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Cover Story

Real-time monitoring of antibody microdistribution during photoimmunotherapy

The efficacy of cancer therapy depends on its ability to deliver drugs to tumors and one major goal of intravenous cancer therapies is delivery of the therapeutic material in sufficient concentration to all parts of the tumor [1,2]. Targeted cancer therapies offer the promise of more effective tumor control with fewer side effects than conventional cancer therapies. An emerging cancer therapy with minimal side effect is photoimmunotherapy (PIT) based on a targeted monoclonal antibody-photo absorber conjugate (APC) [mAb conjugated with a near-infrared (NIR) phthalocyanine dye (IR700)]. The APC induces rapid cellular necrosis after exposure to NIR light [3]. IR700 is not only fluorescent, but also phototoxic, making it a useful theranostic agent. Upon exposure to intense levels of NIR light, the conjugate becomes lethal, but only to those cells to which it is bound [3]. Exposure to NIR light can lead to rapid, target-selective necrotic cell death *in vitro* and effective tumor shrinkage in small animal models [2,3]. PIT induced highly selective cancer cell death, while leaving most of the tumor blood vessels unharmed, resulting in a significantly improved effectiveness of anticancer drugs [4]. Although perivascular cancer cells are destroyed via PIT, very little is known about how deep tumor cells respond. The current macroscopic fluorescence reflectance imaging for monitoring fluorescence of APCs does not have the resolution and depth information on the mAb-IR700 distribution *in situ* [4]. Histological analysis can reveal intratumoral spatial distribution of APCs, but it is invasive and terminal. Real-time monitoring of PIT effects can ascertain whether a PIT session has been effective or whether additional cycles of therapy are needed [3,5].

The paper by the team led by Professor Yu Chen and Dr. Hisataka Kobayashi in this issue investigated the microdistribution of APCs at different locations (e.g., tumor surface vs. deep tumor) during and after *in situ* and *in vivo* PIT using a minimally invasive two-channel fluorescence fiber imaging system and a high resolution two-photon microscope (TPM) with a 1 mm microprism [2]. The study presents a few interesting observations. The Chen group employed green fluorescent protein (GFP) fluorescence as a surrogate for cell death and IR700 fluorescence as a surrogate for the APC accumulation. GFP fluorescence decreased more in the tumor surface than it did in the deep tumor, as was observed in the TPM experiment. This indicates that there is less cell necrosis in the deeper parts of the tumor [2]. The histological results after PIT confirm that there are more necrotic cells in the tumor surface induced by PIT. In all experiments using the two-channel fluorescence needle system or TPM (with or without a microprism) with 20 min of PIT treatment, the IR700 fluorescence recovers very quickly, and the recovery in the deep tumor regions is greater than that of the tumor surface, and even reaches beyond the initial value in the deep tumor. As reported previously, compared with small molecule photosensitizers, mAb – IR700 conjugate stays in the blood circulation longer, allowing unbound mAb – IR700 to redistribute into the remnant target tumor after NIR light irradiation [6]. The increased IR700 fluorescence in the deep tumor in their experiment may be explained by improved intratumoral permeation of APCs as a result of longer blood circulation time. A plot of the recovery values of the tumor surface and deep tumor after PIT suggests that the IR700 fluorescence recovery heterogeneity reflects the structural heterogeneity of different regions of the tumor.

The paper by the Chen/Kobayashi team is important, as these novel imaging methods are critical for further understanding of the PIT mechanism and optimizing the effectiveness of treatment by monitoring the distribution of a theranostic agent and its therapeutic effects, including cellular necrosis, within the tumor microenvironment *in vivo* and in real time. These novel imaging methods are also applicable for monitoring other cancer treatment methods. The work by the Chen/Kobayashi group is expected to contribute significantly to the understanding of the mechanisms of theranostic agents, as well as other tumor-targeted drug delivery systems. After three decades of research in nanomedicine, it is time for harvesting past efforts to produce clinically useful formulations through mechanistic understanding of how nanocarriers work.

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