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Can smart nanomedicine deliver effective targeted cytotoxic treatments to hepatocellular carcinomas while reducing the liver damage?

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Hepatocellular carcinoma (HCC) is currently the second leading cause of cancer-related mortality in the world. HCC occurs almost exclusively in patients with underlying liver disease (cirrhosis) characterized by chronic inflammation, fibrosis and liver dysfunction (1). Surgical treatments are feasible in early stages of the disease, but the majority of patients eventually relapse due to metastatic progression or de novo carcinogenesis in the liver. Disease progression both within the liver and extrahepatic metastases would inevitably occur for other widely used localized therapies, such as radiofrequency ablation, chemoembolization, radiation or others.

In terms of systemic therapy, which has been primarily been developed for advanced disease, the options and their efficacy remain limited despite great efforts in this area (2, 3). The use of cytotoxics – chemotherapy and targeted agents – is often limited by the underlying liver disease. Agents directly targeting the cancer cells (for example EGFR, MET or mTOR inhibitors) have shown lack of efficacy in randomized phase III clinical trials in advanced HCC. So far, the only therapies that have shown increased overall survival in randomized clinical trials have been targeted drugs that significantly affect the stromal compartment. Sorafenib has been the standard first-line therapy for advanced HCC for almost a decade. This drug is a multi-kinase inhibitor, whose targets include kinases involved in promoting cell viability, but also angiogenesis and fibrosis (4). Lenvatinib, another multi-kinase inhibitor with differential spectrum of activity, has recently shown non-inferior overall survival to sorafenib in a head to head phase III clinical trial. In second-line setting, regorafenib, a multi-kinase inhibitor more closely related to sorafenib, recently became the standard of care for HCCs progressing after sorafenib treatment based on increased overall survival in a randomized phase III trial. All of these agents have in common anti-angiogenic activity. Recently, immunotherapy using anti-programmed death receptor 1 (PD-1) antibodies has been approved for second-line treatment of advanced HCC based on promising overall response rate from a phase I/II trial (5). Thus, available therapies for HCC appear to primarily target the stroma or the immune system. Despite the substantial

advances in therapy and in our understanding of the molecular pathways and genomic alterations involved in HCC progression, cytotoxic therapies directly targeting cancer cells are still desperately needed.

In a paper published in this issue of *Hepatology*, Liu et al. used targeted nanomedicine to target HCC cells and demonstrate anti-tumor activity for TNF-related apoptosis-inducing ligand (TRAIL)-based therapy (6). Targeting TRAIL signaling has been previously proposed as an attractive anti-cancer approach (7). However, its clinical development has been limited by the systemic toxicity and poor bioavailability of existing agents, and the development of TRAIL-resistance, including in HCC (8). The authors circumvented these limitations by rationally designing a “smart” tumor-targeted lipid nanoparticle to deliver TRAIL plasmid DNA (pDNA) into HCCs. They improved the circulation time and tumor targeting of the nanoparticles by adding the SP94 peptide-PEG-DSPE on their surface. The positively charged protamine loaded in the calcium phosphate core increased the encapsulation efficacy of pDNA, enhanced the endosomal escape of the nanoparticles, and facilitate the nuclear delivery of TRAIL pDNA. Finally, intracellular release of Ca²⁺ from the calcium phosphate core helped overcome TRAIL resistance via calcium influx-dependent upregulation of its receptor, death receptor 5 (DR5). The authors used animal models of HCC with underlying liver damage. Surprisingly, in addition to induction of HCC cell apoptosis, they also found that TRAIL expression significantly reduced fibrosis in the damaged liver by inhibiting the viability and activation of the hepatic stellate cells (HSCs). Finally, combining this approach with standard sorafenib treatment significantly delayed HCC progression as well as liver fibrosis.

These exciting preclinical data warrant further exploration of this approach to control HCC growth and cirrhosis, alone or in combination with standard therapies. The impact of nanomedicine in cancer has been so far more limited than anticipated, with only few chemotherapeutic conjugates showing benefits of reduced toxicity and, in some cases, with increases in median overall survival by a few months. The elegant nanotechnology-based gene therapy approach described by Liu *et al.* provides proof-of-principle data that a new combination therapy may be more efficacious by efficiently and safely targeting both the malignant and stromal compartments in HCC. It also raises new questions and opportunities for future combinatorial approaches in this very difficult to treat disease.

HCCs are atypical tumors whose rich blood supply is often arterialized. Moreover, since the liver is often the site where nanomedicine tend to accumulate, liver cancer is particularly attractive disease for this approach. But how nanomedicine would impact immune responses in the context of currently available anti-angiogenic therapies, which significantly reduce vascular density and permeability, and blood flow, remains unclear. Moreover, it would be of great interest to determine the impact on tumor immunogenicity and immunotherapy efficacy of an effective pro-apoptotic and anti-fibrotic approach, such the one developed by Liu *et al.* We have previously shown that fibrosis and immunosuppression in the tumor microenvironment can mediate sorafenib resistance (9). We have also shown that reducing fibrosis and immunosuppression may facilitate anti-PD-1 immunotherapy when administered in combination with sorafenib (10). Future studies should determine whether a nanomedicine approach could increase the immunogenicity of HCC and reprogram the

tumor microenvironment to facilitate immunotherapy, which has recently become a standard of care in this disease.

In summary, new therapies are urgently needed for HCC, a complex disease which almost exclusively occurs in a diseased liver. Nanomedicine holds promise for a safer, more targeted delivery of targeted cytotoxic therapeutics, and cleverly designed approaches to target both the tumor and the diseased liver may have a substantial impact in this disease. Perhaps more importantly, further mechanistic understanding of the effects of nanomedicine on the tumor and its stroma may facilitate the development of synergistic combination treatments—such as with existing and emerging immunotherapies—to achieve durable responses and substantially increased survival in this largely intractable disease.

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