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The *MET* oncogene drives a genetic program linking cancer to hemostasis

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To study the early events of transformation in a setting that recapitulates the natural occurrence of sporadic cancer, it would be ideal to develop a model that initiates from single somatic cells harbouring mutations of one or more cancer-related genes, but intermingled with their normal tissue context. We have set up a mouse model of somatic oncogene delivery, relying on the unique properties of late-generation lentiviral vectors[1] (LV). LV enable oncogene targeting by non-viral promoters in post-natal life, and transformation of somatic cells that remain functionally interlocked within the normal tissue. Through LV, we targeted the activated *MET* oncogene to the mouse liver. We detected development of foci of hepatocyte clonal expansion, which slowly progressed towards malignancy. Surprisingly, we also observed the occurrence of a thrombohemorrhagic syndrome articulated in two phases. The first phase (thrombotic) preceded the onset of liver foci, and consisted of venous thromboses and hyperactivation of the coagulation system; in the second phase (haemorrhagic), haemostasis disturbance evolved into consumption coagulopathy, displaying the clinical features of chronic disseminated intravascular coagulopathy (DIC), which invariably provoked lethal haemorrhages in mice.[2] This phenotype is reminiscent of the *Trousseau syndrome*, first described in 1865, which defines haemostasis disorders as a forewarning of occult malignancy; this phenomenon has since been extensively reported in clinical and epidemiological studies, but has so far resisted a mechanistic explanation. We thus analysed the gene expression profile of cells transduced with activated *MET*, finding an overall modulation of the whole *coagulation gene set* (71 genes) and the prominent induction of plasminogen activator inhibitor 1 (PAI-1) and cyclo-oxygenase 2 (COX-2). PAI-1 exerts anti-fibrynolitic activities, promoting blood clotting. COX-2 catalyses a step in the synthesis of prostaglandins, which modulate platelet functions. We found that PAI-1 and COX-2 products were increased in the mouse serum, soon after *MET* transduction and before the appearance of liver foci, thus offering explanation for early onset of the coagulopathy. *In vivo* administration of a COX-2 inhibitor (rofecoxib), or a PAI-1 inhibitor (XR5118), inhibited not only DIC evolution, but also tumour progression, thus providing direct genetic evidence for the long-sought-after link between oncogene activation and haemostasis disturbance.

References

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