The enhanced permeation and retention (EPR) effect has been used as a cornerstone in the research on tumor targeted drug delivery. It was comfortably accepted, and conveniently assumed, by many researchers as the de facto principle for effective treatment of tumors using nanoparticles. At the height of the nanotechnology fever, the EPR effect was an ideal conduit to channel the potential of nanoparticles to treating tumors, at least in mouse models. It seemed as if the tumor targeting was almost guaranteed if a drug was formulated in nanoparticles. As long as the two terms, “nanoparticle system” and “EPR effect”, were combined, the results were predictably good, at least in the mouse xenograft model. The fluorescence intensity at the tumor site was always higher than other organs, typical data supporting the EPR effect. Does that mean it should be taken for granted to draw an equal sign between the EPR effect and effective tumor targeting for any nanoparticle system?

In this issue, Professor Tonglei Li and his collaborators describe their systematic study to examine whether the EPR effect indeed exists. Professor Li’s group examined the biodistribution of paclitaxel nanocrystals in tumor-bearing mice [1]. The average size of the nanocrystals was around 200 nm and no surface treatment was done to the particles. They discovered that less than 1% of the total injected paclitaxel reached the tumor site after intravenous injection through the tail vein. The majority of the nanocrystals were actually taken up by the macrophage phagocytic system (MPS). In the study, tritium-labeled paclitaxel was included in their production of nanocrystals from a solution. Thus, the exact quantity of paclitaxel reaching the target tumor was analyzed accurately by scintillation counting. Taxol®, which was used as a control, also showed less than 1% accumulation in the tumor. Both formulations demonstrated similar anticancer efficacy, but the nanocrystals seemed to elicit less systemic toxicity despite a significant liver uptake. Literature information indicates that paclitaxel in Taxol® is likely to be delivered as the micellar form [2]. The extremely low amount, i.e., <1% of the total administered dose, delivered to the tumor site by both Taxol® and nanocrystals raised a question on the significance of the EPR effect.

Professor Li and his colleagues further conducted bioimaging studies of the treated animals since their nanocrystals also physically integrated into the tumor site after intravenous injection through the tail vein. The major distribution among organs and tissues. After almost two decades of blind belief on the EPR effect, it is time to think outside the box to really move the tumor targeted drug delivery forward.

References


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