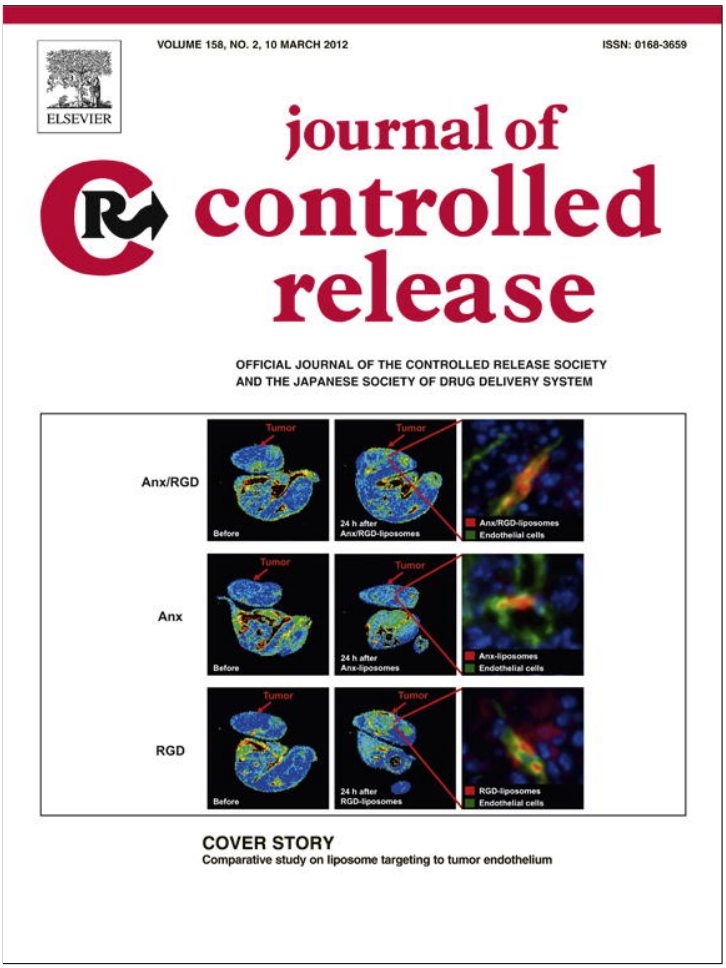

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Cover Story

Comparative study on liposome targeting to tumor endothelium

Accurate assessment of tumor angiogenic activity is critical in prognostic evaluation of cancer progression and monitoring of anti-angiogenic therapy. Such assessment needs to be noninvasive to be practical, and molecular imaging provides an answer. An imaging agent can be delivered with a therapeutic agent simultaneously, and this is known as theragnosis or theranosis. The key to the successful theragnosis is to find a delivery vehicle that selectively accumulates at the target site. The current targeted delivery is mostly based on modifying the surface of a delivery vehicle with a ligand or an antibody. The delivery systems with a single targeting moiety have shown better results than the control, but the overall efficacy, i.e., the fraction of the system reaching the target site, has been still very low, e.g., less than 5% of the total administered dose. Thus, developing better targeted delivery systems has become essential for the successful delivery of theragnostic agents to the target site. One such approach may be using two different targeting moieties.

In an article in this issue, Ewelina Kluza and colleagues from the team led by Professor Klaas Nicolay demonstrate that simultaneous targeting of liposomes to two molecular markers of angiogenesis, $\alpha_v\beta_3$ integrin and galectin-1, improves the molecular recognition of tumor endothelium compared to single receptor targeting [1]. The aim of this study was to determine the benefits of the dual-targeting strategy for *in vivo* imaging of angiogenesis using magnetic resonance imaging (MRI). The translational capabilities of MRI and the subcellular-level spatial resolution of fluorescence microscopy were integrated to assess the performance of the dual-targeted agent with respect to the produced MRI contrast in the tumor and the specificity and efficacy of association to tumor endothelium, respectively. This was accomplished by the use of paramagnetic and fluorescent liposomes, which were functionalized with two peptidic ligands, the galectin-1-specific anginex (Anx) and the $\alpha_v\beta_3$ integrin-specific RGD. The liposomes functionalized with either Anx or RGD were used as single-targeted counterparts.

The targeting specificity was examined by measuring the fraction of the total area of fluorescence signal from the liposomes present on endothelial cells. The targeting efficacy, i.e., the fraction of the tumor endothelium labeled with liposomes, was measured by quantifying the fluorescence signal from the liposomes colocalized with the signal from antibody to the endothelial cells. As one would expect, the dual-targeting of $\alpha_v\beta_3$ integrin and galectin-1 with Anx/RGD-liposomes significantly improved the specificity of contrast agent association with tumor endothelium. It is interesting to note, however, that the targeting efficacy of Anx/RGD-liposomes was compromised as compared with RGD-liposomes. This is most likely related to the three-fold faster blood clearance of Anx/RGD-liposomes than that of RGD-liposomes. The blood clearance of Anx-liposomes was comparable to Anx/RGD-liposomes. The pronounced pharmacokinetic difference is an important factor that strongly influences the *in vivo* targeting properties of the investigated formulations. Different contributions of the specific and non-specific liposome uptake in the tumor led to similar magnitudes of the *in vivo* MRI contrast enhancement when comparing single- and dual-targeted approaches.

The findings by Professor Nicolay and his colleagues have broad implications for the field of tumor-targeting. First, the dual-targeting of $\alpha_v\beta_3$ integrin and galectin-1 improves the specificity of contrast agent association with tumor endothelium *in vivo*, and this offers a more reliable MRI read-out of the tumor angiogenic activity. This concept could readily be translated to other *in vivo* imaging modalities, which also make use of nanocarriers. Moreover, the dual-targeting appears to be an attractive strategy, which can help to overcome the heterogeneity of receptor expression during the tumor development and which can be used both for diagnostic and therapeutic purposes. These points are something that the scientists can easily understand, as they are based on a sound physicochemical principle that multiple interactions provide higher affinity and specificity. One observation that was not easily predicted, however, was that the dual-targeting with higher specificity resulted in faster elimination from the blood circulation. This is indeed one of the most important observations that the drug delivery scientists should be aware of.

The work by Professor Nicolay is one of the few that clearly indicates the importance and necessity of measuring more than one parameter in assessing the targeted delivery to the tumor site. The dual targeting to two different molecular markers will certainly increase the targeting specificity, but the overall targeting efficacy actually decreases. As concluded in the article, it is important to examine at least two properties, i.e., targeting specificity and blood clearance, for accurate assessment of the efficacy of targeted drug delivery vehicles. Finding the optimal balance between the two competing properties will be the key to effective molecular imaging and treatment strategies.

Reference

[1] E. Kluza, I. Jacobs, S.J.C.G. Hectors, K.H. Mayo, A.W. Griffioen, G.J. Strijkers, K. Nicolay, Dual-targeting of $\alpha_v\beta_3$ and galectin-1 improves the specificity of paramagnetic/fluorescent liposomes to tumor endothelium *in vivo*, J. Control. Release 156 (2011) 209–216.

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