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 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 Interestingly, when 4-OHT was withdrawn, which switched off c-Myc, pancreatic islets rapidly regenerated and blood glucose levels returned to normal.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 de-differentiation — 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

CELLULAR MICROBIOLOGY

An inhospitable host

What makes a host inhospitable? Is it when they don't offer you a drink when you arrive at their home? Clearly, this is not what makes a host inhospitable to *Shigella*, although the factor that makes host neutrophils unwelcoming has now been identified. In *Nature*, Zychlinsky and colleagues show that neutrophil elastase (NE) attacks *Shigella* virulence factors, making this bacterium extremely unwelcome.

In macrophages and epithelial cells, *Shigella* escape to the cytoplasm from phagosomes, where they would otherwise be destroyed. Neutrophils, however, trap bacterial cells inside phagosomes. So what is the difference between these host cells?

Zychlinsky and co-workers investigated the effect of human neutrophil extract enriched in granule proteins (hNEGP) on *Shigella*. High concentrations of hNEGP killed *Shigella*, and sublethal concentrations specifically decreased the levels of the secreted type III virulence factors IpaA, IpaB and IpaC, which are required for invasion of the host's cytoplasm. The level of the outer-membrane virulence protein IcsA — which is required for intracellular movement — was also specifically decreased.

Using chemical inhibitors, the authors identified NE as the perpetrator of this degradation, and showed that NE degrades virulence factors at 1,000-fold lower concentrations than those required to degrade other bacterial proteins. Zychlinsky and colleagues further illustrated the specificity of NE by showing that virulence factors were cleaved in preference to, for example, virulence-associated proteins, even though the latter were present in larger amounts in the cultures used.

In intact neutrophils, the authors found that IpaA, IpaB and IcsA were specifically degraded on *Shigella* infection, an event that did not occur in cells treated with an NE-specific inhibitor. So what happens to *Shigella* when NE is absent *in vivo*? In both chemically inhibited human neutrophils and NE-null mice, the authors found that bacterial cells could escape to the cytoplasm, and that this escape correlated with increased *Shigella* survival. By contrast, *Shigella* remained in the phagosomes of wild-type cells.

The authors also found that NE targets the virulence proteins of two other pathogens — *Salmonella* and *Yersinia* — and future work will investigate the NE susceptibility of other bacteria. This work establishes NE as the first neutrophil factor that targets bacterial virulence proteins. So, now we know what makes neutrophils such inhospitable hosts.

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References and links

ORIGINAL RESEARCH PAPER Weinrauch, Y. *et al.* Neutrophil elastase targets virulence factors of enterobacteria. *Nature* **417**, 91–94 (2002)