



Cover Story

Drug transport-based therapeutic resistance in breast cancer liver metastases



Many studies have shown variations in genetic signatures, gene expression, and post-translational modifications among different tumors and within tumors themselves, which creates complex tumor heterogeneities. Although these heterogeneities have been recognized in almost every type of solid cancer, current therapies still treat cancer as a homogenous disease. The importance of mass transport in the tumor microenvironment (TME) has been recognized for decades as a key determinant for the efficacy of systemic chemotherapy [1]. If a sufficient amount of a drug is not delivered to the target cells in TME, it will generate “transport-based therapeutic resistance” [2]. Thus, heterogeneous transport phenomena in tumors can influence whether the tumor develops a therapeutic response or resistance.

Understanding the mechanisms of the tumor drug transport heterogeneity and their relation to therapeutic efficacy will facilitate a better understanding of therapeutic resistance. This, in turn, will provide insight into the development of more effective therapeutic strategies. Professors Arturas Ziemys and Kenji Yokoi and their colleagues have addressed the conjuncture problems among metastases progression, heterogeneities in drug delivery, and therapeutic efficacy using *in vivo* treatment of 4T1 breast cancer liver metastases with pegylated liposomal doxorubicin [3]. Their computational model based on imaging analysis of *in vivo* studies introduced several parameters, such as the permeation time and cumulative permeation probability, characterizing the time needed to permeate a tumor and the probability of permeating all metastases possessed by a subject. The model stipulates the link between the time needed to achieve therapeutic effect and pharmacokinetic properties of the chosen therapeutic strategy. As the Ziemys and Yokoi team's analysis pointed out, the current pharmacokinetic properties are unable to provide the information on the presence of a drug in the immediate vicinity of the tumor extravascular space. Since the transport heterogeneity can create transport phenotypes that can withstand a drug treatment, the surviving tumors become resistant to repeated treatments.

Another study in this issue describes breast cancer metastases in the brain. Dr. Zafir-Lavie and her colleagues have described gene therapy approaches to generate continuous anti-HER2 antibodies in the brains of mice with breast cancer brain metastases [4]. This work tackles the challenge of the blood-brain barrier by intracranial implantation of genetically engineered cells or intracranial injection of a viral vector opposite to the inoculated carcinoma cells. This study, in essence, reinforces the concepts that adequately sustained presence of a therapeutic agent is essential to yield a therapeutic response, and that the inability to cross transport barriers produces transport-based therapeutic resistance.

The studies by both the Ziemys and Yokoi team and the Zafir-Lavie team point to one simple fact in treating tumors: A sufficient amount of

a drug has to reach the target tumor cells for a sustained time period. No drug is effective unless the drug concentration is above the minimum therapeutic concentration until all target cells are dead. This fundamental pharmacokinetic principle has been lost in the tumor-targeted nanomedicine era. Most studies involving nanomedicine simply determine the amount of drug delivered as compared with the control, and describe the relative superiority, rather than the treatment. Almost all nanomedicine studies conclude that the treated group shows reduced tumor size as compared with the control group. Furthermore, the amount of a drug delivered measured in those studies is actually the quantity present around the TME and not to the target tumor cells inside solid tumors. Thus, it is common to see that the treated mice also die soon after the control group.

An important issue in nanomedicine is that there has been no clinical translation of any of the nanoformulations described in the literature. All clinical studies using nanomedicine have failed. In retrospect, it is obvious that none of the nanomedicine tested in clinical studies were designed to transport through the TME to the target tumor cells. The diffusion of drug molecules through the TME is known to be slow due to tight junctions among tumor cells, and the diffusion of nanoparticles will be even slower. It is time for the nanomedicine field to accept the fact that drug delivery to the TME is not the same as delivering to all target tumor cells within the tumors. The study by the Ziemys and Yokoi team points out this problem of tumoral transport-based therapeutic efficacy through their well-designed experiments and computational modeling.

References

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