news

Black sheep of the VEGF family gives hope for cancer therapy

Scott Ewan, scott_ewan@hotmail.com

Can substances that exist within our own bodies help us to defeat cancer? Recent work by the team of David Bates at the University of Bristol (http://www.bris.ac.uk/Depts/Physiology) suggests that this might just be possible. A protein named $VEGF_{165}b$ has been shown to stop small tumours developing the blood vessels they need to get bigger.

Inhibiting angiogenesis

$VEGF_{165}b$ is an isoform of a family of proteins known as Vascular Endothelial Growth Factor, VEGF, which stimulates the growth of new blood vessels (angiogenesis) and which is observed at high levels in all known tumours. The overexpression of VEGF in cancers logically suggests a link between these proteins, their function in blood vessel growth, and the growth of cancers. To date, Genentech's, Avastin™ (bevacizumab) is the only successful VEGF-antagonist drug. Avastin™ is a monoclonal antibody, designed to bind to VEGF, nullifying its angiogenic power. By blocking angiogenesis, it starves tumours of oxygen and nutrients, stunting their growth. In contrast to their anti-tumour efficacy, VEGF-specific monoclonal antibodies can cause some serious side effects. For example, holes in the colon, hypertension, blood clots and serious cardiovascular events have been linked to Avastin™.

'Small molecules currently available just aren't very specific'

Curbing side effects

Bates' team are hoping that curbing side effects is one area where their research might offer advantages. 'The large pharmaceutical companies have been making small molecule inhibitors to VEGF receptors,' said Bates. 'But VEGF inhibitors need to very specific.' VEGF receptors are tyrosine kinases, a very common family of receptors and small molecules currently available just aren't very specific.

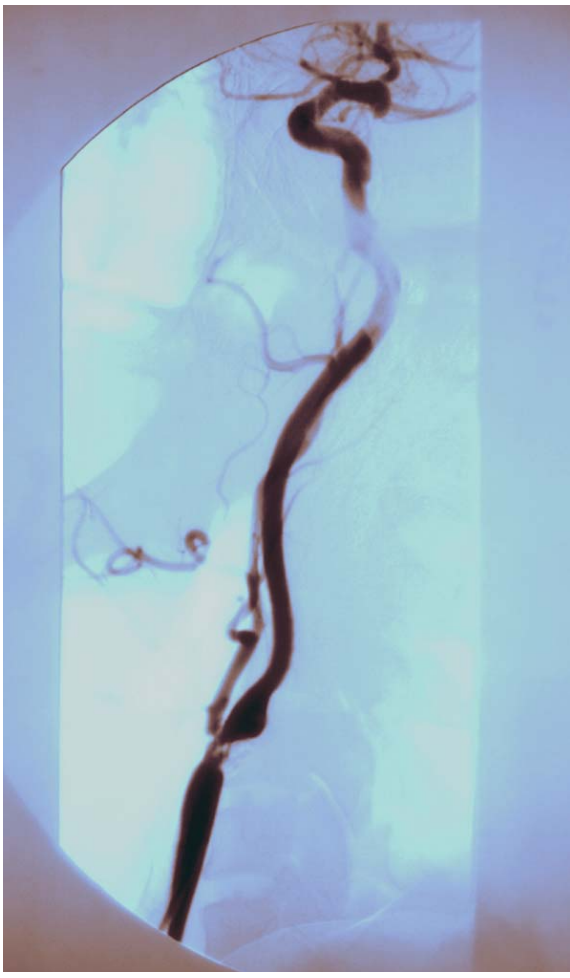
Bass Hassan, Professor of Adult Oncology at the University of Bristol agrees that current therapies are limited in their scope. 'We have looked at non-specific cytotoxic drugs,' Hassan said, 'but they are very difficult to manage, especially in elderly patients. They have effectively reached their limits.' he continued. 'New drugs need to be targeted. Antibodies, coupled with chemotherapy have made great inroads, particularly for lymphomas,' he said in reference to Avastin™ – now a billion-dollar drug.

Picomolar afinity

Bates believes $VEGF_{165}b$ will prove a very effective antagonist to VEGF. Being endogenous, and highly specific, $VEGF_{165}b$ should be very active at both VEGF receptors (VEGF-1 and VEGF-2). Binding has indeed proved solid, with affinities in the picomolar range. 'The binding of $VEGF_{165}b$ is equimolar to that of VEGF,' said Bates. And on the question of *in vivo* efficacy, Bates cited parallels, 'there are no problems with the delivery (by intravascular injection) or bioavailability – $VEGF_{165}$ [a similar splice variant] has already been used – in man – to increase blood vessel growth.' Hassan agrees, 'If it's possible to over express this isoform, effectively you've generated a competitive antagonist.'

Are there risks, however, associated with shutting down angiogenesis? When posed this question, Bates responded, 'Adults only grow new blood vessels in response to wounds or, in women, in the endometrium and ovaries.' This implies that the risks are minimal.

'There's an enormous amount of literature on VEGF out there,' said Gillian Tozer at the University of Sheffield (http://www.shef.ac.uk/dcss/medical/surgical-oncology), 'but very little on the roles of the various isoforms in angiogenesis.' Tozer believes that any drug development programs should go hand in hand with basic research into the functions of the various splice variants. 'We need to know more about some elements. For example, signalling is not totally inhibitory – there's still some active signalling.'



A common splicing system

For the future of $VEGF_{165}b$-centred drug discovery, Bates' research might lead to the discovery of a common splicing system that controls blood vessels growth. It's conceivable that drugs might be developed to control alternate splicing of VEGF mRNA. Tozer believes this approach shows promise. 'There's therapeutic potential – attempts to switch splicing at the mRNA level to create inhibitory splice variants. It is probably still a long way off – but this paper could inspire work in that direction.' 'It is speculation,' added Dr Bates, 'but not quite science fiction. The possibility exists for an entirely new class of drugs to control splicing and to control cancers. We think this is the future.'

Reference

1 Woolard, J. *et al.* (2004) $VEGF_{165}b$, an inhibitory vascular endothelial growth factor splice variant: mechanism of action, *in vivo* effect on angiogenesis and endogenous protein expression. *Cancer Res.* 64, 7822–7835

1359-6446/04/$ – see front matter PII: S1359-6446(04)03336-7