was the hypermethylation of four members of the *SFRP* gene family, which have not been previously associated with colorectal cancer. The products of these genes inhibit the *WNT/FZD1* signalling pathway, so the *SFRP* genes might be a new class of colorectal tumour suppressors. The *SFRP* gene family provides a new set of hypermethylation markers that might be useful in colon cancer detection.

In the future, this screening approach will allow for comparisons of epigenetic modifications between other tumour types, and also aid in the identification of new tumour-suppressor genes.

Kristine Novak

References and links

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WEB SITE

Stephen Baylin's lab: <http://www.hopkinsmedicine.org/graduateprogram/cmm/baylin.html>

ONCOGENESIS

A life or death situation

The oncogene *c-Myc* controls the fine line between life and death, as it can induce both cell proliferation and apoptosis. But whether *c-Myc*-induced cell death can actually restrain tumour growth has remained undetermined. Stella Pelengaris *et al.* have now shown that *c-Myc*-induced apoptosis can indeed prevent tumour formation, and that switching off apoptosis allows the tumorigenic capability of *c-Myc* to proceed unchecked.

A switchable *c-Myc* — in which the gene is fused to the 4-hydroxytamoxifen (4-OHT)-responsive oestrogen receptor (*c-MycER^{TAM}*), so that the protein is activated following the intraperitoneal administration of 4-OHT — was specifically targeted to pancreatic β -cells in mice using the *pIns* insulin promoter. Induction of *c-Myc* initially resulted in cell proliferation, but this was accompanied by a faster rate of apoptosis, such that the net effect was β -cell ablation and hyperglycaemia caused by loss of insulin-producing cells. Interestingly, when 4-OHT was withdrawn, which switched off *c-Myc*, pancreatic islets rapidly regenerated and blood glucose levels returned to normal.

If apoptosis overpowers cell proliferation, inhibiting apoptosis should allow proliferation to proceed unchecked. Expressing the apoptosis inhibitor *Bcl-x_L* under the control of the rat insulin promoter (RIP7) allowed this hypothesis to be tested. *pIns-c-MycER^{TAM}/RIP-Bcl-x_L* transgenic mice had normal pancreatic islet formation until 4-OHT was added, at which point proliferation was induced throughout the pancreatic β -cells. As apoptosis was inhibited by *Bcl-x_L*, this resulted in hyperplasia within 7 days.

But can deregulated expression of *c-Myc* induce tumour formation, which is thought to require the cumulative effect of multiple mutations? Pancreatic β -cells in *pIns-c-MycER^{TAM}/RIP-Bcl-x_L* mice not only hyperproliferated, but also underwent dedifferentiation — as seen by the reduced production of insulin — and extensive angiogenesis. Expression of the intercellular adhesion molecule E-cadherin was lost as well, which is a prerequisite for loss of cell–cell contacts and invasion. *c-Myc* therefore seems to be able to directly induce several of the hallmarks of cancer. Two weeks after induction of *c-Myc* expression, *pIns-c-MycER^{TAM}/RIP-Bcl-x_L* mice had developed pancreatic tumours, and by

8 weeks the tumours were large and vascularized, with sites of local invasion in local blood vessels and draining lymph nodes.

So, expression of a single oncogene — *c-Myc* — is sufficient to induce several steps of carcinogenesis, as long as its innate apoptotic activity is curtailed; but is it also required to maintain the tumours once they have formed? Switching off *c-Myc*, 14 days after its induction, resulted in a reversal of the tumorigenic process: β -cells exited the cell cycle, E-cadherin was re-expressed and cells re-established cell–cell contacts, and endothelial cells and β -cells apoptosed. Even mice that had expressed *c-Myc* for 8 weeks, with extensive tumours that had invaded into lymph nodes, made a full recovery following *c-Myc* deactivation.

These results challenge the paradigm that carcinogenesis is a multistep process that requires many mutations, and indicate that, instead, it can be driven by deregulated expression of a single growth-deregulating oncogene, provided apoptosis is suppressed. If this is found to be true for other commonly mutated oncogenes, new cancer therapeutics should aim to inhibit these few crucial molecular targets.

Emma Greenwood

References and links

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