Proceedings of the 9th International Conference on Theoretical and Applied Nanoscience and Nanotechnology (TANN 2025)
July 13, 2025 - July 15, 2025 | Imperial College London Conference Center, London, United Kingdom
DOI: 10.11159/tann25.013

Tumor Transparency Imaging of Nanotherapeutic Agents in Tumor Microenvironment

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Extended Abstract

Tumor blood vessels have discontinuous endothelium with large pore sizes ranging from 100nm to nearly 1mm in diameter (depending on the location of the tumor). By contrast, vessel walls in normal tissues, such as renal glomeruli and the hepatic/splenic sinusoidal endothelium, have pore sizes of 60nm and 100nm, respectively. Nanoparticle (NP)-based drug delivery approaches work through active or passive targeting of tumor tissues. Active targeting requires NP conjugation to relevant targeting ligands, including antibodies, aptamers, carbohydrates, cytokines, folic acid, hyaluronic acid, and peptides, that can recognize markers on the surface of malignant cells. By contrast, passive targeting is mediated by the inherent characteristics of the tumor itself to deliver NPs [1-3]. As previously reported, macromolecules with molecular weights greater than 40 kDa above the renal threshold, such as drug-loaded liposomes, micelles, plasma proteins, PEGylated proteins and synthetic polymer-based NPs etc., take advantage of the defective vessel structures in a tumor. In passive targeting, leaky tumor vasculature with large fenestrations in the endothelial cells favors NPs 20 – 200 nm in diameter to extravasate into the space adjacent to the vasculature, followed by a considerable increase in NP retention due to poor lymphatic drainage. This phenomenon mediated by leaky blood vessels was first termed the "Enhanced Permeability and Retention (EPR)" effect by Maeda et al. in 1986.This effect is not observed in normal tissue [4,5].

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. 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 ~85μm, however, the maximum percentage of distribution was observed only within 40 to 50μm 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 (~460μm), 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 70μm to 200μm, 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.

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