Cancer nanomedicine

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Exploiting endothelial transcytosis to reach into the brain

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Targeting P-selectin enables safer and more effective nanomedicine delivery through caveolin-1-mediated endothelial transcytosis in preclinical medulloblastoma tumour models.

Medulloblastoma, a type of solid malignant tumour in the cerebellum, is the most common paediatric brain tumour. Three of four medulloblastoma subtypes exhibit an intact and functional blood–brain barrier. The blood–brain barrier is a tightly regulated neurovascular unit comprising a continuous layer of endothelial cells with tight junction proteins at the cell–cell interface, pericytes and astrocytic end-feet, which together maintain normal brain function and homeostasis (Fig. 1)[1]. This neurovascular unit creates a biological barrier that limits mass transport and the efficient delivery of drugs into the brain. To safely and effectively treat brain tumours, such as medulloblastoma, new drug delivery technologies are needed to overcome the blood–brain barrier. Now, writing in *Nature Materials*, Tylawsky and colleagues describe fucoidan nanoparticles that effectively deliver the cancer drug vismodegib into medulloblastoma tissue through an endothelial transcytosis mechanism, that is, by triggering nanoparticle transport across the interior of these cells of the blood–brain barrier[2].

A current clinical challenge is the effective delivery of tumour therapeutics into the brain. The blood–brain barrier substantially limits the amount of drugs reaching the brain, leading to reduced therapeutic efficacy and off-target drug accumulation in healthy tissues and organs, which can induce severe toxicity-related side effects. Addressing this delivery challenge is a major focus of ongoing preclinical and clinical studies that use (1) molecular strategies, such as receptor-mediated transcytosis, carrier-mediated transcytosis, or diffuse and paracellular transport; (2) physical and chemical strategies, such as focused ultrasound with microbubbles, nanoparticles, or osmotic delivery; and (3) cell- and viral-based strategies, such as immune and stem cell delivery, or adenovirus-mediated gene therapies[1]. However, these emerging strategies still require further development, and more specific and efficient delivery approaches are urgently needed.

One promising approach is endothelial transcytosis to deliver cancer nanomedicines into the brain. Upon administration into a sonic hedgehog medulloblastoma mouse model, the nanoparticles bind to P-selectin, a cell surface receptor whose expression on tumour-associated endothelial cells was previously enhanced by X-ray irradiation (Fig. 1). The nanoparticle binding to the P-selectin receptors

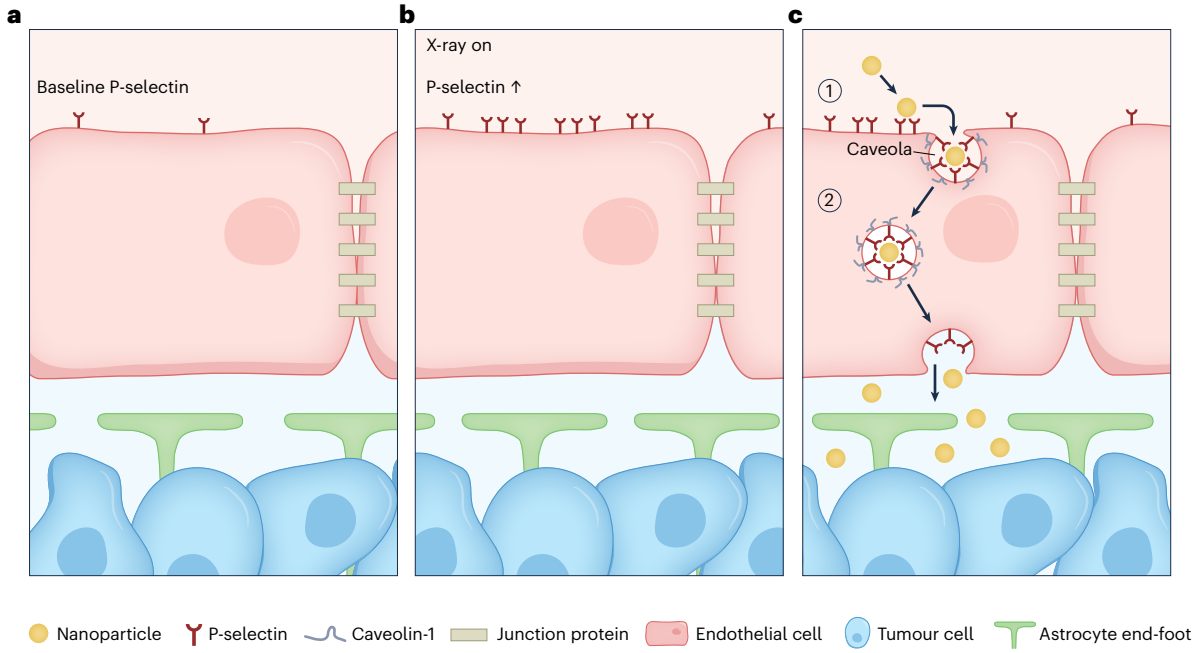

Fig. 1 | Mechanism of nanoparticle transcytosis across the blood–brain barrier endothelium. a,**b**, P-selectin expression level on medulloblastoma-tumour-associated endothelial cells before radiation therapy at baseline (**a**) and upon X-ray irradiation (**b**). **c**, Administered fucoidan nanoparticles bind to P-selectin (1) and subsequently undergo caveolin-1-mediated endothelial transcytosis (2). Figure adapted with permission from ref. [2], Springer Nature Ltd.

via fucoidan triggers the transcytosis process[3], leading to the transport of the drug-laden nanoparticles across the cell from the luminal to the abluminal side of the tumour endothelium, thereby enabling more efficient delivery of vismodegib to the medulloblastoma tumour (Fig. 1). Endothelial cells take a central role in the reported delivery strategy because these cells express the P-selectin receptor and further actively transport the nanoparticles across the tumour endothelium via transcytosis.

