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CANCER

Tumour vessel normalization takes centre stage

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Tumour vasculature is known to be abnormal: whether this feature should be exploited or corrected therapeutically has been the subject of debate. Two reports in *Cancer Cell* suggest that tumour vessel normalization — either by altering angiogenesis through the TIE2 (also known as angiopoietin 1 receptor) pathway or by reducing glycolysis in tumour endothelial cells — reduces metastasis and improves chemotherapeutic drug delivery in animal models.

Anti-angiogenic therapies, which aim to starve tumour cells of nutrients by reducing tumour vascularization, have been less successful than hoped. Reducing tumour vascularization makes tumours more hypoxic and therefore resistant to chemotherapies, renders vessels leaky and therefore prone to tumour cell intravasation, and also reduces the delivery of chemotherapeutics. Normalizing tumour vessels is hypothesized to restore perfusion, thus reducing metastasis and enhancing drug delivery.

TIE2 is expressed in endothelial cells, where it tightens endothelial junctions and stabilizes vessels when activated by its agonist, angiopoietin 1 (ANG1). TIE2 can be activated or inhibited by ANG2 in a context-dependent manner.

To promote normalization of the tumour vasculature, Park *et al.* generated an ANG2-binding and TIE2-activating antibody (ABTAA). The ANG2–ABTAA complex is thought to bind to and activate TIE2. This antibody was delivered at 10–25 mg per kg by intraperitoneal injection every few days for up to 2 weeks after the establishment of the tumour. ABTAA induced tumour vessel normalization (as measured by features including pericyte and collagen type IV basement membrane coverage as well as by the distribution of endothelial junction molecules) in mouse models of glioma, Lewis lung carcinoma (LLC) and breast cancer. Delivery of chemotherapeutic agents to the tumour was increased, and metastasis and tumour cell extravasation were decreased by ABTAA treatment. ABTAA treatment also decreased tumour volume and increased survival, particularly when combined with traditional chemotherapeutic agents, in all three tumour models.

In an alternative approach, Cantelmo *et al.* targeted glycolysis in vascular endothelial cells. Previously, this group had found that targeting glycolysis using the chemical inhibitor 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one (3PO) in ocular and inflammatory disorders reduced pathological angiogenesis. In this study, they found that tumour endothelial cells upregulated glycolytic pathways, which suggests an increased dependence on glycolysis to generate energy.

To investigate further, mice haplodeficient for the gene encoding the glycolytic enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) in cells expressing vascular endothelial cadherin ($Pfkfb3^{+/\Delta^{EC}}$) were subcutaneously implanted with melanoma or LLC cells. Although tumour volume was not affected by haplodeficiency for *Pfkfb3*, tumour necrosis, invasion and metastasis were reduced. These effects were phenocopied by treatment with 25 mg per kg of 3PO, delivered by three intraperitoneal injections per week for up to 2 weeks (depending on the model). Genetic or pharmacologic inhibition of PFKFB3 improved perfusion, lowered tumour hypoxia, tightened the endothelial cell barrier, and increased pericyte coverage, features associated with vessel normalization. As in the study by Park *et al.*, 3PO treatment increased the delivery of cisplatin to the tumour cells and correspondingly decreased tumour growth in melanoma-bearing mice. Importantly, this drug combination nearly completely prevented metastasis.

These data suggest that vessel normalization in tumours could have substantial benefit, mainly by improving chemotherapy delivery and by tightening up endothelial junctions to reduce metastases. Vascular normalization strategies could be useful in numerous types of solid tumours, as many of these have abnormal blood vessels.

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Brain light/Alamy Stock Photo

ORIGINAL ARTICLES Park, J. S. *et al.* Normalization of tumor vessels by Tie2 activation and Ang2 inhibition enhances drug delivery and produces a favorable tumor microenvironment. *Cancer Cell* **30**, 953–967 (2016) | Cantelmo, A. R. *et al.* Inhibition of the glycolytic activator PFKFB3 in endothelium induces tumor vessel normalization, impairs metastasis, and improves chemotherapy. *Cancer Cell* **30**, 968–985 (2016)
FURTHER READING Kreuger, J. & Phillipson, M. Targeting vascular and leukocyte communication in angiogenesis, inflammation and fibrosis. *Nat. Rev. Drug Discov.* **15**, 125–142 (2016)