Endocrinologist Alex Rabinovitch of the University of Alberta in Edmonton (http://www.ualberta.ca/) agrees that the results are promising. He would eventually like to see a head-to-head comparison with other antioxidants, but believes that the compounds' additional immunomodulatory functions are likely to be an advantage over other antioxidants.

There are also safety issues to be considered, especially when it comes to systemic treatment. Piganelli reckons that, 'The earliest place that you might be able to see this is in the protection of the islet cells' due for transplant. But if the compounds turn out to be safe and effective when given systemically to humans, they may be used in individuals at risk before the onset of diabetes, to prevent the loss of most of the β-cells.'

'This is a really exciting finding,' says Incara's Bockkino. 'We would much rather prevent than treat diabetes.'

References

1 Bottino, B. *et al.* (2002) Preservation of human islet cell functional mass by anti-oxidative action of a novel SOD mimic compound. *Diabetes* 51, 2561–2567

2 Piganelli, J.D. *et al.* (2002) A metalloporphyrin-based superoxide dismutase mimic inhibits adoptive transfer of autoimmune diabetes by a diabetogenic T-cell clone. *Diabetes* 51, 347–355

3 Piganelli, J.D. *et al.* (2002) Therapeutic induction of diabetes resistance and antigen-specific hyporesponsiveness using a superoxide dismutase mimic (AEOL10113). *62nd Scientific Sessions of the American Diabetes Association*, San Francisco, CA, USA, 14–18 June 2002, (Abstract 1171-P)

Energy blocker to treat liver cancer

Vida Foubister, freelance writer

A compound that inhibits cellular ATP production has been shown to kill cancer cells in implanted liver tumors in rabbits, without damaging the surrounding tissue. Researchers are optimistic that this new approach, which involves direct intra-arterial injection of 3-bromopyruvate (3-BrPA) into tumors, could be developed to treat hepatocellular carcinoma (HCC) in humans.

HCC on the increase

Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer. Its incidence in the developed world is increasing, because of the dramatic rise in viral-induced hepatitis, which has replaced alcoholic cirrhosis as the disease's number one cause.

Although HCC, with more than one million deaths a year, is one of the most lethal cancers in the world, few treatment options are available to patients. Surgical removal of the tumor and liver transplantation remain the only hope for a cure. But the majority of HCC patients, approximately 85–90%, are not surgical candidates because their underlying liver disease is too advanced to benefit from this approach.

Transcatheter arterial chemoembolization (TACE), the standard therapy for patients with unresectable HCC, takes advantage of the fact that primary liver tumors receive most of their blood supply from the hepatic artery. Because normal liver tissue relies predominantly on the portal vein, it is possible to target tumor cells by injecting the chemotherapeutic agent into the hepatic artery and then embolizing it [1]. Although this treatment reliably shrinks the tumor, existing data from randomized controlled trials has failed to demonstrate that HCC patients who undergo TACE have a significant survival advantage over those who receive supportive care alone [2].

A new approach

Jeff Geschwind, director of interventional radiology research at Johns Hopkins University School of Medicine (http://www.hopkinsmedicine.org/medicalschool/), has long thought that there is a better way to exploit HCC tumors' selective blood supply to a patient's advantage. 'People have been using that to block blood flow and deprive the tumor of oxygen. I always saw it as a roadway to kill the tumor, using the route whereby the tumors get their growth nutrients and oxygen to actually kill it.'

The first step was to find a compound that would block energy metabolism in cancer cells. Geschwind and his colleagues developed a tissue culture screen that identified 3-BrPA as a potent inhibitor of ATP production both by glycolysis and oxidative phosphorylation [3]. Then they tested the compound by direct intra-arterial injection into rabbit liver tumors. They found that it killed up to 90% of cancer cells in four days [4].

Perhaps more surprising was the fact that this highly reactive molecule caused no damage to the liver tissue surrounding the treated tumors. 'This is especially crucial when you're dealing with patients who already have a diseased liver, because that's what usually kills them. It's not the cancer, it's the liver failure,' explains Geschwind. Chemoembolization,

