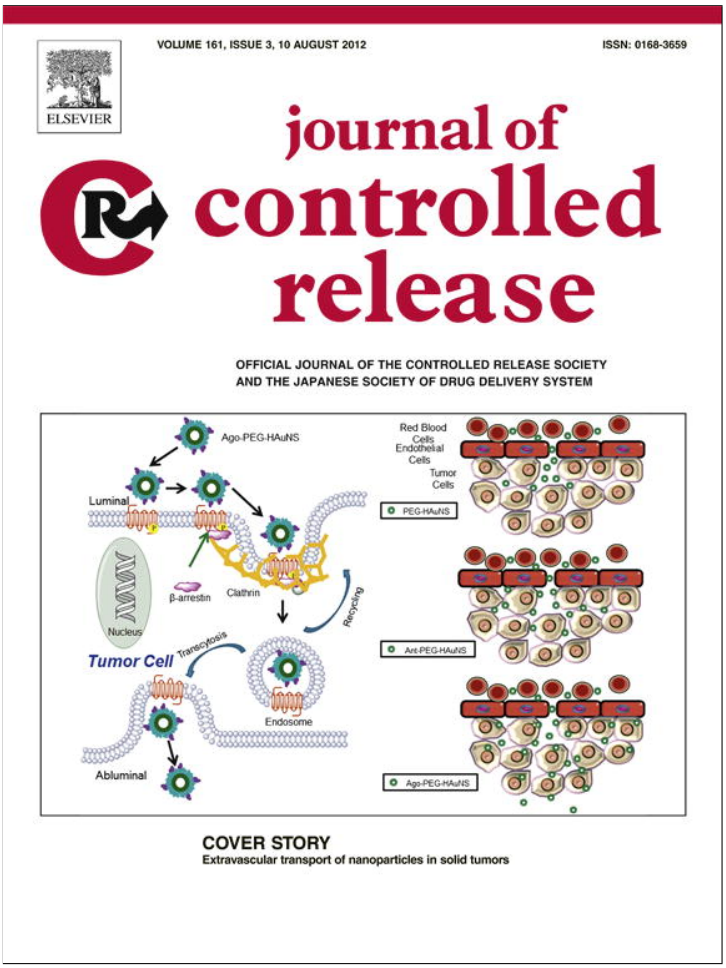

Journal of Controlled Release 161 (2012) 967

Contents lists available at SciVerse ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Cover Story

Extravascular transport of nanoparticles in solid tumors

Targeted nanoparticle-based delivery systems have been extensively studied in anticancer therapies to increase the tumor uptake of therapeutic agents and to reduce their side effects. Some of the systemically administered nanoparticles reach target sites by blood circulation and extravasation. If a specific ligand against a receptor on cancer cells is present on the surface of nanoparticles, they are expected to increase the binding to the cells through ligand–receptor interactions. Transport of nanoparticles after they have extravasated through tumor blood vessels has not been studied in detail. In particular, it remains unclear how the ligands affect extravascular transport of nanoparticles in solid tumors. A rate-limiting step to efficient tumor uptake is diffusion of nanoparticles within the tumor interstitium. The poor tumor penetration of nanoparticles has been attributed mainly to: (i) high interstitial pressure compared to surrounding tissues, which minimizes convective transport; (ii) hindered diffusion due to extracellular matrix components and tightly packed cells; and (iii) binding-site barriers [1].

In this issue of JCR, Professor Li and his colleagues postulated that the nature of targeting ligands attached to the nanoparticle surface affects extravascular transport and, thus, the tumor-targeting efficiency of nanoparticles [2]. They selected melanocortin type-1 receptor (MC1R), a member of the G protein-coupled receptor family, as a model receptor system to test their hypothesis. They conjugated MC1R agonist or MC1R antagonist on the surface of PEGylated hollow gold nanospheres (HAuNS, 40 nm in diameter), and the respective receptor binding affinity of the resulting nanoparticles was carefully titrated by controlling the number of ligand molecules conjugated to the surface of nanoparticles. They found that nanoparticles conjugated with MC1R agonist, but not MC1R antagonist, were efficiently dispersed from the tumor vessels via receptor-mediated endocytosis and transcytosis.

The study by Professor Li's group illustrates that active transport mechanism, i.e., receptor-mediated transcytosis, can facilitate extravascular transport of nanoparticles. Their finding is significant in that it not only reveals a possible mechanism for enhanced nanoparticle delivery to solid tumors, but also provides an alternative approach for overcoming the barrier to efficient dispersion of nanoparticles in tumor interstitium. Such approaches are likely to facilitate the delivery of anticancer agents beyond 40–50 μm (3–5 cell layers) away from the tumor vasculature. This efficient delivery can make tumor cells be exposed to lethal doses and less susceptible to the development of resistance [3]. Although proof-of-concept has been demonstrated in the current study, the idea of receptor agonist-mediated extravascular transport must be examined using systems other than MC1R in future studies to fully realize the promises of enhanced delivery of anticancer agents with targeted nanoparticles. It is also important to realize that the effect of the agonist-mediated enhanced extravascular transport occurs only after the nanoparticles reach the target site by blood circulation and extravasation. The presence of agonists on the nanoparticle surface does not improve the delivery to the target site, but it can enhance the subsequent extravascular transport.

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21 April 2012

0168-3659/$ – see front matter
doi:10.1016/j.jconrel.2012.07.016