restriction of growth and spread of tumours, as well as improving the potential effectiveness of other anticancer treatments,' she adds.

FGF-2 fragments

FGF-2 is a single-chain polypeptide that acts as an angiogenic stimulator. Previous research has shown that monoclonal antibodies against FGF-2 block FGF-2-stimulated angiogenesis[1]. FGF-2 also increases metastatic potential in tumour cells, and levels of the angiogenic factor are inversely correlated with survival in patients with renal, breast, endometrial, prostate or colorectal cancer.

Under normal conditions, FGF-2 works in conjunction with other stimulators (such as VEGFs and interleukin-8) and angiogenesis inhibitors (such as angiostatin and endostatin proteins) to maintain a homeostatic balance. However, the presence of tumour cells shifts the balance in favour of new blood vessel growth by up-regulating angiogenic stimulation and down-regulating angiogenic inhibition[1–3].

The vaccine

Proliferation and migration of endothelial cells in response to FGF-2 is mediated by a two-component receptor system that binds two portions of the FGF-2 peptide – the heparin-binding and receptor-binding domains. Plum and colleagues synthesized two peptides identical to these domains. They then produced two liposomal vaccines that also contained lipid A to stimulate an immune response[1]. However, mice vaccinated with the receptor-binding domain fragment showed little or no immunoreactivity whereas those vaccinated with the heparin-binding domain produced a strong response[1]. The heparin-binding domain vaccine also inhibited experimental angiogenesis in vaccinated mice and prevented melanoma and lung carcinoma metastasis.

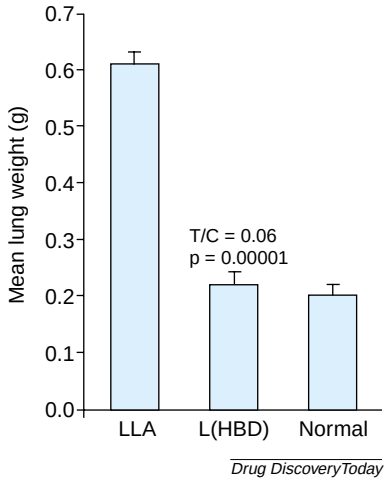

Figure 1. Inhibition of Lewis lung carcinoma-low metastatic experimental metastases in five mice vaccinated with either the new vaccine [liposomal heparin binding domain – L(HBD)] or liposomal lipid A (LLA; control). The 'normal' mice were neither vaccinated nor challenged with the lung cancer cells. After 17 days, L(HBD) inhibited lung metastases by 95%[1]. [Reproduced with permission of Entremed.]

Potential problems

As well as angiogenesis, FGF-2 is also involved in embryonic development, wound healing and other processes that could, in theory, be adversely affected by the new vaccine. The researchers are therefore cautious about its long-term effects. Fortier states, however, that future research articles will address the effects of the vaccine on these processes. In the meantime, the vaccine is being developed with a view to future clinical studies.

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Genome sequences reveal key genetic element in PD

Janet Fricker, Freelance writer

Researchers from the National Human Genome Research Institute (NHGRI; Bethesda, MD, USA) have uncovered a novel genetic element that could be crucially involved in Parkinson's disease (PD). This element is involved in transcriptional control of levels of α-synuclein, believed to be important in both inherited and non-inherited forms of PD[1]. They hope that increased understanding of the control of the expression of this protein could lead to the development of novel therapies for PD.

α-Synuclein

PD results from the loss of dopaminergic neurons in the substantia nigra and other regions of the brain. In their efforts to find the cause of PD, researchers have been focusing on the mysterious protein α-synuclein, a presynaptic nerve terminal

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protein that was originally identified as a precursor of the non-β-amyloid component of Alzheimer's disease plaques[2].

'If α-synuclein is knocked-out in mice, levels of synaptic vesicles are reduced, suggesting that it might be involved in coding, transporting and/or protecting the synaptic vesicles,' explains Robert Nussbaum, Chief of the Genetic Diseases Research Branch of the NHGRI and leading author of the study.

Genetic basis of PD

The human α-synuclein gene (*SNCA*) was identified as playing a role in PD when a locus for early-onset PD was mapped to the same region of chromosome 4 as *SNCA*[3]. Two different missense mutations in *SNCA* cause early-onset, autosomal dominant PD with high penetrance, accounting for only a handful of patients with PD. A second locus, the *PARKIN* gene, has been implicated in additional families with autosomal recessive and dominant PD. For the remaining 95% of PD patients, the genetic contribution to the disease remains controversial and the cause is thought likely to be a more subtle interaction between genes and the environment.

'There are slight differences in manifestation between genetic and non-genetic PD,' says Nussbaum. 'The genetic disease is of earlier onset and patients have less tremor and more rigidity.' However, α-synuclein protein deposits are present in the Lewy bodies of all PD patients, regardless of whether they carry the abnormal genes[4]. Nussbaum and colleagues speculate that involvement of wild-type α-synuclein in patients with PD of non-genetic origin could be the result of post-translational modification or protein damage, altered regulation of expression, abnormal degradation or a combination of all three.

SNCA and PD

'The next questions are how you get abnormal α-synuclein without mutations, why the protein accumulates and how it damages the neurons,' says Nussbaum. 'One theory is that PD is stimulated by some final common pathway and results from the α-synuclein protein being abnormally folded, either because of a genetic mutation or owing to damage or incorrect processing of the protein.'

To identify factors that influence α-synuclein function, the group generated and analysed the complete sequence of the human and mouse genomic regions encompassing *SNCA*, and scanned the two genomes for repeat elements. Their approach rested on the hypothesis that DNA sequences outside of protein-coding regions that exhibit significant conservation at the nucleotide level between the two species might reveal potential regulatory sequences.

Earlier association studies had suggested a correlation between certain alleles of the NACP-REP locus and the development of PD[5]. The repeat is polymorphic in humans with different people having different numbers of repeats. To their surprise, the team found the mouse also had repeat sequences located in an analogous position near the promoter of the mouse *Snca* gene. Further support for their hypothesis came from the fact that deletion of the human NACP-REP1 repeat region resulted in a fourfold decrease in promoter activity in cultured 293 T cells.

Future work

Further studies are now planned to investigate the effect of different human NACP-REP1 alleles on the development of PD. They will also be studying the effect of different repeat sequences in various mouse species on gene expression. Margaret Pericak-Vance (James B. Duke Professor of Medicine and Director of the Center for Human Genetics, Duke University Medical Center, Durham, NC, USA) said that 'this work again illustrates the need to consider regulation of expression as well as polymorphisms leading to changes in the protein when evaluating candidate genes for complex diseases.'

When the role of α-synuclein in PD is better understood, it should be possible to design drugs that prevent its accumulation and therefore the development of PD. 'Ultimately, it might be possible to use small molecules to interfere with the transcription of the α-synuclein protein. It might be that you do not need to shut the protein off completely, just damp it down,' says Nussbaum. 'Another approach would be to find agents that help the cell degrade the protein more efficiently or change the configuration of the protein so that it can be degraded.'

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