Cancer nanomedicine

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Artificial intelligence assists nanoparticles to enter solid tumours

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Single blood vessel analysis by artificial intelligence (AI) reveals heterogeneous vascular permeability among different tumour types, which is leveraged in rationally designing protein nanoparticle-based drug delivery systems to achieve active trans-endothelial permeability in tumours.

Adjusting the pharmacokinetic profile of highly sensitive and/or toxic drugs is one of the key features of nanoparticle-guided drug delivery. Since the early developments of nanomedicines during the 1970s (refs. 1–3), drug delivery has mostly focused on addressing solid tumours and enhancing the accumulation of cancer chemotherapeutics while reducing their often very harsh off-target effects on healthy tissues. This received further attention in the 1980s by Hiroshi Maeda's discovery of the enhanced permeability and retention (EPR) effect: synthetic or biological macromolecules (including albumin) were found to passively extravasate from blood vessels through leaky tumour vasculature into solid tumour tissues and progressively accumulate there over time.[4] Since then, this mechanism has been considered a critical rationale for the development of a variety of tumour-targeting synthetic nanocarriers[5], albeit, only with limited success in terms of efficacious clinical translation and relevant benefits for patients. Now writing in *Nature Nanotechnology*, Zhu et al., apply large data characterisation tools for identifying nanoparticle accumulation mechanisms in 32 different tumour models[6].

So far, only 14 systemically administered cancer nanomedicines have been approved for clinical use worldwide (the majority of which is mostly based on liposomal formulations of already

