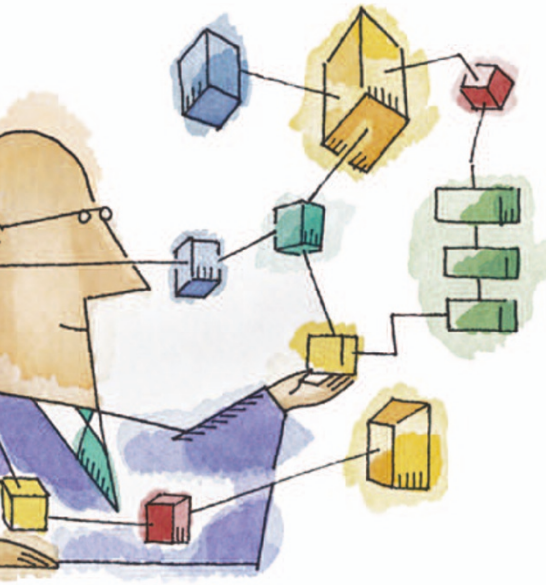
TUMORIGENESIS

The collagen connection



Patients with an inherited blistering skin disorder — recessive dystrophic epidermolysis bullosa (RDEB) — often develop epidermal squamous-cell carcinoma (SCC). Functional defects in type VII collagen are responsible for RDEB, and Susana Ortiz-Urda and colleagues have disovered that SCC development in these patients is dependent on collagen-VII-mediated interactions between the tumour and its microenvironment.

Intriguingly, a small subgroup of individuals with RDEB never develop invasive SCC, and the investigators wondered why, when all patients with RDEB have flaws in the same protein, some are susceptible to this cancer and others are not. Initially, they assessed the tumorigenicity of primary keratinocytes from patients with RDEB. The cells were transformed using oncogenic RAS and the NF-κB inhibitor IκBα, and then they were transplanted into immunodeficient mice. In this assay, cells from non-RDEB individuals form epidermal tumours that appear the same as SCC. Tumours also grew from the keratinocytes from eight of the twelve patients with RDEB that were sampled, but not from cells from the remaining individuals with RDEB, confirming two distinct RDEB types — tumorigenic and non-tumorigenic.

The two populations could be further distinguished by the expression of collagen VII: primary keratinocytes from patients with tumorigenic RDEB express a portion of collagen VII, whereas the cells from the non-tumorigenic RDEB subset (known as $RDEB^{Null}$) do not. Furthermore, expressing collagen VII in the $RDEB^{Null}$ cells restored their ability to form tumours. Ortiz-Urda and colleagues narrowed down the region of the protein responsible for tumour formation by expressing various fragments of collagen VII in $RDEB^{Null}$ cells. The sequence they identified (FNC1) restored tumorigenicity to $RDEB^{Null}$ cells, and antibodies against FNC1 prevented normal primary keratinocytes from forming tumours.

There are a range of neoplastic processes that FNC1 might affect — tumour-cell proliferation, survival and/or invasion — and the authors examined each of these. The FNC1

ONCOGENES

Trousseau's sign

The spontaneous formation of blood clots can be an indicator of neoplastic disease and was first described by Trousseau in 1865. Boccaccio and colleagues have now identified the genetic link between blood hypercoagulation and cancer.

The proto-ongogene *MET*, which encodes the hepatocyte growth factor/scatter-factor receptor, is known to be important for invasive growth during tissue morphogenesis and repair, and is also mutated in a number of human cancers. Boccaccio and colleagues expressed a constitutively active form of human MET under the control of the albumin promotor to limit its expression to mouse hepatocytes. Cancer most often arises from the transformation of somatic cells, so the authors used a self-inactivating lentiviral vector to target these cells in adult mice. A GFP-expressing lentivirus was used as a control.

MET was successfully expressed in the somatic hepatocytes, and nodules of dysplastic cells were evident after 3 months. By this time, however, many of the MET-expressing mice had already developed blood clots, evident in their tails, and by 6 to 7 months, as a result of the exhaustion of the blood-coagulation system, many had haemorrhages in all major organs — a condition known as disseminated intravascular coagulation (DIC). Only 5 of 25 mice survived this and, of these, only a few went on to develop overt liver neoplasia.

Hepatocytes are important for the synthesis of a number of blood-clotting factors, so to rule out a hepatocyte-specific effect the authors expressed MET in mammary epithelial cells and transplanted these into the spleens of mice. These mice also developed DIC.

Microarray analysis has indicated that MET upregulates the expression of several genes associated with blood homeostasis. Indeed, the mRNAs encoding two factors, plasminogen activator inhibitor type 1 (PAI1) and cyclooxygenase-2 (COX2) are among the most upregulated of the 12,000 genes assessed. PAI1 inhibits fibrin degradation and COX2 regulates platelet function, so the authors investigated whether the increased expression on these two proteins could explain the prothrombotic state. They found that PAI1 and COX2 were highly expressed in the MET-transformed mammary cells and were also expressed in the dysplastic liver nodules. Treatment of the mice with inhibitors of PAI1 or COX2 suppressed the onset of DIC, and, after prolonged treatment, the dysplastic liver foci also started to regress.

These data indicate for the first time that a single gene can both promote tumour formation in a small subset of cells and systemically affect blood coagulation by virtue of its effects on the expression of other genes. The therapeutic implications of these findings need to be carefully considered.

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References and links

ORIGINAL RESEARCH PAPER Boccaccio, C. *et al*. The *MET* oncogene drives a genetic programme linking cancer to haemostasis. *Nature* **434**, 396–400 (2005)