Researchers propose new strategy to improve efficiency for nanotherapeutic delivery in tumors

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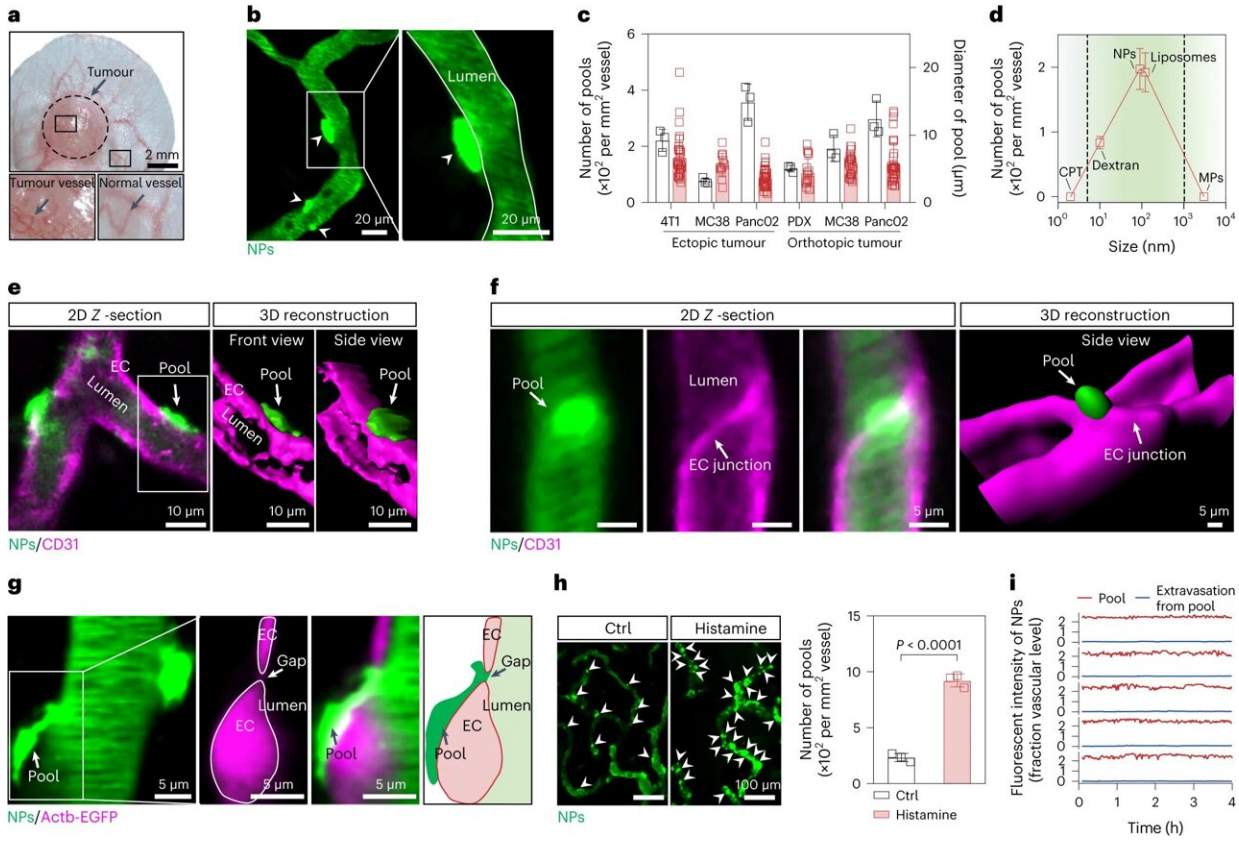

