ANTICANCER DRUGS

Switch control

Although anti-angiogenic factors such as endostatin can block tumour growth in mice, there have been difficulties in translating these effects to patients. Bergers and colleagues have shown that the makeup of the tumour vasculature varies at different stages of tumour development, so inhibitor efficacy might depend on its application during a specific phase of tumorigenesis.

During their hyperproliferative premalignant stage, tumours produce a variety of factors to cause an 'angiogenic switch' that induces the normally quiescent surrounding tissue to support the formation of new blood vesssels. Bergers *et al.* have been studying the angiogenic switch using the *RIP1Tag2* line of transgenic mice, which develop pancreatic B-cell carcinomas in a multistep pathway. This model allows researchers to test the effects of various therapeutic approaches on distinct stages of tumour development.

In previous studies, the authors observed stage-specific efficacy of various angiogenesis inhibitors. For example, the vascular endothelial growth factor (VEGF) receptor inhibitor SU5416 blocks the angiogenic switch and prevents the growth of premalignant tumours, but does not induce regression of late-stage, well-vascularized tumours (analogous to those of typical Phase III clinical trial participants). This reveals the importance of VEGF signalling during the angiogenic switch and initial tumour growth, but not in large tumours with an established vasculature.

In the May issue of *The Journal of Clinical Investigation*, Bergers *et al.* report the efficacy of broader specificity receptor inhibitors, such as SU6668 — a small-molecule kinase inhibitor that primarily inhibits signalling through PDGF receptors, but also through VEGF receptors. Although SU6668 slowed early tumour growth in *RIP1Tag2* mice, it was most effective in blocking the growth of late-stage tumours, leading to stable disease. The authors observed that the treated tumours were less vascular, and had a reduction in the association of blood vessels with pericytes — smooth-muscle-related cells that surround and support the vascular endothelium.

GLUTEN INTOLERANCE

Inhibitors for human TGM2 enzyme

Also known as coeliac sprue, gluten intolerance is a widely prevalent genetically determined condition that affects almost 1% of the population. At present, there are no therapeutic agents for this disease, and the only known treatment is a strict, lifelong gluten-free diet. In the March issue of *Chemistry and Biology*, new research describes the design of proteolytically stable peptide inhibitors of the enzyme involved in the production of autoantigens from gluten, tissue transglutaminase (TGM2).

Ingestion of gluten proteins, from the common food grains wheat, rye, and barley, by coeliac patients results in the flattening of the epithelial villous lining of the small intestine, which leads to malabsorption of nutrients, weight loss and a whole host of other symptoms, including intestinal malignancies. Several short proline- and glutamine-rich sequences, identified from wheat gluten, activate gluten-responsive T cells extracted from coeliac patients, but not those from control individuals. Interestingly, most of these peptides are also substrates of TGM2, which is also known to be the principal focus of the auto-antibody response in coeliac sprue.

Selective inhibition of TGM2 might be a useful therapeutic strategy for avoiding the immunotoxic response to dietary gluten, an idea supported by reports that mice deficient in TGM2 are viable and phenotypically normal. In the design of one of the inhibitors, Hausch *et al.* replaced the glutamine in the immunodominant gluten peptide with a 6-diazo-5-oxo-norleucine residue to obtain a highly active and tight-binding inhibitor of TGM2 with low cellular toxicity. The inhibitor inactivated TGM2 by binding within the enzyme's active site, and so could interfere with the disease pathogenesis. Experiments demonstrated that the inhibitor interfered with enzyme activity in cultured cells, and effectively inhibited TGM2-mediated differentiation of an established cell model of intestinal enterocyte maturation.

This potent and selective TGM2 inhibitor will be a valuable tool for further research into coeliac disease, although whether it will be effective in humans remains to be seen. Interestingly, aberrant TGM2 activity is believed to play a role in neurological disorders such as Alzheimer's, Parkinson's and Huntington's diseases, indicating potentially wider use for any ultimately approved TGM2 inhibitors.

Melanie Brazil

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Pericytes were found to be the only tumour cells that express PDGF receptors, making them an important new target of anti-angiogenesis therapy.

Furthermore, treating the *RIP1-Tag2* mice with a combination of a VEGF inhibitor (SU5416) and a PDGF inhibitor (SU6668 or Gleevec) was more efficacious against all stages of islet carcinogenesis than either single agent. Combinations such as these might therefore be used to target interdependent cellular constituents of the tumour vasculature in patients — VEGF receptor inhibitors to block vascular endothelial cell function and PDGF inhibitors to block pericyte support of blood vessels.

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WEB SITE

Gabriele Berger's laboratory:
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LEAD DISCOVERY

Piecing together phosphatase inhibitors

Protein tyrosine phosphatase 1B (PTP1B) has been the focus of considerable drug discovery efforts owing to evidence of its role in downregulating insulin signalling, which indicates that PTP1B inhibitors could ameliorate the insulin resistance characteristic of type 2 diabetes. However, many PTP1B inhibitors identified so far are peptide-based, and because of the conserved nature of the active site among tyrosine phosphatases, obtaining selectivity is difficult. As reported in the *Journal of the American Chemical Society*, Szczepankiewicz and colleagues have tackled these challenges by exploiting a combination of NMR-based screening and rational design, and have identified a potent non-peptidic PTP1B inhibitor that shows good selectivity.

First, to find novel scaffolds that could be used in the design of potent PTP1B inhibitors, Szczepankiewicz *et al.* screened a library of 10,000 compounds by using NMR to assess binding. This has the advantages that even small fragments that bind fairly weakly can be identified, and that information on the binding mode can also be obtained. A compound that seemed to mimic the natural phosphotyrosine substrate was identified (which had K_i ~100 μM), and then optimized with the aim of fully occupying the active site. X-ray crystallography confirmed that the optimized compound bound in the active site.

As selectivity for PTP1B is unlikely without binding to regions outside the active site, the authors looked to extend the active-site-binding compound into a previously identified second binding site near to the active site with the aim of improving both selectivity and binding affinity. A compound that bound in this second site was identified by exploiting another NMR screen, and then joined to the active-site-binding compound using a linker designed on the basis of the X-ray data for this compound to give a compound that potently inhibited PTP1B (K_i ~20 nM).

In screens against a panel of phosphatases, the selectivity of the linked compound against LAR, SHP-2, CD-45 and calcineurin was excellent, ranging from 36-fold to >10,000-fold, and moderate selectivity (twofold) was seen over TCPTP, which is notable given the extremely high level of sequence identity between TCPTP and PTP1B. Comparison of the selectivity of the active-site-binding compound with that of the linked compound confirmed that the second-site ligand was largely responsible for selectivity, as expected. So, by tailoring the second-site ligand, it should be possible to develop potent and selective inhibitors of other therapeutically relevant phosphatases.

Peter Kirkpatrick

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