shown to be the result of better adhesion of the bacteria to the host cell.

Some of these *in vitro* findings were tested back in the rodent model. Here, the authors found that nuclear localization of β-catenin was increased only in the early stages of infection by the oncogenic strain, implicating this as the crucial time for carcinogenesis. They also confirmed that β-catenin was found in the nucleus more often in epithelial cells harvested from humans infected with *cag*$^+$ strains than those infected with *cag*$^-$ strains or no *H. pylori* infection at all.

The results indicate that the increased risk of cancer in long-term *H. pylori* infections might be a consequence of selection pressure on the bacteria to adhere to the host cells in order to remain in the stomach. However, the precise genetic change involved remains to be identified.

Patrick Goymer

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WEB SITE

Richard Peek's lab: http://ddrc.mc.vanderbilt.edu/faculty/peek.html

measuring concentration of the dye in tumours and highly vascular organs. They speculate that the nanocell might be retained preferentially in tumours because tumour vasculature is 'leakier' than normal vasculature, and allows tumour tissue to absorb large particles.

How does the temporal delivery system elicit such a good response? The authors found that the nanocells containing both drugs caused higher levels of apoptosis than the other treatments, as well as the lowest expression of hypoxia-inducible factor 1α (HIF1α), which they attribute to the high concentration of doxorubicin inside the tumour.

So what next for this new system? The nanocells used in this study could be developed further by adding probes that target the tumour vasculature more specifically. The authors point out that temporal drug delivery could substantially improve the efficacy of existing drugs, thereby reducing the risk and time for developing new therapies.

Jenny Bangham

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WEB SITE

Ram Sasisekharan's lab: http://web.mit.edu/tox/sasisekharan/

TUMORIGENESIS

(H)IFs and buts

Hypoxia-inducible factor (HIF) is implicated in the development of renal tumours in patients with the inherited cancer syndrome von Hippel–Lindau disease, but is HIF also important for the development of benign tumours of the adrenal medulla (phaeochromocytomas) in these patients? Results from William Kaelin and colleagues, published in this months' *Cancer Cell*, indicate that this is not the case.

Some von Hippel–Lindau (*VHL*) mutations cause renal cell carcinomas but not phaeochromocytomas, and some *VHL* mutations cause phaeochromocytomas but not renal cell carcinomas. Most, but not all, *VHL* mutations disrupt the regulation of HIF, so is HIF disruption important in phaeochromocytoma development? Intriguingly, patients with germline mutations in the succinate dehydrogenase subunit genes (*SDHB*, *SDHC* and *SDHD*), in neurofibromatosis 1 (*NF1*) and in *RET*, also develop phaeochromocytomas. *SDH* mutations can increase HIF expression, but HIF has not been implicated in NF1- or RET-mediated tumorigenic pathways.

Phaeochromocytomas are comprised of chromaffin cells, derived from sympathetic neuronal progenitor cells. These cells are normally subject to selection during embryogenesis. Cells that make productive synapses acquire a supply of nerve growth factor (NGF) and survive and differentiate. Those that do not, die by apoptosis because of a lack of NGF-mediated survival signals. This death pathway is dependent on the expression of c-JUN. So, William Kaelin and co-workers decided to take a closer look at VHL function in rat phaeochromocytoma (PC12) cells. They found that expression of the c-JUN antagonist JUNB is increased by the loss of VHL. Transcription of *JUNB* is regulated by atypical protein kinase C (aPKC) family members. The activity of aPKC seems to be regulated by VHL, and the authors' results support the existing hypothesis that loss of VHL activates aPKC, which in turn activates *JUNB*. Since JUNB antagonises c-JUN-induced apoptosis on withdrawal of NGF, loss of VHL promotes neuronal survival by a JUNB-dependent mechanism. Importantly, JUNB regulation, but not HIF regulation, is universally altered by *VHL* mutations that predispose to phaeochromocytoma development.

This indicates that JUNB, rather than HIF, is important in the VHL-mediated development of this tumour.

What about SDH mutant proteins and HIF expression in the development of phaeochromocytomas? Previous studies showed that NGF-induced apoptosis in PC12 cells involves the expression of a prolyl hydroxylase, EGLN3, which is related to the HIF-regulator EGLN1. The authors established that EGLN3 (but not EGLN1) was both necessary and sufficient for NGF-induced apoptosis and that EGLN3 did not affect HIF. Instead, inhibition of SDH function inhibits EGLN3 activity because the insufficient conversion of succinate to fumerate, which SDH catalyses, leads to a build up of succinate. Succinate inhibits EGLN3 and thereby blocks neuronal apoptosis.

The authors conclude that the development of phaeochromocytomas is because of a lack of developmental apoptosis in the neuronal progenitor population during embryogenesis, leaving neuronal cells that have the capacity to form these tumours. Germline mutations in *VHL* and *SDH* (and *NF1* and *RET*) all disrupt this process during development, giving rise to the increased risk of phaeochromocytoma seen in patients with these mutations. Despite the fact that both *VHL* and *SDH* mutations can affect HIF expression, HIF is not important in this context.

Nicola McCarthy

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William Kaelin's web site: http://www.hhmi.org/research/investigators/kaelin_bio.html