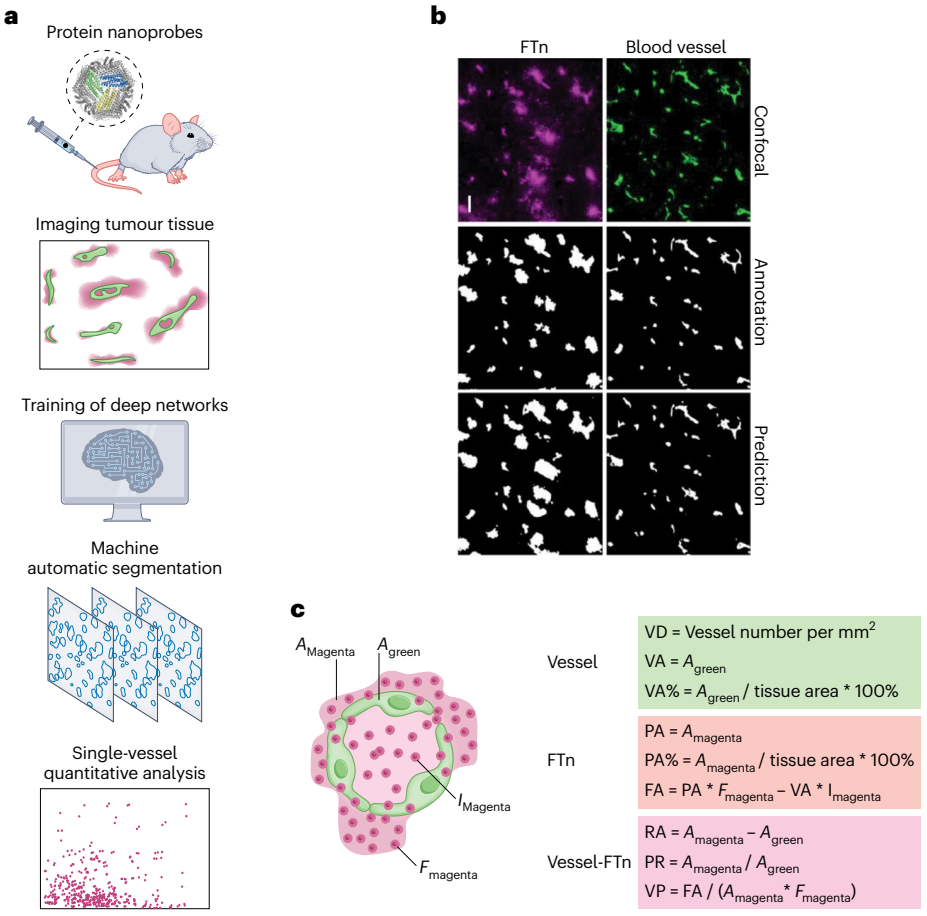

Fig. 1 | A machine-learning-assisted single-vessel analysis for predicting nanoparticle permeability in tumour vasculatures towards nanomedicine-supported cancer treatment. a, Drug and tracer-loaded ferritin nanocages were applied to different tumour models in vivo and characterised by image segmentation-based machine learning technology to classify and subsequently modulate nanoparticle vascular permeability into solid tumours. **b**, Representative confocal image, manual annotation and AI-based prediction for vessel channel and ferritin nanoprobes (FTn) penetration channel. **c**, Four basic parameters of automatic machine output and nine quantitative indices of single-vessel assessment. Figure adapted from ref. 6.

approved small-drug chemotherapeutics)[5]. Thus, the relevance of nanocarrier-based cancer therapy and the overall role of the EPR effect on nanoparticle-mediated delivery into solid tumours has been the subject of particular controversy amongst researchers[7,8]. At the same time, evidence of EPR could be collected for long-circulating, drug-loaded nanocarriers, for example, that their accumulation remains highly size-dependent[9] and may also be subjected to dynamic rearrangement of the tumour vasculature[10]. In more recent studies, alternative delivery routes have further been suggested beyond passive accumulation by active trans-endothelial transport mechanisms[11].

The study by Zhu et al. provides further insights into nanoparticle tumour accumulation[6]. As a prerequisite, the authors use their well-established ferritin-nanocage system as a reliable and precisely modifiable carrier model. It provides controllable size features, remains circulating in the bloodstream in analogy to its endogenous ferritin analogues, and allows well-defined drug loading or tracer labelling for monitoring by fluorescence or electron microscopy techniques. The authors inject these carriers intravenously into mice bearing 32 different types of subcutaneous tumours and afterwards collected fluorescent images from tissue sections of more than 67,000 tumour blood vessels. With the help of an image segmentation-based machine learning technology, they could establish AI-assisted methods of analysing large amounts of microscopic data under high-throughput conditions and rapidly classify the vascular permeability of the different tumour tissue samples (Fig. 1).

Through transmission electron microscopy, the authors could also reveal that passive extravasation mechanisms were still dominant for those tumours that had been classified as highly vascularly permeable before. Doxorubicin-loaded ferritin-nanocages could directly reduce their growth in contrast to other tumours that the machine learning technology had classified as low permeable. Nonetheless, some ferritin-nanocages could still be found in the latter tumours and electron microscopy analyses revealed active trans-endothelial processes being involved primarily.

Interestingly, the latter accumulation could be enhanced by modifying the ferritin-nanocages with a pH-responsive peptide domain for endosomal escape and an albumin-binding domain for Golgi-mediated transcytosis. This could also be utilised to improve the delivery of doxorubicin into the low permeable tumours and yield reduced tumour growth. Subsequent characterisation of the treated tumours by the image segmentation-based machine learning technology confirmed the mechanism of improved nanocarrier trans-endothelial transport (Fig. 1). Altogether, the authors unequivocally demonstrate how AI can assist in delineating the heterogeneity of tumour vascular permeability and nanomedicine-based interventions.

Towards patient-beneficial translation, however, this strategy still depends on collecting relevant cancer biopsies for tumour vessel characterization. In principle, the machine learning technology could assist in classifying tumour blood vessel permeability more effectively and, afterwards, selecting what kind of nanocarrier would be ideal for successful cancer treatment. The transferrin nanocages provide suitable theragnostic features for monitoring tumour trans-endothelial accumulation and recommending personalised treatment. Instead of collecting a reliable amount of relevant tissue samples, alternative biomarkers or non-invasive imaging tools would be more helpful to fully reflect the three-dimensional vascular permeability of the tumour (and ideally its metastases, too). In addition, combination therapies with vascular permeability enhancers in the cancer microenvironment as well as recent developments in cancer immunotherapy, may become suitable to understand better and make use of cancer vascular permeability for each cancer and patient individually. Further studies are required to minimise the gap between preclinical research and clinical translation.

Sadly, about two years ago, during the COVID-19 pandemic, Hiroshi Maeda passed away and could not witness how AI may assist in closing this gap.

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Competing interests

The author declares no competing interests.