Reelin in brain development studies

The proteins that coordinate the development of the brain and control the movement of cells are very complex. So far, at least 30 genes have been identified that regulate neuron migration. Among the most recent additions to this list are two lipoprotein receptors, the apolipoprotein E2 (ApoE2) receptor and the very-low-density lipoprotein (VLDL) receptor[1,2]. These two receptors provide the missing link between reelin (RELN) and disabled (DAB), two components of a signalling pathway already known to be involved in brain development. As this signalling pathway also has links with proteins involved in the pathogenesis of Alzheimer's disease (AD), this finding is a significant step towards the understanding of this disease.

After the serendipitous discovery of the locus of the reelin gene (*Reln*) in 1994, researchers have been trying to elucidate the reelin signalling pathway[3]. Reeler mice are so called because they keep falling over when they try to move. The observation that the brains of these animals lack the normally highly organized layered structure of the cortex suggested that *Reln* encoded a protein that controlled cell migration during development. Tom Curran, Chair of Developmental Neurobiology at St Jude Children's Research Hospital (Memphis, TN, USA) and his colleagues went on to identify the gene and clone it. *Reln* was found to encode a large protein, which appeared to be an extracellular molecule.

Subsequent work suggested the presence of other proteins that could cause abnormalities identical to those described in reeler mice. Curran, collaborating with other groups, found that mutations in the disabled-1 (*Dab 1*) gene also disrupted the formation of brain layers in the cortex (for a review, see Ref. 4). This gene encodes an intracellular protein that is phosphorylated at the tyrosine residues, suggesting that the molecule is involved in a signalling pathway. Curran said, 'We had reelin, regarded as a guidepost outside the cell that is laid down in specific brain regions and is recognized by migrating cells, and disabled that we know is present in migrating cells. Somehow, a signal is passed from reelin to disabled to cause changes in tyrosine phosphorylation. So we looked for the missing link, the receptor for reelin.'

Finding the reelin receptor

A clue came from work by Joachim Herz and coworkers (UT Southwestern Dallas, TX, USA), who were studying lipoprotein receptors using gene knockout mice. These workers found that mice without the VLDL receptor gene were relatively healthy, as were those without the ApoE2 receptor gene. Those mice that lacked the genes for both receptors, however, were identical in phenotype to the reeler mice and similar in brain anatomy[5].

Both Herz's group[2] and Curran's group[1] demonstrated that reelin binds very effectively to both the VLDL receptor and the ApoE2 receptor. Herz's group also showed that disabled binds to these receptors. Meanwhile Curran and coworkers demonstrated that CR-50 (a monoclonal antibody that inhibits the function of reelin) prevented reelin from binding to the VLDL receptor and that the presence of apolipoprotein E reduces the ability of reelin to bind to both receptors[1].

These observations are of interest to researchers studying the pathogenesis of AD, for several reasons. Firstly, disabled can also bind to the amyloid protein, which accumulates in the brain of people with AD. Secondly, the protein made by the *APOE* (apolipoprotein E) gene binds to both the VLDL receptor and the ApoE2 receptor, and there is evidence that certain polymorphisms of the *APOE* gene in the human population are associated with a higher risk of developing AD. Finally, as Curran pointed out, if apolipoprotein E can inhibit the reelin pathway, it is possible that reelin might also influence the metabolism of apolipoprotein E.

Curran concluded, 'For anyone who is running a drug discovery programme to identify drugs for the treatment of AD or neurodegeneration, we are saying "here is something else you should be looking at". We would like to work with people studying human disease material to investigate whether components of the reelin pathway are changed: for example, whether there is a change in tyrosine phosphorylation of disabled.'

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1359-6446/00/$ – see front matter PII: S1359-6446(99)01452-X