not seen in tumours at the times tested. By contrast, HPMA-copolymer–TNP-470 was detected for up to 48 hours in serum and tumours. The free drug induced weight loss at low doses and was very toxic when given at high daily doses. The authors showed that the free drug crossed the blood–brain barrier in the LLC model and caused neurological side effects. Free drug was also found in the spleen and liver. By contrast, HPMA-copolymer–TNP-470 did not induce weight loss, was not detected in the spleen, liver or brain and did not affect neurological function, even when given at high doses.

Conjugation of TNP-470 to the HPMA copolymer substantially improves the therapeutic index of this inhibitor. Other polymer–drug conjugates are showing promise in clinical trials, and the goal is to move HPMA-copolymer–TNP-470 into clinical trials as well.

Ezzie Hutchinson

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One of the ways that stromal cells affect MM cells is by expressing growth factors. Staudt and colleagues found that the expression of vascular endothelial growth factor (VEGF), which regulates tumour growth and angiogenesis, was increased when stromal cells were co-cultured with c-MAF-expressing MM cells. This response was dependent on the interaction between integrin β7 and E-cadherin as antibodies abolished this induction.

So, c-MAF alters MM–stromal-cell interactions and increases VEGF expression, which is important for MM growth. It also enhances proliferation through the production of cyclin D1. Whether CCR1 also has an effect on MM cells remains to be determined. This important discovery has begun to unravel the complex biology of MM and has identified a new class of oncogenes that increase interactions between tumour and stromal cells. Targeting c-MAF could therefore provide future therapies for MM.

Emma Croager

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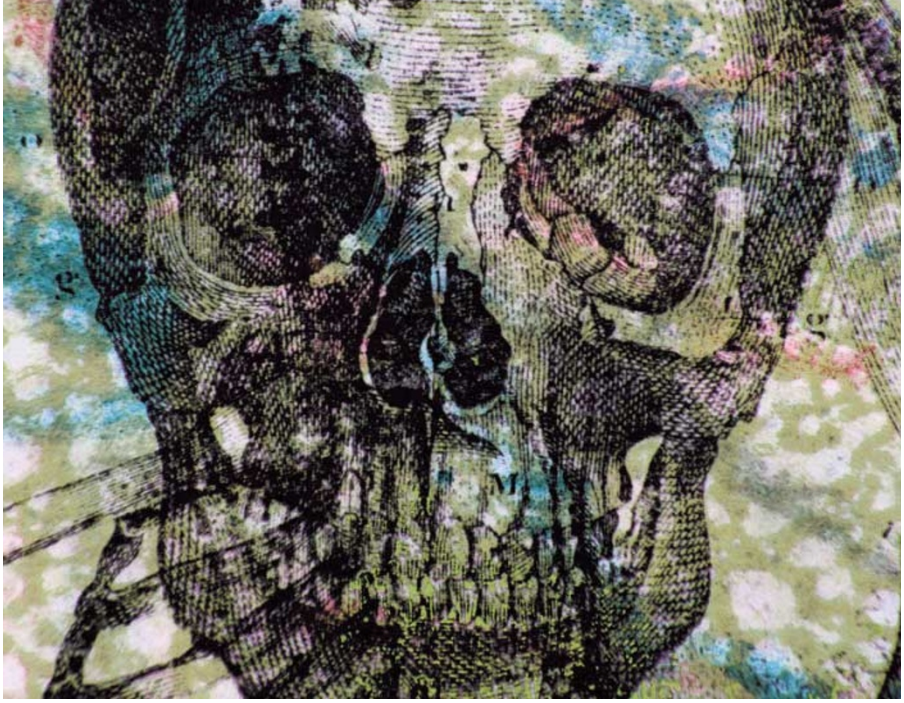
WEB SITE

Louis Staudt's lab: http://lymphochip.nih.gov/staudt.html



CHEMOSENSITIVITY

MUCking up cell death

Cancer cells can survive treatment with anticancer drugs by becoming resistant to cell death — often by acquiring defects in components of the apoptotic pathway. Donald Kufe and colleagues now report in *Cancer Cell* that MUC1 overexpression, which occurs in most carcinomas, could be a new way by which cancer cells avoid death.

MUC1 is cleaved in the endoplasmic reticulum and forms a heterodimer comprising the amino and carboxyl termini that localizes to the cell surface. The C terminus can be phosphorylated at tyrosine-46 (Y46) by the epidermal growth factor receptor (EGFR), and this induces its binding to β-catenin, so forming a link between the EGFR and WNT signalling pathways. When transfected into MUC1-negative HCT116 colorectal cancer cells, the C terminus of wild-type MUC1 was found to localize to mitochondria, as well as the cell surface. However, the C terminus of a MUC1 Y46F mutant, that could not be phosphorylated, displayed significantly less mitchondrial localization. Heregulin — but not EGF — further stimulated the mitochondrial localization of the C terminus of wild-type MUC1.

So, what function might the C terminus of MUC1 have when bound to the mitochondrial membrane? One possibility is that it regulates the intrinsic apoptotic pathway, which operates through release of cytochrome *c* from mitochondria. When HCT116 cells are treated with DNA-damaging agents such as the chemotherapeutic agent cisplatin, about 40% undergo apoptosis within 24 hours. This is associated with various subcellular changes, including an increase in cytochrome *c* release and cleavage of pro-caspase 3. These changes are attenuated when wild-type MUC1, but not the MUC1 Y46F mutant, is expressed, and the cells do not undergo apoptosis. Interestingly, MUC1 also attenuates apoptosis induced by TRAIL, which acts through the extrinsic death-receptor pathway.

The mitochondrial localization of the C terminus of MUC1 does not seem to be restricted to colorectal cancer cells — both lung and breast carcinoma cells that endogenously express MUC1 show this localization pattern. Downregulating MUC1 in these cells using RNA interference results in their sensitization to chemotherapeutic agents such as cisplatin and etoposide.

But does MUC1 also affect chemosensitivity *in vivo*? Cells that either did or did not express MUC1 were injected subcutaneously into nude mice, where they formed tumours. The mice were treated with cisplatin, but tumour growth was only inhibited in those that did not express MUC1.

So, MUC1 seems to affect the chemosensitivity of cells to anticancer drugs. Targeting MUC1 to increase the effectiveness of anticancer drugs could be an important strategy in those cancer types in which it is overexpressed.

Emma Greenwood

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