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Vascular Immunotargeting: Take the Highway to the First Exit

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All tumors are different. Thus, therapy for hepatocellular carcinoma (HCC) has become less dependent on systemic chemotherapy than treatment of other solid tumors, thanks to recent advances of locoregional therapies: radiofrequency and microwave ablation and transarterial chemoembolization (TACE). TACE aims to localize chemotherapeutic drugs solely to the tumor, avoiding the systemic toxicities. Further advancing TACE will empower many oncological therapies.

Because TACE embolizes a limited number of small vessels, it treats small patches of the organ, missing neighboring micrometastases. Embolization-induced ischemia starves tumors, but may also limit delivery of drugs to primary tumors and micrometastases. To realize the full potential of locoregional drug delivery, a technology is needed that delivers the chemo solely to the entire liver or entire segments, while maintaining low levels of drug in the rest of the body. This would have implications for cancers beyond HCC.

Such an idea is not new, given that Paul Ehrlich envisioned targeting drugs more than a century ago. In the last decade, drug delivery systems (DDSs; e.g., liposomes) came into medical practice and clinical trials. Some of these DDSs include affinity ligands (e.g., antibodies) that bind to target molecules, which helps accumulate drugs in the site of interest and guides subcellular addressing.

One natural target for DDSs is the endothelium, the cellular monolayer that lines the lumen of blood vessels. It serves numerous functions implicated in disease, including control of blood pressure, transport across blood vessels, inflammation, and immune responses. Co-opting transendothelial pathways may help deliver drugs across the vascular wall to the extravascular targets. The endothelium is highly accessible by the bloodstream to antibodies and DDSs.

Targeting DDSs to endothelium is quite versatile. It may be worthwhile to intervene in the endothelium systemically, for example, to treat generalized vascular dysfunction such as

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observed in septic shock. Alternatively, to treat locally—which is more challenging and important in many diseases—we need to target drugs to endothelia in a given vascular bed, types, or regions of blood vessels.

To achieve targeting to a specific vascular bed, the initial, and still most common, implementation uses antibodies to endothelial cells (“vascular immunotargeting”). Endothelial cells have distinct features in different organs, different types of vasculature, and different pathological states. Some endothelial “determinants” are enriched in different domains in quiescent and abnormal vasculature.^{1–3} A vascular-bed-specific antibody may allow targeting of drugs to a chosen organ’s vasculature.

Another approach exploits flow dynamics. Some determinants are expressed at similar levels by all endothelia. DDSs targeted to such pan-endothelial sites (e.g., using antibodies to platelet and endothelial cell adhesion molecule 1 [PECAM-1], a.k.a., CD31) accumulate in the lungs after intravenous injection, because: the lungs contain 20%-25% of the body’s entire endothelial surface; the lungs are perfused by >50% of the blood ejected from the heart in the ventricular systole; and the lungs are the first organ encountered by therapeutics after intravenous injection.

In the early 2000s, pan-endothelial determinants found a new use in providing preferential targeting to organs other than the lungs. This was accomplished by switching from an intravenous catheter to an intra-arterial catheter of an artery feeding the vascular bed of interest, providing a “first-pass effect” that allows for uptake in the downstream organ, similar to how the lungs benefit from a first-pass effect after intravenous injection. The intra-arterial catheter administration of DDSs targeted to PECAM-1 enabled drug delivery to a given organ’s endothelium—in the brain, mesentery, and the heart.^{4–6} This paradigm may be useful for transient local interventions such as protection of endothelium against transplantation ischemia.^{7, 8}

In this volume of *Hepatology*, Nora Winkler and co-authors extend this principle to a different type of target: hepatic tumors, using intra-arterial catheters in the hepatic artery.⁹ It is widely known, in the field of nanomedicine, that the liver takes the majority of any DDS injected by any route, mainly because of the uptake by Kupffer cells and liver sinusoidal endothelial cells residing in the hepatic sinusoids.¹⁰ However, other hepatic targets, such as HCC tumors and their vasculature, have been much more difficult to reach with DDSs.

To our knowledge, this is also the first attempt to define the role of target density, ligand affinity, binding kinetics, and perfusion rate in the phenomenon that the researchers dubbed “endothelial antibody capture.” The investigators characterized depletion of the circulating ligand by local vasculature. Not surprisingly, the closer the ligand level was to saturation, the less effective is endothelial capture (and the higher the probability of off-target effects). These findings have direct clinical relevance, pending recapitulation in other animal models and ultimately in patients.

A macronanoscale hybrid approach using intra-arterial catheters to route drug carriers delivers drugs to a vascular bed of interest, such as the hepatic tumors of this study or other diseased tissues. Given that intra-arterial catheters are practical in only select clinical

scenarios, it is imperative to clearly define the specifications of DDSs for the envision utility and its benefit/downside ratio. Now with their DDS initially worked out, Winkler et al. have an opportunity for many important follow-on studies.

First, it will be important to understand how they achieved a higher %ID than previous intra-arterial studies with pan-endothelial determinants. Second, there must be investigations of the intraorgan distribution of vascular targeted drugs; for example, which endothelial subtypes and regions the antibodies are binding to. For example, the microcirculation of HCC is lined by endothelium that no longer has traits of the liver sinusoidal counterpart.¹¹ Third, to motivate clinical translation, they should show that vascular immunotargeting is able to achieve better chemotherapy distribution throughout the entire liver, especially as compared to TACE. Fourth, for a given ligand conjugated to a nanocarrier, they can determine how its hepatic uptake is affected by ligand valence, size, shape, elasticity, pharmacokinetics, and other pertinent parameters of the DDSs. Finally, the most challenging and intriguing goal is the real-time imaging of tissue and cellular localization of the carriers and cargoes at a submicron level of resolution, which may reveal entirely surprising mechanisms.

Such mechanistic studies will allow further optimization of drug delivery, so that targeted therapeutics will finally become practical medicine, fulfilling Paul Ehrlich's dream of "magic bullets" and the decades-long movement toward locoregional drug therapies for malignancies like HCC. Once again, HCC treatment will be leading the way for other cancers.

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