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Cover story

Spatio-temporal heterogeneity in tumor liposome uptake: Characterization of macro- and microdistribution

It's been 20 years since Doxil® was approved as the first liposome formulation for a chemotherapeutic agent. Since then, this name has been cited over a thousand times during the last 20 years. Despite advances in reducing the normal tissue toxicity of conventional chemotherapeutics, however, little improvement in therapeutic efficacy has been observed with Doxil. Therapeutic potential of nanoparticles needs to be carefully examined for full exploitation. The absence of real progress in clinical applications of nanoparticle formulations has brought careful analysis of the nanotechnology in drug delivery, in particular tumor-targeted drug delivery, with a flair of uncertainty [1,2]. The limited advances in tumor-targeted drug delivery using nanoparticles are, in part, due to the constraints of physical and biological barriers which are often ignored [3]. Research on tumor-targeted drug delivery, or any topic for that matter, is an evolutionary process where trial-and-error guides the path toward incremental progress. The evolutionary process always results in progress mainly due to sheer large numbers of trials taken. Errors, or failures, are in fact necessary steps for valuable lessons. In the drug delivery field, a re-evaluation of metrics that are routinely employed in developing a candidate nanocarrier is pertinent.

In this issue, the study by Professor Christine Allen and her colleagues highlights the over-reliance on the assessment of bulk tumor accumulation of nanosystems in xenograft mouse models as being indicative of their in vivo efficacy [4]. The simple fact of very complicated tumor-targeted drug delivery is that the results of the xenograft mouse model have not been translated into expected increases in therapeutic efficacy. Of the various reasons for such a lack of mouse–human correlation are poor understanding and characterization of inter- and intratumoral heterogeneity, affecting distribution of nanosystems and subsequent drug absorption. Such heterogeneity inherent in tumor properties (e.g., vascular structure and function) affects the tumor distribution of nanosystems. The tumor microenvironment (TME) presents manifold barriers to the delivery and efficacy of nanosystems. Physical barriers hinder the homogeneous distribution of nanosystems. Furthermore, physiological barriers arising from an inefficient vascular network confer cellular resistance to therapy (e.g., through hypoxia) [5]. Such multi-faceted resistance contributes to poor responses to anti-cancer therapy, and requires a comprehensive characterization.

The Allen team challenges current paradigms in drug delivery to solid tumors; namely, the assumption that macroscopic parameters such as systemic (i.e., blood) and bulk tumor levels can predict microregional levels of liposome deposition, and overall anti-tumor efficacy. Rather, the Allen team emphasizes that microdistribution of the nanosystem and of TME parameters plays a critical role in determining the efficacy of a formulation. A stable, dual-modality imaging liposome formulation was developed for a quantitative image-based assessment of macro- and microdistributions in an orthotopic tumor xenograft model. Computed tomography (CT) imaging provided a quantitative measure of liposome distribution at the sub-millimeter level, while optical microscopy enabled sub-micrometer assessment of liposome penetration and localization in relation to the microvessel density (MVD). Tumor and normal tissue uptake were quantified over a 5-day period, yielding a conventional assessment of biodistribution. Beyond bulk uptake, however, regional tumor analysis revealed a heterogeneous distribution of both liposomes and tumor MVD. In particular, the highly vascularized tumor rim was characterized as an area of maximum liposome accumulation, revealing the contribution of the vasculature in defining nanoparticle distribution in this tumor model. Furthermore, tumor penetration was characterized as a measure of intratumoral transport, exposing a temporal influence irrespective of regional localization within the tumor (delineated as rim, periphery or core regions). Such characterization introduces a methodological platform to further elucidate the relationship between macro- and microscopic parameters in nanoparticle distribution, and their role as potential determinants of clinical efficacy.

An important lesson that the Allen group provides is the courage to re-evaluate our perceived conventions against the routine practices by the majority. Their work was extended to a systematic assessment of the impact of space and time on liposome distribution. Integration of the influence of tumor pathophysiology on distribution makes the evaluation of the efficacy of nanosystems more accurate. Improved understanding on the impact of modulators of the TME is expected to make the results of xenograft mouse studies more clinically relevant.

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