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Cover Story

Optimal nanoparticle design for effective transport through the blood-brain barrier

Efficient drug delivery for the treatment of brain diseases remains a grand challenge due to the low permeability of the brain vasculature imposed by the blood-brain barrier (BBB) [1]. To enable effective drug delivery to the brain, focus has been given to the use of nutrient receptors present on the luminal surface of the brain capillary endothelial cells (BCECs) as targets for drug or nanoparticle accumulation. One important example of this is the use of the transferrin receptor (TfR), which normally transports iron across the BBB. The use of TfR as a means for the brain drug delivery has been popular for several decades, and recently, advances in protein engineering has enabled improvements for the transport of antibodies across the BBB via the TfR [1]. While improved transport has been achieved in the nanomedicine field, the overall transport efficacy across the BBB still remains very small [1]. The improved transport of nanoparticles across the BBB has been achieved by changing the valency and affinity of the TfR-targeting antibody [2], or by modifying the number of ligands or antibodies on the nanoparticle surface [3]. Regarding the latter, available data in the literature suggests that there may be an optimum number of ligands for improved brain transport [3].

The paper by Professor Moos and his coworkers from Aalborg University and the Technical University of Denmark investigates the impact of the antibody density on nanoparticle surfaces on the brain transport systems [4]. Their study with parallel use of liposomes and gold nanoparticles (AuNPs) has shown that a low limit of antibody functionalization exists for efficient binding of nanoparticles to BCECs. Varying the numbers of antibodies per nanoparticle was also reflected in the general biodistribution. The absolute accumulation of nanoparticles in the brain was seemingly very small (< 0.1% injected dose (ID)/g). This poor delivery to the brain highlights the general challenge in developing nanomedicines that can be efficiently delivered through the BBB. The accumulation can be improved by using endogenous transferrin as a ligand, or modifying the binding mode of the targeting antibody to the TfR [2,3]. Regardless of state-of-the-art improvements, however, the field of brain drug delivery still experiences even lower levels of nanoparticle or drug accumulation than the tumor drug delivery field [5]. Considering the nanoparticle delivery to tumors at the level of 1%, the delivery to the brain is an order of magnitude lower.

While the study by the Moos team provides an interesting head-to-head comparison of liposomes and AuNPs for brain accumulation and peripheral biodistribution, the physicochemical differences between the two types of nanoparticles were also reflected in the study, e.g., the baseline uptake of PEGylated AuNPs into primary BCECs *in vitro* was many-fold higher than that of liposomes, likely due to differences in the density of nanoparticles. While AuNPs may be less relevant for clinical use compared to liposomes, their use as model nanoparticles has previously resulted in useful information on the delivery through the BBB [3].

The work by the Moos team highlights a few significant problems in the nanomedicine field. First, the umbrella term “nanomedicine” has been wrongly interpreted to indicate that all nanoparticles are similar in their (so-called) tumor-targeting ability, and thus, similar results can be expected regardless of their physicochemical properties. Each nanomedicine is different, and collectively calling a wide variety of nanoparticles as nanomedicine does not solve the problem of poor delivery to the target site, whether it be tumors or the brain. This has been one of the bottlenecks for further advances in the nanomedicine field. Second, the Moos team is courageous to describe their results as they are without any spinning of the results. It could have been easier to say that the nanoparticles with the optimum antibody density improved the transport to the brain by 100%, etc. Instead, they accepted the fact that the delivery to the brain is only about < 0.1% ID/g, alerting the field that even with the targeted delivery system, the actual delivery is still too small. There comes another question. When the actual delivery to the target site is in the range of 1% of the total injected drug, is it reasonable to call it “targeted drug delivery”? There may be many reasons why the drug delivery field still cannot break its way out of nanomedicine [6]. Honest presentation of the data without any preconceived expectation or unnecessary exaggeration of nanomedicine research may be one way to set us free.

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