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COMMENTARY

Opening endothelial gap while decompressing matrix: A coordinated mechanism enhancing drug delivery in pancreatic cancer treatment

KEY WORDS

Pancreatic ductal adenocarcinoma;
Microthrombi;
Endothelial gap;
Matrix decompression;
Drug perfusion;
Nanomedicine

Pancreatic ductal adenocarcinoma (PDAC) is one of the most difficult solid tumors in terms of therapeutic treatment and drug delivery. PDAC is characterized by a highly restrictive tumor microenvironment that is composed of dense extracellular matrix, elevated solid stress, increased interstitial fluid pressure (IFP), and compressed vasculature. These complex physiological and pathological barriers collectively create a hypoperfused tumor state leading to challenges in drug delivery efficacy[1-3].

Tumor-targeting nanomedicine has long been conceptualized as utilizing enhanced permeability and retention (EPR) effect to infiltrate tumor tissues. Therapeutic performance of nanomedicine would largely rely on adequate blood perfusion, transvascular extravasation and interstitial penetration *in vivo*[4]. Unfortunately with desmoplastic tumors like PDAC, conventional EPR-based delivery systems are not often efficient nor applicable. Strategies have been explored to increase vascular leakage thus improving drug extravasation in tumor location; with matrix-rich PDAC, excessive leakage also elevates IFP and compromises subsequent convective transport[4,5]. As such, simply opening the vascular barrier would be insufficient for nanomedicine delivery to penetrate cancers with dense stroma and poor perfusion.

In this featured article, Yang et al.[1] proposed a viable approach to overcoming barrier restriction by developing a microthrombi-targeted dasatinib (DAS) nano-micelle, CPHD/DAS, which synchronizes endothelial gap opening together with matrix decompression. This preparation design is conceptually notable because the mechanism treats EPR amplification not as a static increase in vascular permeability but a dynamic process collectively governed by vascular leakage, stromal mechanics and interstitial fluid pressure. The strategy is built on two key pathological features of PDAC, *i.e*., abundant fibrin-rich microthrombi and dense stromal matrix. By conjugating fibrin-binding CREKA peptide to amphiphilic hyaluronic acid-deoxycholate carrier, it created a nano-micellar delivery system capable of accumulating around tumor microthrombi. This targeting design provided a PDAC-specific anchoring mechanism beyond passive accumulation. At the same time hyaluronic acid-based micellar structure provided stable drug loading and hyaluronidase-responsive release in tumor microenvironment.

DAS is a suitable payload for the proposed coordinated delivery mechanism because of its dual regulatory effects. Locally released DAS inhibits platelet activation hence weakening platelet-mediated repair of vascular breaches and promoting endothelial gap opening; DAS also suppresses pancreatic stellate cell activation, reducing matrix deposition and relieving stromal compression. As such CPHD/DAS could modulate both vascular and stromal barriers ultimately achieving drug transport into PDAC[1,6,7].

One particularly noteworthy aspect of the study is the distinction between sole vascular opening and synchronized

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vascular-stromal regulation. The experiment demonstrated that increasing vascular leakage without matrix decompression would elevate IFP and reduce functional perfusion over the time. In contrast, CPHD/DAS-mediated matrix decompression was capable of counteracting pressure burden associated with endothelial gap opening, subsequently leading to sustained improvement of functional vessels, tumor perfusion and intratumoral drug penetration.

Results from this study would have broader implications for rational nanomedicine design. EPR amplification should not be simply evaluated by the extent of vascular permeability or initial nanoparticle extravasation. In desmoplastic tumors, excessive leakage without pressure relief might impair rather than improve subsequent drug delivery. For PDAC and other hypoperfused, matrix-rich tumors, effective nanomedicine delivery may necessitate coordinated remodeling of multiple transport barriers instead of sole enhancement of the vascular leakage.

In summary, the article by Yang et al. has provided a unique and viable paradigm for improving drug perfusion in treating pancreatic cancer. By opening vascular gap while decompressing stromal barrier at the same time, CPHD/DAS transformed transient vascular leakage into sustained drug delivery. This rational delivery mechanism may inspire future nanomedicine designs for desmoplastic tumors where conventional EPR-based delivery systems remain inadequate.

Conflicts of interest

The author declares no conflict of interest.

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