news

KDI tripeptide from laminin: a novel approach to treat neurodegenerative disorders

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In 1979 George Martin and colleagues [1] reported on a novel specialised glycoprotein that they named laminin, which was extracted from EHS sarcoma, which produces abundant basement membrane. For many years, it was thought to be responsible solely for anchoring cells to components of the extracellular matrix. In the following years, however, it became clear that laminin had many other diverse biological functions including promoting cell survival, signalling through laminin receptors and tubulogenesis [2].

Laminin in the CNS

More recently, researchers, notably Päivi Liesi of the Department of Biological and Environmental Sciences and head of the Brain Laboratory at the University of Helsinki, have been working on the biological roles of laminin in the CNS. Interestingly, Liesi's group was able to demonstrate that a peptide domain of laminin (KDI; lysine-aspartate-isoleucine) was capable of promoting functional regeneration of rat spinal cord injuries [3]. Liesi and colleagues, in a recent paper in the *Journal of Neuroscience Research* [4], have gone on to show, using patch-clamp electrophysiology in human cultured neocortical neurons, that the KDI tripeptide domain is a universal, potent and (in the case of the AMPA receptor) non-competitive inhibitor of ionotropic glutamate receptors (iGluRs). The receptors examined included the AMPA, kainate and NMDA subclasses of iGluRI.

Glutamate excitotoxicity

The excessive release of glutamate following brain injury is responsible for the phenomenon of glutamate excitotoxicity, which is mediated through glutamate receptors and results in apoptotic cell death. The combination of KDI's ability to ameliorate excitotoxicity and regenerate damaged nerve cells is particularly exciting, in that such a molecule could be expected to have benefit in a range of neurodegenerative disorders that could include Alzheimer's disease, ALS, Parkinson's disease and potentially other debilitating neurodegenerative diseases.

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As Liesi commented: 'The wider significance of his research is that KDI treatment may become the first natural and targeted therapy for people with central nervous system injuries resulting in paralysis and a range of diseases such as Alzheimer's and ALS, for which there are currently no cures.'

Other researchers are equally excited at the prospect of proof-of-concept trials with the tripeptide. George Martin, one of the discoverers of laminin, and a former collaborator of Liesi's, mentioned: 'One of the wonderful things about this is that Dr Liesi's discoveries are ready now for prime-time testing in patients. We do not have to go through a long drug development procedure that might take 10 years.'

Proof-of-concept trials

Hopefully, the proof-of-concept trials will establish the utility of the KDI tripeptide approach and that the tripeptide itself may be advanced as a potential drug candidate. However, even if the trials are positive, the KDI tripeptide may not be able to be developed as a drug in. There are many issues that can prevent the development of a potential active agent. However, it would appear that the target of KDI's action on iGluRs could be of a size that would allow the production of small organic drugs capable of acting upon it. These findings may open up new avenues of research into the development of pan active iGluR modulators.

References

1 Timpl, R. *et al.* (1979) Laminin – a glycoprotein from basement membranes. *J. Biol. Chem*. 254, 9933–9937
2 Ekblom, P. *et al.* (2003) Expression and biological role of laminin-1. *Matrix Biol.* 22, 35–47
3 Wiksten, M. *et al.* (2004) Regeneration of adult spinal cord is promoted by the soluble KDI-domain of γ1 laminin. *J. Neurosci. Res.* 78, 403–410
4 Möykkynen,T. *et al.* (2005) The neuroprotective KDI domain of γ1 laminin is a universal and potent inhibitor of ionotropic glutamate receptors. *J. Neurosci. Res*. DOI: 10.1002/jnr.2052 (Epubn ahead of print; http://www3.interscience.wiley.com/cgi-bin/jhome/34828)

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