The authors emphasize that larger studies must be performed to conclude that patients whose CTCs acquire *ERBB2* amplifications should be treated with trastuzumab, as well as to determine whether these changes also occur in metastases.

This is one of many recent studies showing that tumours are constantly changing and can become responsive to different drugs at different stages of tumour progression. The development of methods to safely monitor phenotypic changes during tumour progression will be an important aspect of the development of targeted therapies.

Kristine Novak

References and links

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TUMOUR PROGRESSION

Invasion suppressed

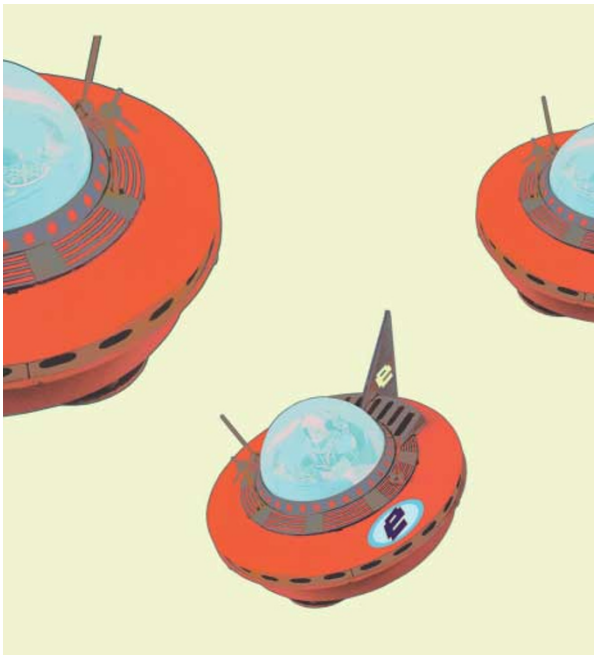
Protease activation is an important component of tumour progression and enzymes such as the matrix metalloproteinases have been pursued as therapeutic targets. Douglas Hanahan, Matthew Bogyo and colleagues now show that another family of intra- and extracellular proteases — the cathepsins — are also required for tumour angiogenesis and invasive growth, and that a cathepsin-specific chemical inhibitor significantly suppresses these processes.

To identify genes that are involved in tumour progression, Hanahan and colleagues performed gene-expression analysis of the various stages of tumour development in *RIP1–Tag2* mice; these mice develop pancreatic tumours because of the transgenic expression of SV40 T-antigen oncogenes in pancreatic β-islet cells. They noticed that genes encoding a set of cathepsins — members of the superfamily of papain proteases that encompass serine-, cysteine- and aspartyl-type proteases — were upregulated as tumours progressed. Six cysteine cathepsin genes — *Ctsb*, *Ctsc*, *Ctsh*, *Ctsl*, *Ctss* and *Ctsz* — were expressed at low levels in normal islets and were variously upregulated beginning in hyperproliferative and angiogenic hyperproliferative islet progenitors, or only in tumours.

Analyses of pancreatic sections using a fluorescent small-molecule probe that binds to active forms of cathepsin revealed that enzymatic activity *in vivo* was undetectable in normal pancreas, but was evident in angiogenic hyperproliferative islets, tumours and at invasive tumour fronts.

Are these cathepsins required for tumour progression? The authors showed that daily injection of a broad-spectrum, cell-permeable inhibitor of cysteine cathepsin activity reduced the number of angiogenic hyperproliferative islets by 49%, decreased developing tumour volume by 67% and prolonged the survival of mice with advanced tumours — not through tumour regression, but by inducing stable disease.

When the inhibitor was given to mice with established solid tumours, the vascular supply to these tumours was disrupted, particularly in the tumour core. The authors speculate that cathepsins promote the sprouting of new vessels once angiogenesis is established. Importantly, inhibition of cathepsin activity did not suppress all hyperproliferative islets from acquiring a blood supply; the few islets that did aquire a blood supply developed normal vascular networks, so cathepsin-independent pathways can also promote angiogenesis.



Cathepsins, however, do not only contribute to angiogenesis during tumour progression. The authors also observed that the cathepsin inhibitor reduced the proliferative capacity of the tumorigenic β-islet cells. Although the mechanism for this is unclear, the authors conclude that cysteine cathepsins also modulate cell proliferation.

The localization of cathepsins to the invasive edges of tumours indicated that these proteases might also regulate invasion of surrounding tissues. The authors examined the levels of E-cadherin — an adhesion molecule that is characteristically downregulated in invasive tumours — as a marker of invasive capacity. They found that in mice treated with the cathepsin inhibitor, E-cadherin was downregulated in fewer pancreatic tumours compared with controls and that this corresponded with a reduction both in widely invasive and micro-invasive tumours. The authors speculate that proteolytic suppression of E-cadherin function by cathepsins could be important for tumour invasion.

Notably, the authors also show that *in vivo* activity of cysteine cathepsins in another mouse tumour model — that of cervical carcinogenesis induced by human papilloma virus — is similarly upregulated. Given that the *RIP1–Tag2* mice bearing pancreatic neuroendocrine tumours showed a therapeutic response and showed no toxicity when treated with the cathepsin inhibitor, targeting cysteine cathepsins might hold promise for future solid-tumour treatments at various stages of disease progression.

Nicola McCarthy

References and links

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