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Tumor Transparency Imaging of Nanotherapeutic Agents in Tumor Microenvironment

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Extended Abstract

The aim of this study was to investigate the spatial distribution of drug delivery nanoparticles in relation to the tumor vasculature, region of hypoxia and clonogenic cells in intact transparent tumor tissues. The spatial distribution showed an apparent lack of nanoparticle penetration into the deep tumor site [1]. The nanoparticles were mostly accumulated inside the tumor blood vessel and some were extravasated into tumor tissue. Quantitative verification indicated that the penetration depth of nanoparticle was ~85 μm, however, the maximum percentage of distribution was observed only within 40 to 50 μm distance from the nearest vessels. To validate the existence of viable cells deep inside the tumor, we intended to study the spatial distribution of hypoxia and clonogenic cells in intact transparent tumor tissues. This study presents a direct demonstration for the spatial distribution of hypoxia and clonogenic cells in relation to the intratumoral blood vessels. HIF1α was selected as a marker to observe hypoxia region, and CD44 was selected as a marker to identify clonogenic cells in the tumor microenvironment. Characteristic distance mapping illustrated that HIF1α expression in the tumor ranged from 62 to several hundred μm (~460 μm), which verifies that HIF1α is expressed far away distance from the intratumoral blood vessel. Whereas, the distribution of CD44 was decreased with increasing distance from blood vessels, however, CD44 was still expressed in a significant amount ranging from around 70 μm to 200 μm, and the maximum distribution of CD44 was observed until around 300μm from the nearest blood vessels. These findings apparently reveal that hypoxia and clonogenic cells do not receive enough drug delivery nanoparticles, and beyond the maximum penetration of nanoparticles. Thus, the penetration ability of the passively targeted nanoparticle, which solely depends on EPR effect, is not sufficient to diffuse deep inside the tumors and target viable cells.

References

[1] D. Rosenblum, "Progress and challenges towards targeted delivery of cancer therapeutics," *Nat. Commun.*, vol. 9, no. 1, pp. 1410-1412, 2018.