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Cover story

Targeted delivery to monocytes

A fundamental problem to the application of many drugs is their lack of ability to reach specific tissues or cellular reservoirs with high efficiency. Drugs are distributed throughout the body, and selective delivery only to the target site is still an elusive dream. The so-called sanctuary sites that are notoriously difficult to target include the central nervous system and cells of the hematopoietic lineage. Efficient delivery of drugs to these specific sites is of particular importance for therapeutics that are unable to pass cellular barriers and that may cause side effects in off-target tissues. To circumvent this problem targeting molecules that bind to a specific transporter or receptor are often used. The use of the targeting molecules certainly increases the portion of the drug delivered to the target site as compared with the control, and the main issue is the degree of such an increase.

The immature form of heparin-binding epidermal growth factor (HB-EGF) is a membrane associated protein that is expressed by a variety of cell types, including those of the hematopoietic lineage. HB-EGF expression by hematopoietic cells, including monocytes, granulocytes and lymphocytes, is regulated by a wide range of inflammatory stimuli [1]. HB-EGF is also known as the diphtheria toxin (DT) receptor, since DT makes use of this molecule as an internalizing receptor [2]. A non-toxic variant of DT, called cross-reacting material 197 (CRM197), has been widely used in the clinic in vaccination programs [3] and in treatment of various cancers where CRM197 is known to inhibit tumor growth [4]. Previous findings also demonstrate that HB-EGF is a target for CRM197 at the blood–brain barrier [5].

In an article in this issue Dr. Geert J. Schenk and his colleagues have demonstrated a novel application for CRM197 by targeting HB-EGF at the cell membrane and cytoplasm of monocytes with high efficiency [6]. The study has shown not only delivery of fluorescently labeled CRM197, but importantly also delivery of more intricate, larger cargos. This new targeting approach enables receptor specific uptake of CRM197-guided liposomes both *in vitro* and *in vivo* (see the cover figure). In the drug delivery field, many targeting moieties have been tested in selective delivery to the tumor site, but the percentage of the delivered drug is still low. Thus, one question to be asked is what unique properties of CRM197 present to distinguish it from other established targeting molecules. There are two major advantages of the approach based on CRM197. First, membrane bound HB-EGF does not have a known endogenous substrate, precluding competition for receptor binding. Second, cytoplasmic delivery is realized through a well characterized innate endosomal escape mechanism [7]. The latter is a feature that is highly desirable, as treatment strategies are oftentimes aimed at cytoplasmic target sites. CRM197 has both targeting and endosomal escaping mechanisms, and these combined properties are highly useful for delivery of many macromolecular drugs and siRNA or microRNA.

The use of this novel CRM197-based targeting method opens up a new possibility to treat hematological malignancies that require selective treatment of monocytes more effectively. This may be achieved by either modifying existing drugs with CRM197 or loading CRM197-coupled drug delivery systems (e.g., liposomes) with existing therapeutics to improve their efficiency. Since CRM197 is already in use for the treatment of various cancers, it appears to be an excellent candidate as a carrier for drug targeting to tumor cells of the hematopoietic lineage, i.e., acute myeloid leukemia. In addition, targeting to monocytes and preventing their transmigration to the brain may inhibit progression of multiple sclerosis. Other conditions for which specific drug delivery to monocytes may prove advantageous include diseases with an inflammatory component, such as encephalitis, meningitis and rheumatoid arthritis. The method described here represents a novel strategy to efficiently target monocytes in diseases that require the selective treatment of this cell type. Further development is necessary to accurately evaluate its potential as a true targeting moiety that can deliver substantial portion of the administered dose to the target site, especially for treatment of tumors. However, the current study by Dr. Schenk and his team have clearly shown a great potential of CRM197 as a new, valuable targeting moiety that the drug delivery scientists can exploit, especially for the targeting to monocytes.

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