NPs form subendothelial pools at endothelial junctions in tumors. **a**, Stereoscopic microscopy images of murine mammary carcinoma 4T1 tumors in the mouse ear. **b**, IVM images showing NP pools (white arrow) in 4T1 tumors after i.v. injection of 1,1′-dioctadecyl-3,3,3′,3′-tetramethylindodicarbocyanine, 4–chlorobenzenesulfonate salt (DiD)-labeled PEG-*b*-PLGA polymeric NPs. **c**, Quantification of the numbers and diameters of NP pools in different tumor

models (that is, ectopic 4T1, MC38 and Panc02 tumors, and orthotopic PDX breast cancer, MC38 and Panc02 tumors) (n = 3 biologically independent samples). **d**, The number of NP pools in 4T1 tumors of mice after injection with fluorescence-labeled CPT, dextran, NPs (~90 nm), DOPC liposomes (~120 nm) and microparticles (MPs; 2–5 μm) (n = 3 biologically independent samples). **e**, Z stacks composed of individual image slices of 4T1 tumors (left) were compiled and rendered into 3D reconstructions (right) for spatial positioning analysis of NP pools. EC, endothelial cell. **f**, IVM images and 3D reconstructions of NP pools and CD31-labeled endothelial cells, showing that NP pools were located at endothelial cell–cell junctions. **g**, Spatial positioning analysis of subendothelial NP pools in *Actb–EGFP* fluorescent reporter mice bearing MC38 tumors. Images show that pools were located on the abluminal side of endothelial cells and occurred at the endothelial junctional gaps. **h**, IVM images showing subendothelial NP pools in 4T1 tumors of mice after treatments with PBS (i.t. injection, Ctrl) or histamine (i.t., 1.65 mg kg^{-1}). Number of NP pools per mm^2 vessel in 4T1 tumors of mice after treatment with histamine (n = 3 biologically independent samples). $P = 6.2 \times 10^{-5}$. **i**, Fluorescence intensity changes of NPs in individual NP pools and fluorescence intensity traces of NP extravasation from the pool over time (n = 3 biologically independent samples). The images presented are representative of at least three independent experiments. Data in **c**, **d** and **h** are shown as mean ± s.d. Significant differences were assessed using a two-tailed unpaired Student t-test (**h**). Credit: *Nature Nanotechnology* (2023). DOI: 10.1038/s41565-023-01498-w

A team led by Prof. Wang Yucai and Associate Prof. Jiang Wei from the University of Science and Technology of China (USTC) of the Chinese Academy of Sciences (CAS) revealed the mechanism of the tumor vascular basement membranes (BM) blocking nanoparticles (NPs) for the first time and developed an immunodriven strategy to increase the NP penetration through the BM barrier. Their work was published in *Nature Nanotechnology*.

Previous research on the nanotherapeutic transport from the vasculature

to the tumor mainly depended on the Enhanced Permeability and Retention effect (EPR), which believes that NPs can cross the tumor vascular endothelial barrier, the last defense of NP penetration, by exploiting the high permeability of tumor vessels. However, clinical trials discovered that NPs only transport around 0.7% of drugs into the tumor issue, suggesting other mechanisms for hindering NP penetration.

To shed light on this underappreciated mechanism, the team employed multistep non-invasive intravital microscopy and revealed that the BM that surrounds the endothelial cells and mural cells of tumor vessels severely impede the extravasation of NPs, forming perivascular NP pools in subendothelial void.

After accurately analyzing the spatial positioning, microstructure and causes of the NP pools, the team further found enzyme degradation of the BM could significantly reduce the NP pooling, boosting the transport efficiency of nanomedicine. Based on this finding, the team developed an immunodriven strategy by using the localized proteolytic enzymes released by inflammatory leukocytes to create a temporary window on the BM, enabling an explosive release of NPs deep into tumor, significantly enhancing the enrichment of nanomedicines and therapeutic effect.

The study not only proposes a novel nanomedicine transport strategy distinct from EPR, but also provides a new theoretical support for the application of nanotherapeutics in cancer, advancing the understanding of transvascular transport mechanism of NPs.

More information: Qin Wang et al, Breaking through the basement membrane barrier to improve nanotherapeutic delivery to tumours, *Nature Nanotechnology* (2023). DOI: 10.1038/s41565-023-01498-w

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