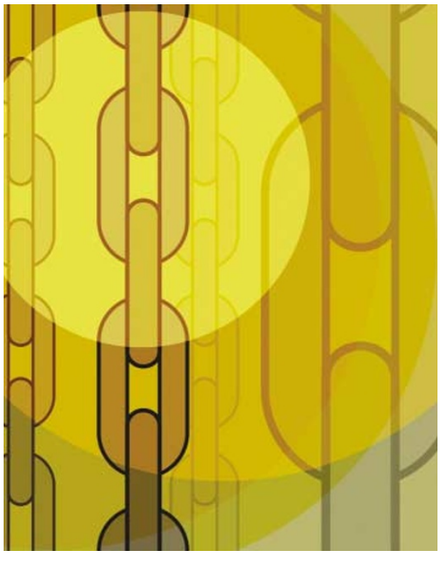
ANGIOGENESIS

Interlinked



Testosterone, blood and the eye would seem to have little in common, yet there is a link and it involves prostate cancer. Tumours require neovascularization to grow and this depends on a balance between key regulators. In the prostate, androgens such as testosterone drive angiogenic inducers such as vascular endothelial growth factor (VEGF) to stimulate blood-vessel growth. Androgen withdrawal causes endothelial-cell apoptosis followed by epithelial-cell apoptosis, which continues even after levels of VEGF recover, so other factors must have a role. Now, Doll and colleagues have identified pigment epithelium-derived factor (PEDF) — known to inhibit angiogenesis in the eye — as a key inhibitor of stromal vasculature, as well as epithelial-cell growth in the prostate, and show that it is also regulated by androgens.

The authors generated Pedf-deficient mice (*Serpinf1*$^{-/-}$) to study the role of Pedf in normal growth and development. Deleting *Serpinf1* caused excessive angiogenesis not only in the eye, but also in two hormone-sensitive organs — the prostate and the pancreas. By 3 months old, the *Serpinf1*$^{-/-}$ mice had developed prostatic hyperplasia.

So, does PEDF regulate growth and microvessel density in the human prostate too? Doll *et al.* examined PEDF expression in normal human prostate tissue and found strong staining in both epithelial and stromal cells; benign prostate hyperplasia tissue was also intensely stained, but PEDF staining was either minimal or absent in prostate tumours.

Doll and colleagues used prostate cell lines — normal epithelial cells (PrEC), stromal cells (PrSC) and cancer cells (including PC-3) — to study the function and regulation of PEDF more closely. All the cell lines secreted PEDF, although the angioinducive factors were dominant as media conditioned by these cell lines did stimulate endothelial-cell migration in an *in vitro* assay. Of the cancer cell lines studied, PC-3 cells secreted the most PEDF and the media from this cell line had the lowest angioinducive activity — this activity was substantially increased by addition of antibodies to PEDF.

So, the data indicate that PEDF secreted by prostate cells is anti-angiogenic, but what is the link with androgens? Treatment of PrSC cells with increasing amounts of dihydrotestosterone decreased PEDF secretion sequentially and castration of rats increased PEDF staining in prostate tissue. PEDF expression was minimal in human prostate biopsy specimens before androgen ablation therapy, but after therapy there was strong staining in tumour epithelial cells and focal staining in stromal cells. PEDF is therefore an important contributor to the anticancer effects of androgen ablation.

Ezzie Hutchinson

References and links

ORIGINAL RESEARCH PAPER Doll, J. A. *et al.* Pigment epithelium-derived factor regulates the vasculature and mass of the prostate and pancreas. *Nature Med.* **9**, 774–780 (2003)

IN BRIEF

EPIGENETICS

Deficiency of Mbd2 suppresses intestinal tumorigenesis.

Sansom, O. J. *et al. Nature Genet.* **34**, 145–147 (2003)

Mbd2 functions as a transcriptional repressor by binding to methylated CpG islands. As mouse intestinal tumorigenesis requires methylation, does loss of Mbd2 affect tumour formation? Loss of Mbd2 in the tumour-prone *Apc*$^{Min/+}$ mouse resulted in fewer and smaller intestinal adenomas, and the mice survived for longer. *Mbd2*-null mice are viable and fertile, so if MBD2 is also not essential in humans, *MBD2* could be a useful therapeutic target.

TUMOUR SUPPRESSORS

NF2 deficiency promotes tumorigenesis and metastasis by destabilizing adherens junctions.

Lallemand, D. *et al. Genes Dev.* **17**, 1090–1100 (2003)

The NF2 tumour suppressor is homologous to the ERM family of membrane–cytoskeletal-associated proteins, but how it regulates cell proliferation from this location is unclear. McClatchey and colleagues have now addressed this question and have shown that Nf2 localizes to adherens junctions in wild-type cells, and its loss prevents the formation of stable cell–cell junctions. This, in turn, means that cells are unable to undergo contact-dependent growth arrest, so they continue to proliferate. This provides a mechanism by which Nf2 might act as both a tumour and metastasis suppressor.

GENOMIC ANALYSIS

Mutational analysis of the tyrosine kinome in colorectal cancer.

Bardelli, A. *et al. Science* **300**, 949 (2003)

Bardelli *et al.* have used a sequencing and bioinformatic approach to address the extent to which tyrosine kinase genes are mutated in colorectal cancer. They analysed one branch of the kinase tree by sequencing 138 genes from 35 colorectal cancer cell lines, and then the mutated genes in another 147 colorectal cancers. A minimum of 30% of colorectal cancers might contain a mutated tyrosine kinase gene. Seven genes were mutated more than once, and the mutations might be activating. Interestingly, few of the mutated genes had previously been linked with human cancer, which emphasizes the benefit of this approach.

THERAPEUTICS

A nonpeptidyl mimic of superoxide dismutase, M40403, inhibits dose-limiting hypotension associated with interleukin-2 and increases its antitumor effects.

Samlowski, W. E. *et al. Nature Med.* **9**, 750–755 (2003)

Interleukin-2 is a valuable therapy for metastatic renal-cell carcinoma and malignant melanoma, but severe hypotension is a frequent side effect. Samlowski *et al.* now show that the superoxide dismutase mimetic M40403 can block IL-2-induced hypotension in mice. This allows the dose of IL-2 to be increased, which, in turn, increases its anticancer effect.