Other cell surface receptors have been reported in the literature for transcytosis-based drug delivery applications in the brain. Examples include transferrin receptors, insulin receptors, low-density lipoprotein receptors (LDLR), and LDLR-related protein 1 receptors. However, these receptors are ubiquitously distributed, leading to peripheral and off-target delivery, compromising a treatment's safety and efficacy[4]. A high level of specific receptor expression on tumour-associated endothelial cells is essential to minimize off-target delivery and toxicity. Tylawsky et al. identified P-selectin as a receptor candidate on activated brain-tumour-associated endothelial cells. P-selectin is a cell adhesion molecule that binds P-selectin glycoprotein ligand-1 on circulating leukocytes to recruit them to inflamed sites[5]. P-selectin further binds to polysaccharides, such as heparan sulfate and fucoidan. Expression of P-selectin surface receptors occurs on activated endothelial cells stimulated by inflammatory cytokines or radiation[6,7]. Tylawsky et al. enhanced P-selectin expression in tumour-associated endothelial cells through X-ray irradiation while sparing adjacent healthy brain tissue. The demonstrated radiation treatment provides spatiotemporal control over the P-selectin expression.

Another interesting finding of the study is the subsequent nanoparticle transcytosis initiated by endocytosis on the luminal side. The transcytosis process is dependent on caveolin-1, a protein involved in the caveolae-mediated intracellular transport[8]. Using a genetically engineered sonic hedgehog medulloblastoma mouse model, Tylawsky et al. show efficient fucoidan nanoparticle transcytosis and drug delivery to the tumour tissue upon X-ray treatment with 0.25 Gy. While the authors do not investigate the mechanisms of intracellular vesicle sorting and abluminal exocytosis, the effective nanoparticle delivery suggests efficient transcytosis resulting in an improved therapeutic index of vismodegib for medulloblastoma treatment.

Endothelial transcytosis may thus be an elegant strategy to efficiently deliver nanoparticles to various solid tumour types, potentially enabling safer and more effective nanomedicine treatments. In line with recent evidence suggesting that the dominant mechanism of nanoparticle entry into solid tumours is active endothelial transcytosis[9], the authors' research additionally supports the field's quest to identify new ways to increase nanoparticle delivery efficiency[10]. However, more studies are needed to explore the clinical feasibility of this delivery strategy for nanomedicine development. For example, there is an opportunity to investigate the generalizability of radiation-induced P-selectin expression targeting in other solid tumour models while further assessing potential safety risks upon concurrent P-selectin expression on platelets and other endothelial cells. Targeting P-selectin with nanomedicines may further affect the receptor's physiological function and availability for leukocyte recruitment during inflammation or certain immunotherapies. Additionally, more detailed mechanistic research on endothelial transcytosis is needed to fully understand the efficacy of nanomedicine delivery to solid tumours, including medulloblastomas.

Overall, this study demonstrates an exciting opportunity for endothelial transcytosis to overcome biological barriers in nanoparticle-based drug delivery. Exploiting the endothelial transcytosis pathway may advance the development of safer and more effective cancer nanomedicines for treating brain malignancies and potentially other solid tumours.

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References

1. Arvanitis, C. D., Ferraro, G. B. & Jain, R. K. *Nat. Rev. Cancer* **20**, 26–41 (2020).
2. Tylawsky, D. E. et al. *Nat. Mater.* https://doi.org/10.1038/s41563-023-01481-9 (2023).
3. Sheth, V., Wang, L., Bhattacharya, R., Mukherjee, P. & Wilhelm, S. *Adv. Funct. Mater.* **31**, 2007363 (2021).
4. Terstappen, G. C., Meyer, A. H., Bell, R. D. & Zhang, W. D. *Nat. Rev. Drug Discov.* **20**, 362–383 (2021).
5. Vestweber, D. & Blanks, J. E. *Physiol. Rev.* **79**, 181–213 (1999).
6. Hallahan, D. E., Staba-Hogan, M. J., Virudachalam, S. & Kolchinsky, A. *Cancer Res.* **58**, 5216–5220 (1998).
7. Shamay, Y. et al. *Sci. Transl. Med.* **8**, 345ra87 (2016).
8. Donahue, N. D., Acar, H. & Wilhelm, S. *Adv. Drug Del. Rev.* **143**, 68–96 (2019).
9. Sindhwani, S. et al. *Nat. Mater.* **19**, 566–575 (2020).
10. Wilhelm, S. et al. *Nat. Rev. Mater.* **1**, 16014 (2016).

Competing interests

The authors declare no competing interests.