therapy using recombinant α -Gal is clinically available for Fabry disease patients, the efficacy of this approach is still limited, mainly concerning vascular tissue. Because Fabry disease prominently affects the vascular endothelium, endothelial cells represent a main target for treatment of this disorder. To deliver the therapeutic enzyme to these cells, the authors coated α -Gal onto prototype polymer nanocarriers along with a monoclonal antibody to intercellular adhesion molecule 1 (ICAM-1), an adhesion molecule that is abundantly expressed on endothelial cells in pathological conditions. The efficacy of targeting of the proposed strategy, as compared to the non-targeted enzyme, is demonstrated using elegant multicolor fluorescence techniques in endothelial cells cultures, representative of both macro- and micro-vasculature, and additionally verified in animal models using radioisotope tracing of the enzyme cargo. Of particular interest is the use of a battery of parameters by which the authors characterize the targeting properties of their formulation. It is typical to measure only one parameter, the percentage of injected dose (%ID), showing the relative distribution of the injected nanocarriers through different organs in the body. Professor Muro's group, however, measured three additional parameters that are of utmost importance in reporting the results of drug

targeting. They include: (i) the percentage of injected dose per gram of tissue (%ID/g) for comparing the targeting potential of the nanocarriers among organs of different sizes (such as the liver versus the heart, for instance); (ii) the localization ratio (LR; %ID/g organ : %ID/g in blood) to correct for the different circulation rate of targeted versus non-targeted counterparts and represent a more accurate measure of the tissue-to-blood distribution; and (iii) the specificity index (SI; LR of anti-ICAM/ α -Gal nanocarriers : α -Gal) to compare the real improvement in the delivery of targeted-to-non-targeted counterparts.

Another particularly interesting aspect of the work by Professor Muro is that lysosomes are the ultimate sub-cellular destination intended for the delivery strategy reported in the article. The endogenous α -Gal is located in lysosomes within cells. Lysosomes are acidic and highly hydrolytic vesicular compartments, where the majority of materials internalized by cells rapidly degrade. While lysosomes present difficulties in delivering drugs to main cellular targets, such as cytosol, nucleus, and mitochondria, lysosomal destination is an ideal attribute of the work featured in this issue.

Although ICAM-1 targeting has been used in the past for targeting of therapeutics to endothelial cells, the work by Professor Muro and her colleagues is unique in that it represents a rather complete study of all the various key aspect of drug targeting, including characterization of the stability and release pattern of a therapeutic agent from targeted nanocarriers, their circulation and organ biodistribution, cellular targeting, intracellular trafficking, and biochemical effects.

Most articles in the literature on targeted drug delivery report only one parameter, usually %ID, and this usually does not represent a whole picture of targeted drug delivery. It is common to see the increase in the %ID value by introducing the so-called targeting moiety over the control. Such increase by the targeted system is sometimes several folds over the control, but the overall percentage of the delivery is still minor. To really understand whether the targeted drug delivery system really works or not, additional parameters, such as %ID/g, LR, and SI need to be examined. It is not easy to examine all these parameters, but these parameters are essential for accurate evaluation of the effectiveness of the targeted drug delivery. It is hoped that more studies in the future report multiple, important parameters described in Professor Muro's paper, so that the results obtained in different laboratories can be compared accurately, and the results generated using one animal species can be interpreted correctly when they are extrapolated to other species.

Legend for the cover images

Left panels are transmission electron microscopy images showing green pseudocolored anti-ICAM/ α -Gal nanocarriers bound to the

purple pseudocolored endothelium in a blood vessel, 30 min after intravenous injection in mice. The particles on the top panel are bound to the endothelial surface, whereas the particles on the bottom panel are internalized within vesicular compartments by endothelial cells. The right panel is a merged image of both contrast-phase and fluorescence microscopy showing endothelial cells in culture (the cells borders and nuclei are visible) containing green FITC-labeled anti-ICAM/ α -Gal nanocarriers that reside within lysosomal compartments that are labeled by Texas Red dextran, resulting in yellow color.

Reference

- [1] J. Hsu, D. Serrano, T. Bhowmick, K. Kumar, Y. Shen, Y.C. Kuo, C. Garnacho, S. Muro, Enhanced endothelial delivery and biochemical effects of α -galactosidase by ICAM-1-targeted nanocarriers for Fabry disease, *J. Control. Release* 149 (2010), 323–331.

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