Discontinuation of anti-VEGF cancer therapy promotes metastasis through a liver revascularization mechanism

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The impact of discontinuation of anti-VEGF cancer therapy in promoting cancer metastasis is unknown. Here we show discontinuation of anti-VEGF treatment creates a time-window of profound structural changes of liver sinusoidal vasculatures, exhibiting hyper-permeability and enlarged open-pore sizes of the fenestrated endothelium and loss of VE-cadherin. The drug cessation caused highly leaky hepatic vasculatures permit tumour cell intravasation and extravasation. Discontinuation of an anti-VEGF antibody-based drug and sunitinib markedly promotes liver metastasis. Mechanistically, host hepatocyte, but not tumour cell-derived vascular endothelial growth factor (VEGF), is responsible for cancer metastasis. Deletion of hepatocyte VEGF markedly ablates the 'off-drug'-induced metastasis. These findings provide mechanistic insights on anti-VEGF cessation-induced metastasis and raise a new challenge for uninterrupted and sustained antiangiogenic therapy for treatment of human cancers.

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