Novel MMP inhibitor has potential for treatment of stroke

The use of new and selective inhibitors of matrix metalloproteinases (MMPs) may have significant therapeutic potential in stroke patients, report US researchers. The role of MMPs, and MMP-9 in particular, has been suggested in the pathogenesis of neurological disorders, but efforts to inhibit MMP activity have been largely unsuccessful in human clinical trials, says study author Stuart A Lipton (The Burnham Institute, La Jolla, CA, USA). "They failed because of side-effects", he says, "but we have developed a totally new way of inhibiting MMPs."

Previous research has shown that concentrations of both MMP-9 and MMP-2 are high after a stroke. Attempts to ameliorate MMP-mediated brain damage in human clinical trials have been unsuccessful because of low specificity and high toxicity. Lipton and colleagues developed a thirane gelatinase inhibitor, called SB-3CT, which is highly specific for MMP-9 and MMP-2 (J Neurosci 2005; 25: 6401–18).

"The drug is activated by the catalytic side of MMPs", says Lipton. "So when MMP activity increases, the drug is increasingly activated to inhibit the activity."

"Not only is the drug very specific for these two MMPs, which will eliminate many of the side-effects, but also it is very particular, in that it inhibits pathological activity far more than normal activity", he adds. "That is why we think that this class of drugs has a great deal of potential."

In a mouse model of stroke, mice that received SB-3CT seemed to be protected from brain damage, compared with mice that did not receive the treatment. In the mice treated with SB-3CT, MMP-9 activity significantly declined whereas no changes were noted in the activity of other MMPs. Brain damage in the treated mice was only 30% of that in the controls. In addition, tissue plasminogen activator (tPA), the only treatment approved for stroke in the USA, is also neurotoxic, and part of that effect is mediated by activating MMPs. We may be able to use this drug to offset the side effects of tPA, explains Lipton.

This paper replicates research that has already been published by several groups, comments Eng H Lo (Harvard University, Cambridge, MA, USA). "Our lab has shown that the main complication of the only FDA-approved stroke therapy is caused by tPA-triggered MMP-9 upregulation. MMP inhibitors can reduce this dreaded complication of tPA for stroke therapy."

Roxanne Nelson

Frontotemporal dementia: an endosomal problem?

Mutations in an endosomal sorting protein are associated with a rare form of frontotemporal dementia (FTD), report UK and Danish researchers. "We have been trying to identify the gene associated with FTD for the past 10 years", explains joint project leader Elizabeth Fisher (Institute of Neurology, University College London, UK). "Our discovery that affected members of a large Danish family with FTD have a mutation in CHMP2B, which encodes a subunit of the endosomal ESCRTIII complex, throws light on a possible new mechanism of neurodegeneration."

FTD, the second most common cause of presenile dementia, is a heterogeneous disorder. The most common familial form is caused by mutations in the tau gene, which lead to widespread tau inclusions in the brain. By contrast, FTD3 has no distinctive neuropathological features but is characterised by onset of dementia in people aged in their late 50s and by behavioural changes. Fisher and her colleagues linked the FTD3 phenotype to a region of chromosome 3 in an affected Danish pedigree that includes more than 450 people. "Our graduate student Gaia Skibinski searched data from the human genome project for candidate genes in this region and homed in on one known only by an anonymous set of numbers", explains Fisher. "Then, by use of web-based bioinformatic tools, she discovered that this gene is related to a yeast gene involved in endosomal function, and because defective endosomal function has recently been implicated in several neurodegenerative diseases, we investigated this candidate further."

The researchers found a specific mutation within CHMP2B in 11 affected members of the Danish family that was not present in unaffected family members or in control DNA samples. They also found a second CHMP2B mutation in an unrelated individual with familial FTD. In addition, they discovered that expression of the mutant gene in cultured neuronal cells causes the formation of aberrant endosomal structures (Nat Genet 2005; published online July 24, DOI: 10.1038/ng1609).

"These data are original and interesting", comments neurobiologist Andrew Bean (University of Texas Medical School at Houston, TX, USA), "in that they bolster the emerging recognition that defects in intracellular trafficking are a significant cause of neuronal disease. However, finding additional individuals with CHMP2B mutations will be important, and mechanistic studies describing how CHMP2B mutations affect various aspects of endocytic trafficking are needed to complete the picture."

Jane Bradbury