Commentary

Magnetic resonance imaging-guided stratified selection of patients for nano-therapy

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Among the tumor-targeting strategies, employing the enhanced permeability and retention (EPR) effect of a tumor is a simple and straightforward one, frequently used for solid tumor targeting (1,2). Especially for the development of anticancer therapeutic nanoparticles (TNPs), the efficiency of their uptake via EPR effect has been treated as a crucial factor to determine their therapeutic efficacy (3,4). However, due to the substantial variation of EPR effect from patient to patient and even across sites within an individual patient, clinical applications of TNPs have progressed slowly (5,6). To improve the nano-therapeutic efficacy of TNPs, researchers always focus on the strategic development to artificially augment EPR effects in clinical settings. Such strategies involve increasing systolic blood pressure via slow angiotensin II infusion or utilization of NO-releasing agents (7). However, in a recent work published in Science Translational Medicine, Miller *et al*. suggested to select patients for TNP therapies based on their own stratified EPR effects which were quantified by a magnetic NP (MNP) (8). In detail, ferumoxytol, a clinically approved MNP for magnetic resonance imaging (MRI), was used to predict the accumulation and efficacy of a TNP in tumor cells or in tumors. The authors claimed that this strategy could be employed to identify patients with a higher likelihood of NP accumulation and therapeutic response, and finally, suit the remedy to the case.

It is smart for the authors to use MNP as the contrast agent for tumor MRI and the quantifier to spontaneously quantify the EPR effect of the same tissue (organ). However, to prove the feasibility of this method, a series of issues need to be satisfactorily addressed. These issues include: how MNP distributes in different tumor compartments and cell types, how MNP distribution correlates with TNP distribution, how the MNP distribution relates to the EPR effect of the same tissue, and whether the MRI by MNP can be used to stratify patients for nano-therapy. In this work, Miller *et al*. did a lot of studies to build up the correlations between MNP accumulation and drug response efficacy. In detail, to study the intratumoral distribution of the NPs in mice, single-cell resolution imaging of fluorescently labeled MNPs and TNPs were performed. Specifically, despite their marked differences in size and composition, the MNPs could demonstrate the colocalization areas for the model TNP within the tumor microenvironment and the circulating microvasculature with >85% accuracy and >95% accuracy, respectively. Using the imaging data, the authors conducted computational analysis of MNP transport, which enabled predictive modeling of TNP distribution and identified the key parameters governing intratumoral NP accumulation and macrophage uptake. Finally, by injection of a paclitaxel-encapsulated NP in tumor-bearing mice, the authors applied MRI to predict the drug accumulation and the initial treatment response in a preclinical efficacy study.

Even though the above results have preliminarily validated the practicability of this method and might facilitate the translation of TNPs, additional proving tests need to be conducted. For instance, to minimize the influence of the physicochemical properties of TNP, the authors kept the physicochemical properties (size, shape, payload release kinetics, and transport properties of the released drug) of the model TNP constant, which may

not necessarily represent the behavior of a TNP in an individual case. In other words, whether the EPR effect is affected by the change of the physicochemical properties of TNP should be investigated (9). This issue is also critical for the design of better TNPs (e.g., how to alter their key parameters to maximize the distribution of TNPs within tumors). If there does exist a relationship between the physicochemical properties of TNP and its intratumoral accumulation, more TNPs with different physicochemical parameters need to be designed for this proof-of-concept study. Moreover, for clinical translation, more human disease models, such as primary tumor models, should be included.

Nevertheless, this work provides a novel strategy to evaluate individual EPR effect for a more efficient nano-therapy, and can be subjected to the currently popular concept of stratified therapy in oncology (10,11). While in a typical "one fits all" standard therapy, there is always a clinically recognized proportion of patients who do not benefit from standard medication but show minor response and major toxicities (12). Consequently, individualized therapy is one of the most important topics in modern patient management and translational research (13). Stratified therapy is the first step towards individually tailored therapy. In stratified therapy, the biggest challenge has always been how to identify patients likely to benefit from the treatments considered. According to this work, the MRI obtained with the MNP is the only information to identify patient for stratified therapy. Even if we assume that the MR image is representative and adequate to make a conclusive diagnosis clinically, how to define patients with high predisposition to TNP accumulation and therapeutic efficacy was not clear. At least a quantitative criterion has to be established and validated in patient selection for nano-therapy, we think.

In conclusion, the idea of using MNP to predict TNP therapeutic efficacy provides clinic with a new way to exploit EPR effect and overcome its heterogeneity in individual patient. At present, there are very few experimental results regarding how to predict the EPR effect and subsequent TNP therapeutic efficacy. This work provides a novel strategy of predicting the in vivo kinetics, distribution, and therapeutic efficacy of TNP. The potential of clinically relevant imaging modalities and agents to select patients with high EPR effect for TNP treatment is preliminarily evaluated in this work. Further work would be to examine the relationship between physical parameters of NP and EPR effect, to check whether MNPs can indicate which cancer types are more responsive to TNP delivery, and to build up the correlation between MNP uptake and long-term TNP efficacy. Future challenges will be how to use MR images to quantitatively predict the EPR effect of an individual patient and thus the patient ultimately benefit from this stratified therapy. Hopefully, this MNP-based imaging approach to identify suitable patients for TNP therapy would help the translation of new nanomedicines and lead to the evolution of stratified approach in nano-therapy.

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Footnote

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References

1. Torchilin V. Tumor delivery of macromolecular drugs based on the EPR effect. Adv Drug Deliv Rev 2011;63:131-5.
2. Iyer AK, Khaled G, Fang J, et al. Exploiting the enhanced permeability and retention effect for tumor targeting. Drug Discov Today 2006;11:812-8.
3. Brigger I, Dubernet C, Couvreur P. Nanoparticles in cancer therapy and diagnosis. Adv Drug Deliv Rev 2002;54:631-51.
4. Cabral H, Kataoka K. Progress of drug-loaded polymeric micelles into clinical studies. J Control Release 2014;190:465-76.

5. Maeda H. Toward a full understanding of the EPR effect in primary and metastatic tumors as well as issues related to its heterogeneity. Adv Drug Deliv Rev 2015;91:3-6.
6. Prabhakar U, Maeda H, Jain RK, et al. Challenges and key considerations of the enhanced permeability and retention effect for nanomedicine drug delivery in oncology. Cancer Res 2013;73:2412-7.
7. Fang J, Nakamura H, Maeda H. The EPR effect: Unique features of tumor blood vessels for drug delivery, factors involved, and limitations and augmentation of the effect. Adv Drug Deliv Rev 2011;63:136-51.
8. Miller MA, Gadde S, Pfirschke C, et al. Predicting therapeutic nanomedicine efficacy using a companion magnetic resonance imaging nanoparticle. Sci Transl Med 2015;7:314ra183.
9. Albanese A, Tang PS, Chan WC. The effect of nanoparticle size, shape, and surface chemistry on biological systems. Annu Rev Biomed Eng 2012;14:1-16.
10. Shaw EC, Johnson PW. Stratified medicine for cancer therapy. Drug Discov Today 2012;17:261-8.
11. Uhl M, Hau P. High-grade glioma: refined diagnostics steering stratified therapy. Case Rep Oncol 2013;6:387-90.
12. Riemenschneider MJ, Louis DN, Weller M, et al. Refined brain tumor diagnostics and stratified therapies: the requirement for a multidisciplinary approach. Acta Neuropathol 2013;126:21-37.
13. Hau P, Stupp R, Hegi ME. MGMT methylation status: the advent of stratified therapy in glioblastoma? Dis Markers 2007;23:97-104.

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