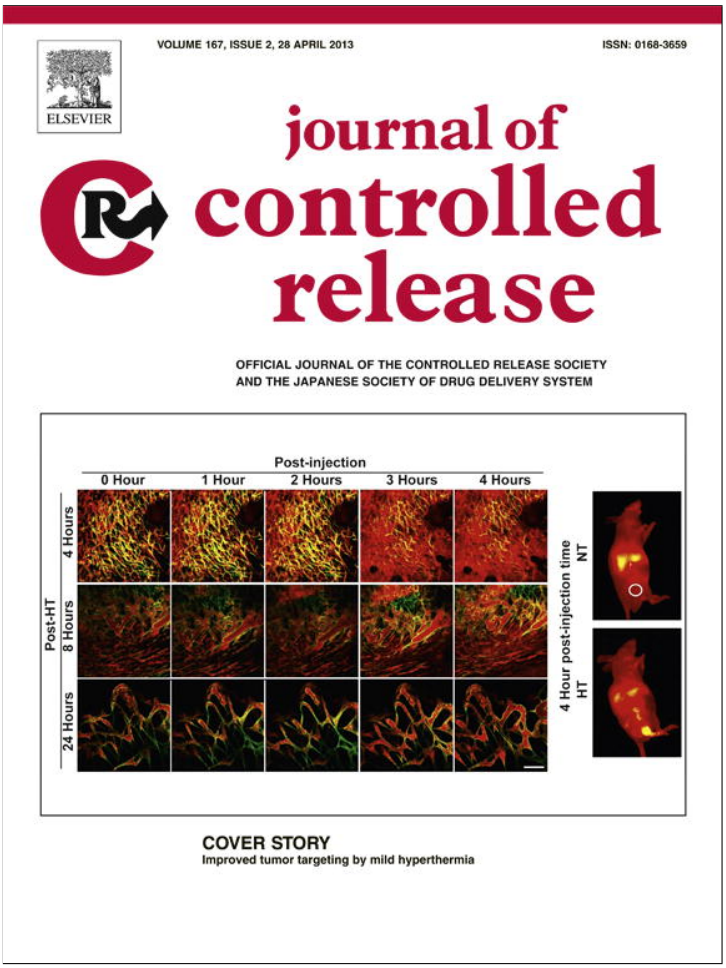

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Cover Story

Improved tumor targeting by mild hyperthermia

Mild hyperthermia has been used clinically in combination with radiotherapy or chemotherapy to obtain a better tumor response and overall survival [1]. Mild hyperthermia, also referred to as fever range hyperthermia because of its temperature of 42 °C, has a sensitizing effect on tumor cells and can be used as a tool to improve delivery of chemotherapeutics to tumors. Mild hyperthermia can be used as an external trigger to induce release of chemotherapeutics from temperature sensitive and responsive nanocarriers. Mild hyperthermia is expected to facilitate nanoparticle accumulation in tumors, by inducing more permeable tumor vasculature, increasing blood flow, elevating interstitial fluid flow, while interstitial fluid pressure is equilibrated. In 2000, Kong et al. first reported that mild hyperthermia of 42 °C enhanced liposome extravasation through tumor vasculature, where perivascular liposome accumulation was primarily observed [2].

In this issue, the paper by Li et al. describes high resolution intravital confocal microscopy and dorsal skin flap window chamber models to evaluate liposome extravasation phenomena in living mice bearing four major tumor types in cancer research [3]. The researchers in the paper used clinically applied thermal doses that can be directly translated to human patients. The threshold of a thermal dose to initiate hyperpermeable tumor vasculature for liposome extravasation was determined. Massive liposome extravasation through tumor vasculature was achieved in murine B16 melanoma, BFS-1 sarcoma, LLC carcinoma and human BLM melanoma upon mild hyperthermia of 41 °C for 1 h. To achieve adequate and efficient liposome accumulation in the tumor interstitial space beyond the level achieved by inherently leaky tumor vessels, augmentation of vascular leakiness seems mandatory. The interstitial penetration depth of liposomes varies among not only different tumor types but also different locations within a tumor. Significantly heterogeneous intratumoral liposome extravasation was revealed, and the heterogeneity of tumor vasculature permeability was pinpointed to any vessel regardless of its location in tumor periphery or center.

Deep liposome penetration was measured up to at least 27.5 μm in radius from permeable vessels in murine B16 melanoma and LLC carcinoma, while perivascular liposome accumulation is mostly observed in murine BFS-1 sarcoma and human BLM melanoma. Using high resolution intravital microscopy, longitudinal imaging was performed to study the effect of local heating on endothelial integrity. When vessels in healthy tissues did not respond to the applied mild hyperthermia, such a thermal dose still caused gap formation between endothelial cells up to 10 μm in tumor vasculature. Actual liposome extravasation was captured at cellular levels. It is highly interesting that the hyperpermeable tumor vasculature remained functional and leaky for 8 h post-hyperthermia. The fraction of heat-responsive tumor vasculature reached more than 50% in murine B16 melanoma and LLC carcinoma. Mild hyperthermia improved intratumoral liposome accumulation was also illustrated in subcutaneous tumor models by whole body optical imaging, where intratumoral targeting was achieved. The observation on interstitial liposome accumulation offers insights on tumor perfusion, interstitial fluid flow and pressure, which are the driving forces for liposome penetration through the extravascular extracellular space. Li et al. speculate that the interstitial fluid flow and matrix density significantly differ among tumor types, for which liposome extravasation depth and intensity greatly vary. Moreover, the permeability of a specific tumor vessel depends on not only vessel perfusion but also the intrinsic profile of the endothelial lining and the surrounding microenvironment. This may explain the variation between a permeable fraction of a tumor vessel and a non-permeable fraction of the same tumor vessel.

The paper by Li et al. clearly shows a great potential of mild hyperthermia as a valuable tool for enhanced delivery of an anticancer agent to a target tumor. Combining mild hyperthermia to nanocarrier-based drug delivery is expected to benefit a large number of patients with solid tumors. While this study provides another reason to be optimistic in treating cancer patients, caution should be exercised in extrapolating animal data to applications in humans. A recent clinical study on low temperature-sensitive liposomes delivering doxorubicin did not produce clear evidence of clinical effectiveness. In the war against cancer having new tools is essential, but proper use of the tools for their maximum capacity may be even more important.

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