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Cover Story

Enhanced bacterial cancer therapy with hydroxychloroquine liposomes

The current drug delivery research has been dominated by nanotechnology, in particular tumor-targeted nanomedicine. Its clinical translation, however, has been minimal despite extensive research for three decades. One question to ask now is why the progress in clinical applications has been so slow and what can be done about it? At the same time, drug delivery scientists can think differently to connect the dots of existing technologies to make them better.

Professor Xun Sun and her team present a new, simple, but very powerful, approach for cancer therapy using bacteria and autophagy inhibitor [1]. The old observation that bacteria can be employed to cure cancer has led to development of the facultatively anaerobic Salmonella typhimurium VNP20009. It is a genetically modified strain that can target tumors by virtue of its preference for the hypoxia in the tumor cores, in contrast to the more oxygenated outer tumor regions. Unlike most anticancer drug delivery systems, VNP20009 has been shown to localize preferentially inside the tumor tissues following systemic injection [1]. A Phase I clinical trial in 2001, however, did not show the tumor regression in cancer patients, presumably because a protective autophagy response resulted in destruction of the therapeutic bacteria. Subsequent studies have shown that inhibiting autophagy can promote bacteria-mediated cancer cell killing by increasing apoptosis activity. A widely used autophagy inhibitor is hydroxychloroquine (HCQ), a drug used for treatment of malaria, rheumatoid arthritis and lupus. HCQ increases the pH inside acidic vesicles, such as lysosomes, and thereby prevents the degradation of bacteria trapped inside.

The distribution of HCQ throughout the body limits the therapeutic dose within cancer cells. The Sun group encapsulated HCQ inside liposomes (HCQ-Lip) to observe 4-fold increase in accumulation in tumors 24 hours after intravenous administration in mice. When tumor-bearing mice were intravenously injected with a single dose of VNP20009 and HCQ-Lip every other day, the levels of VNP20009 in tumor tissues increased 3.8-fold, resulting in much slower tumor growth and longer survival in a murine model of aggressive melanoma. This innovative strategy of combining tumor-targeting VNP20009 and autophagy-inhibiting HCQ-Lip is simple enough to be easily translated into clinical application.

This issue also presents 5 other articles related to tumor treatment. The approaches range from using a streptavidin-mirror DNA tetrahedron hybrid delivery system [2], apoptosis-promoting circular aptamers [3], a hyaluronic acid-zein nanogel [4], a theranostic thermosensitive liposome labelled with both MRI and NIRF imaging agents in combination with focused ultrasound [5], and an imaging-guided approach based on boron neutron capture therapy [6]. While each of these approaches shows improved results as compared with the control treatment in preclinical models, the main issue of delivering enough drugs to the target tumor remains unresolved. The fact that nanomedicine formulations developed for tumor treatment have failed in clinical trials shows that the distribution of drug delivery systems in mice does not represent that in humans. The differences in the blood volume, tumor size in relation to the body size, and the tumor environment between mice and humans are so large that an extrapolation of the results in mice to humans cannot be made.

The innovation shown by the Sun team is that the approach used in mice can be used in humans. It relies on a modest increase in accumulation of HCQ-Lip that, in turn, enhances the efficacy of VNP20009. The 4-fold increase in the accumulation of HCQ-Lip at the tumor site is not much different from previous nanomedicine studies, but its use in combination with VNP2009 makes the approach powerful, although seemingly very simple. The nanomedicine field has been progressing very fast with ever more elegant design of delivery vehicles. The reality, however, is that the drug delivery systems have a better chance of being clinically effective as they become simpler. Sprinkling new, connecting-the-dots approaches with existing technologies would make the progress more clinically relevant.

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