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CANCER

Therapy for colorectal cancer liver metastases: understanding resistance

> “…insights into resistance mechanisms might enable … new or improved therapeutic approaches”

Two new studies explore mechanisms of resistance to anti-angiogenic therapies in the context of colorectal cancer liver metastases (CRCLMs). The findings show the importance of the tumour microenvironment and provide evidence that extracellular matrix (ECM) remodelling and vessel co-option could be clinically relevant mediators of this resistance.

In the first study (published in *Nature Medicine*), the researchers investigated tumour vascularization. “It has been generally assumed that all metastases must recruit blood vessels by inducing the growth of new blood vessels, a process that is stimulated by vascular endothelial growth factor (VEGF),” explains author Andrew Reynolds. “This assumption prompted the clinical development of anti-angiogenic agents that target VEGF-signalling, including bevacizumab … and many others.” However, the survival benefit of these agents can be modest and in some cases unproven, which prompted Reynolds and colleagues to explore why anti-angiogenic therapies can have limited efficacy.

Taking advantage of liver tissue samples and medical records from patients with CRCLM who received preoperative bevacizumab and chemotherapy, the researchers found a strong association between poor response to bevacizumab and CRCLM tumours with a replacement histopathological growth pattern (HGP). Vessel co-option occurs in this tumour type, whereby cancer cells incorporate pre-existing blood vessels from surrounding tissues instead of using angiogenesis. Moreover, there seemed to be an increased prevalence of the replacement HGP in patients with CRCLM who progress after bevacizumab–chemotherapy, with patients with this tumour growth pattern having less clinical benefit (overall survival) from bevacizumab than patients with other tumour growth patterns in which angiogenesis occurs. Interestingly, vessel co-option was not just a feature of CRCLM, with the replacement HGP also prevalent in breast cancer liver metastases tissue samples.

Switching to a mouse model of CRCLM, Reynolds and co-workers validated their findings from human tissue samples and confirmed experimentally that vessel co-option in CRCLMs required cancer cell motility (via Arp 2/3). Importantly, combined inhibition of angiogenesis and vessel co-option seemed to be more effective at controlling tumour burden in mice with CRCLM than anti-angiogenesis therapy alone.

In the second study (published in *Science Translational Medicine*), Rahbari *et al.* also explored the underlying mechanisms of resistance to anti-angiogenic therapy, but the focus was instead on stress-induced blood vessel collapse and the role of the ECM, which can affect drug perfusion and delivery. Immunohistochemical analysis of liver specimens from patients with CRCLMs revealed increased hyaluronic acid (HA) in metastases in the liver compared with uninvolved liver parenchyma, with marked increase in HA expression in CRCLM tissue from patients treated with preoperative bevacizumab and chemotherapy.

In two mouse models of CRCLM, the investigators showed that anti-VEGF therapy substantially increased expression of HA and sulfated glycosaminoglycans (both components of the ECM) without affecting collagen deposition. Interestingly, density of these ECM components was strongly associated with increased tumour stiffness after anti-VEGF therapy in mouse models. Experiments indicated that increased hypoxia seemed to induce the increased HA expression by activated hepatic stellate cells after anti-VEGF therapy.

Crucially, in mouse models, HA depletion (via hyaluronidase treatment) increased perfusion and improved chemotherapy efficacy after anti-VEGF therapy for CRCLM. “Thus, targeting the noncollagenous ECM is a potential strategy to enhance the efficacy of systemic treatments,” suggest authors Rakesh Jain and Dai Fukumura.

These new insights into resistance mechanisms might enable the development of new or improved therapeutic approaches, or indeed a more personalized approach using tumour biology (identified using biomarkers or imaging) to select those patients who will respond best to certain therapies.

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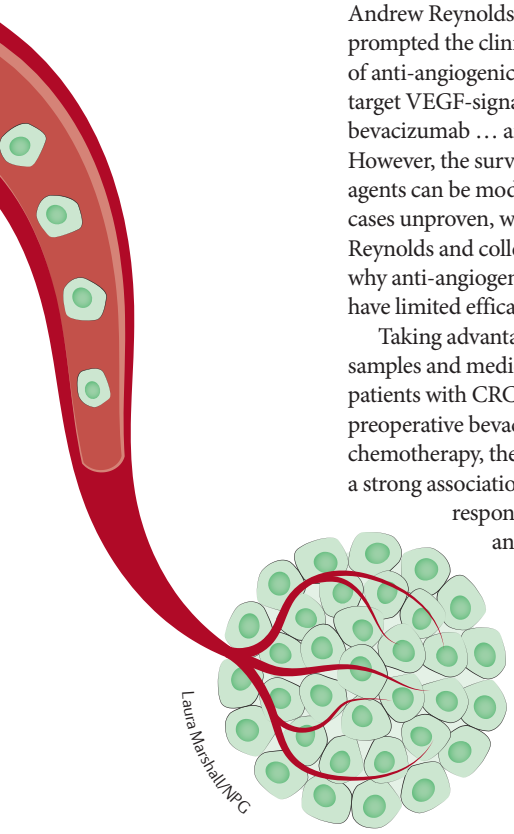

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ORIGINAL ARTICLES Frentzas, S. *et al.* Vessel co-option mediates resistance to anti-angiogenic therapy in liver metastases. *Nat. Med.* http://dx.doi.org/10.1038/nm.4197 (2016) | Rahbari, N. N. *et al.* Anti-VEGF therapy induces ECM remodeling and mechanical barriers to therapy in colorectal cancer liver metastases. *Sci. Transl. Med.* **8**, 306ra135 (2016)