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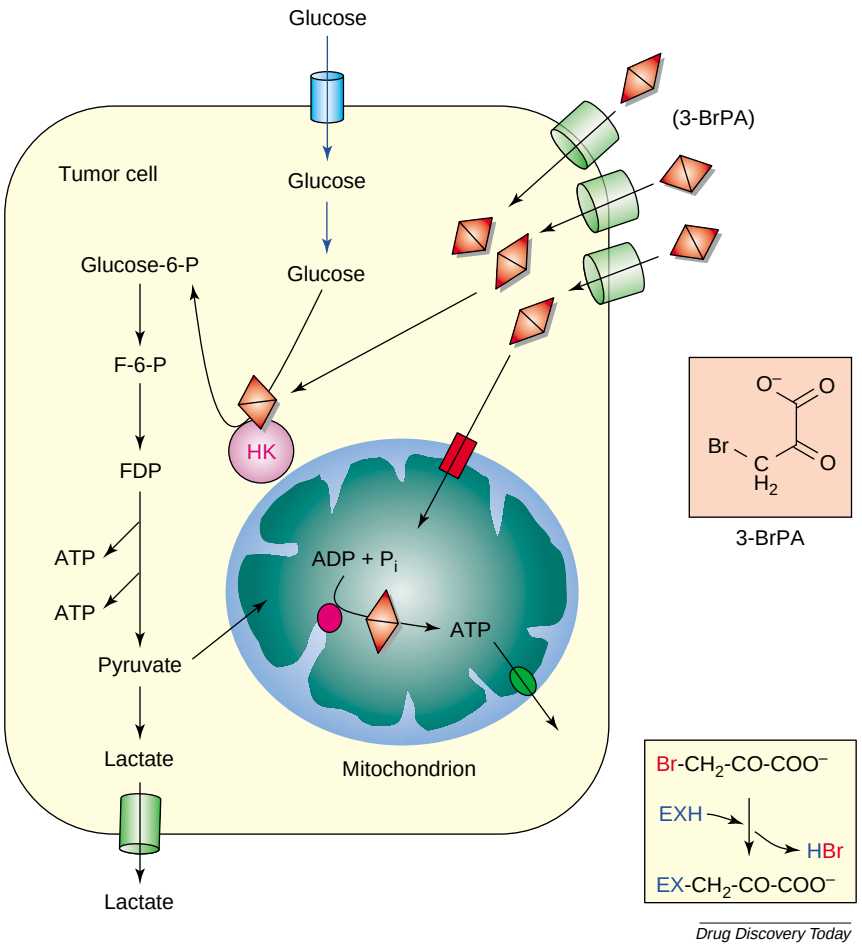

Figure 1. 3-Bromopyruvate (3-BrPA) blocks ATP production in tumor cells by inhibiting mitochondrially bound hexokinase and oxidative phosphorylation. Its structure and reactivity with enzyme (E) functional groups (-XH) are also shown. Reproduced, with permission, from ref. [4].

by contrast, was shown to cause severe damage to the liver tissue surrounding the treated tumor.

Also unexpected was the compound's lack of toxicity, as well as its ability to suppress the growth of metastatic lung nodules when delivered systemically through a rabbit's marginal ear vein.

Mode of action

Cancer cells are known to have aberrant energy metabolism; they consume more glucose than normal cells, and rapidly convert it to lactic acid. Within these cells, there are two sites where 3-BrPA acts to block the production of ATP (Fig. 1). One target is type II hexokinase, an enzyme in the glycolytic pathway that is bound to the mitochondria in aggressive tumors and converts glucose to glucose-6-phosphate [5]. The other site, although not yet specifically identified, appears to be a protein involved in oxidative phosphorylation within the mitochondria.

It is unclear why normal liver cells are not affected by 3-BrPA. 'Either it's not leaking out of the tumor, or else there are natural agents in the cells that can neutralize it, such as glutathione,' says Peter Pedersen, a Professor of Biological Chemistry at Johns Hopkins. Tumor cells might also have an enhanced transport system for 3-BrPA that causes the compound to accumulate more rapidly and thus compete successfully against the cell's natural defense mechanism.

Future work

The Johns Hopkins researchers want to eradicate the liver tumors completely, either by repeat injections or by hour-long infusions of the same dose of 3-BrPA. They also plan to follow the rabbits over time, to assess further the toxicity of the compound and the animals' potential for long-term survival.

A key step towards testing this compound in clinical trials, which could begin no sooner than in four or five years, will be to see if tumor samples from patients have the same sensitivity to 3-BrPA. 'The other hurdle in humans is the fact that the majority of hepatocellular carcinoma cases occur against a background of liver disease. 'We just don't know about the safety of 3-BrPA in the cirrhotic liver – whether that would be spared as readily as these rabbit livers are,' says Adrian Di Bisceglie, Chief of Hepatology at Saint Louis University (http://www.slu.edu/).

Karol Sikora, AstraZeneca UK's (http://www.astrazeneca.co.uk/) Global Clinical Expert for Cancer, would also like to see a less complex mode of administration that carries fewer risks. 'Systemic delivery, intravenously or ideally orally, that would be the ultimate,' he says.

References

1 Ramsey, D.E. *et al.* Chemoembolization of hepatocellular carcinoma. *J. Vasc. Interv. Radiol.* (in press)
2 Geschwind, J.-F.H. *et al.* Chemoembolization of hepatocellular carcinoma: results of a meta-analysis. *Am. J. Clin. Oncol.* (in press)
3 Ko, Y.H. *et al.* (2001) Glucose catabolism in the rabbit VX2 model for liver cancer. *Cancer Lett.* 173, 83–91
4 Geschwind, J.-F.H. *et al.* (2002) Novel therapy for liver cancer: direct intra-arterial injection of a potent inhibitor of ATP production. *Cancer Res.* 62, 3909–3913
5 Ko, Y.H. and McFadden, B.A. (1990) Alkylation of isocitrate lyase from *Escherichia coli* by 3-bromopyruvate. *Arch. Biochem. Biophys.* 278, 373–380