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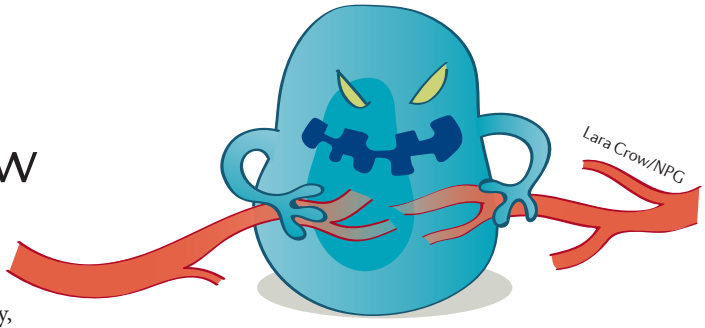
ANGIOGENESIS

Going with the flow



> combined inhibition of angiogenesis and vessel co-option or deposition of ECM components might be a more effective strategy for the treatment of liver metastases

Antiangiogenic therapy with drugs that block vascular endothelial growth factor (VEGF) signalling to inhibit the formation of new blood vessels in the tumour has been successful in the treatment of several types of cancers, for example, metastatic colorectal cancer (mCRC). However, the efficacy of this strategy is limited owing to mechanisms that are still poorly understood. Now, two studies have revealed two possible mechanisms that might explain why VEGF inhibition can be rendered ineffective.

After observing unexpected changes, such as vessel compression and portal hypertension, in liver metastases from patients with mCRC treated with VEGF inhibitors, Rahbari *et al.* were interested in investigating these effects on blood perfusion and drug delivery. They analysed levels of the extracellular matrix (ECM) component hyaluronic acid (HA) and found higher expression in the metastases compared with the uninvolved liver parenchyma. Moreover, HA expression was significantly increased in liver metastatic tissue obtained after treatment with bevacizumab compared with samples from the same patients before exposure to the drug.

The authors then used two syngeneic mouse models of liver mCRC (SL4 and CT26) to further study the mechanisms involved in these changes. B20 — a VEGF-blocking antibody — increased tumour stiffness in both models in a dose-dependent manner as well as levels of HA, its receptor CD44 and sulfated glycosaminoglycans (sGAGs). Further experiments revealed a decrease in microvessel density after 3 days of B20 treatment that was accompanied by an increase in hypoxia at day 6 and followed by HA expression in those hypoxic regions. Finally, the authors treated mice with B20 with or without polyethylene glycol conjugated to hyaluronidase (PEG-HAse) to assess whether depletion of HA could prevent the changes induced by anti-VEGF therapy. Treatment with PEG-HAse resulted in a 74% reduction of HA in liver metastases from SL4 mice, and increased tumour perfusion. A combination of PEG-HAse with B20 and chemotherapy moderately prolonged survival of SL4 mice compared with treatment with only B20 and chemotherapy (19.06 days versus 17.13 days; $P = 0.008$), suggesting that HA targeting could enhance the efficacy of anti-VEGF therapy combined with chemotherapy in the treatment of liver metastases from CRC.

In turn, Frentzas, Simoneau *et al.* wanted to investigate whether vessel co-option — a process whereby cancer cells incorporate pre-existing vessels from surrounding tissue instead of inducing new vessel growth — is a mechanism of resistance to antiangiogenic therapy in liver metastases. They evaluated the histopathological growth patterns (HGPs) and the response to therapy in samples of liver metastases resected from patients with CRC who had been treated with a combination of bevacizumab and chemotherapy before surgery. The authors found that patients who did not respond to the treatment presented with lesions with a type of HGP — replacement HGP — in which cancer cells infiltrate the liver parenchyma and co-opt pre-existing sinusoidal vessels. They also analysed new liver metastases occurring after treatment, and observed that replacement HGP was significantly increased in these new lesions. In liver metastatic samples from patients with breast cancer — a type of cancer that generally does not respond to antiangiogenic therapy — the authors also observed predominance of replacement HGP in nearly all cases.

Finally, the authors evaluated whether combined inhibition of vessel co-option and angiogenesis could be more effective at limiting tumour growth than angiogenesis inhibition alone. To that end, they treated mice bearing tumours in which actin-related protein 2/3 subunit 3 (ARPC3) — which mediates the nucleation of actin filaments in cancer cells to drive the cancer cell movement that is required for vessel co-option — had been knocked down with a combination of B20 and the chemotherapeutic agent capecitabine. Tumour burden was significantly suppressed by the combination treatment in these mice compared with control mice.

These two studies suggest that combined inhibition of angiogenesis and vessel co-option or deposition of ECM components might be a more effective strategy for the treatment of advanced liver metastases than current strategies that, combined with chemotherapy, only target angiogenesis.

M. Teresa Villanueva

ORIGINAL ARTICLES Rahbari, N. N. *et al.* Anti-VEGF therapy induces ECM remodeling and mechanical barriers to therapy in colorectal cancer liver metastases. *Sci. Transl Med* **8**, 360ra135 (2016) | Frentzas, S. *et al.* Vessel co-option mediates resistance to anti-angiogenic therapy in liver metastases. *Nat. Med.* **22**, 1294–1302 (2016)