DDT Vol. 6, No. 18 September 2001

# Laminins – a new target for brain cancer therapy?

**Kathryn Senior**, Freelance writer

Researchers have identified a new mechanism thought to be involved in several types of brain tumours including the high-grade glioma, glioblastoma multiforme (GBM). Using gene-microarray technology, Julia Ljubimova (Maxine Dunitz Neurological Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA) and colleagues have identified the α-4 chain of laminin as a potential therapeutic target, which could lead to improved patient monitoring and, ultimately, new effective therapies against these tumours which, historically, have been difficult to treat[1].

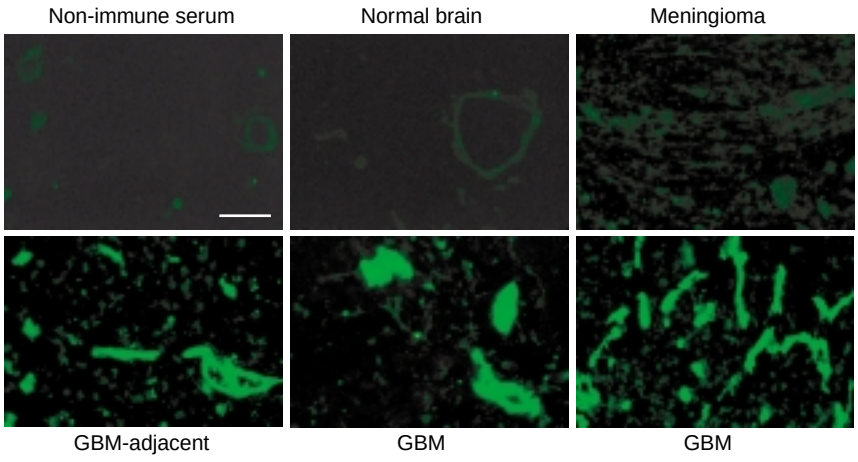


**Figure 1**. Expression of α-4 chain of laminin-8 in normal brain and brain tumours. Abbreviation: GBM, glioblastoma multiforme.

## GBM prognosis

GBM is generally a highly aggressive tumour: 'The five-year survival rate with GBM is only 2–5%,' points out Ljubimova. Most of these tumours are highly invasive and recurrences at the primary site often develop shortly after surgery to remove the primary tumour. 'This situation necessitates a comprehensive search for new and specific targets for the treatment of glial tumors, which could lead to valuable therapeutic avenues,' she adds.

Currently, treatment depends on the tumour histology, the stage of tumour progression and the age and physical condition of the patient, but there are limited options. Although the principal treatment is surgery, this procedure carries a significant risk of morbidity, and recurrences are common because the cancerous cells have usually already metastasized. Radiotherapy is also used, but only 40% of tumors are radiosensitive, and chemotherapy is often not effective.

Ljubimova stresses that, despite the variety of clinical, morphological and molecular parameters used to classify human malignancies today, patients receiving the same diagnosis of GBM from a pathologist can have markedly different clinical courses and treatment responses. Gene-array technology might help to explain why some patients experience a remission, whereas others, apparently with exactly the same type of tumour, die within a few weeks.

## Differential gene expression

Ljubimova and colleagues used 11,000 gene microarrays to identify gene expression profiles in different types of brain tumour, including GBMs and low-grade astrocytomas or benign extra-axial brain tumours. Tissues adjacent to the GBM were also studied and the gene profiles from each patient were compared with normal brain tissue.

All types of brain tumour studied overexpressed 14 known genes compared with normal human brain tissue. For the majority of the 14 genes, expression was lower in the low-grade astrocytomas than in the GBM cases, and was barely detectable in normal brain. Gene-array findings were confirmed by semiquantitative RT-PCR and immunostaining with two different antibodies. 'In the five cases of GBM, we identified a pattern of expression in the 14 genes that is linked with a shorter time to recurrence. This information might be useful when trying to determine which patients are at risk from relapse after treatment,' explains Ljubimova.

Interestingly, recurrence was most likely when the aggressive gene-expression pattern was also seen in tissue within a 2 cm margin of the GBM, even though these cells were histologically normal[1]. 'This could be very significant,'



1359-6446/01/$ – see front matter  PII: S1359-6446(01)01974-2

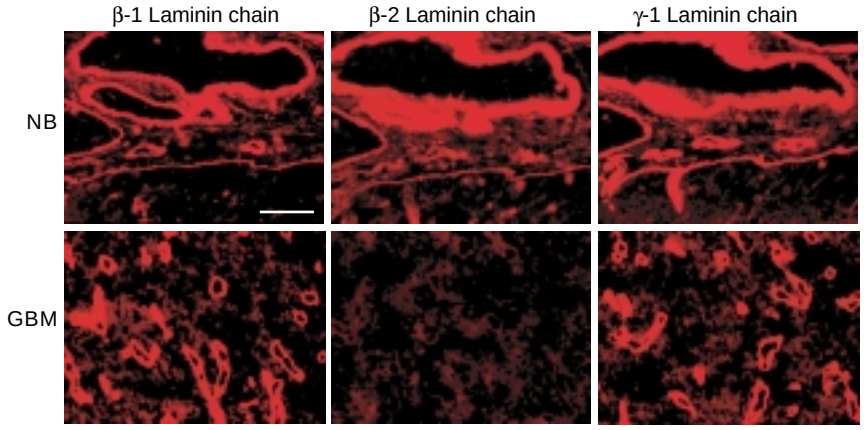


**Figure 2**. Brain tumour sections illustrating that glioblastomas do not express β-2 laminin chain. Abbreviations: NB, normal brain; GBM, glioblastoma multiforme.

comments Ljubimova. 'It could mean that these tissues had microinvasive foci that contributed to the tumour-like expression pattern, or that tumour-derived factors are affecting the surrounding tissue, encouraging tumour development and progression,' she says.

### α-4 Chain of laminin is upregulated in GBM

Ljubimova and colleagues identified two genes that were consistently upregulated in both high- and low-grade gliomas, as well as histologically normal tissues adjacent to GBMs. One gene, which encodes epidermal growth factor (EGF) is known to be overexpressed in gliomas[2]. However, overexpression of the gene that encodes α-4 chain of laminin (Fig. 1) is a novel observation.

Laminins are a large family of glycoproteins that contain α, β and γ-chain subunits, and are involved in tissue architecture and regulation of cell migration, differentiation and proliferation[2]. The laminin α-4 chain forms part of the laminins 8, 9 and 14, which differ from each other by β- and γ-chain composition[4]. The majority of GBMs showed an increased expression of laminin-8 chains in blood-vessel walls, whereas low-grade tumours overexpress laminin-9 chains (Fig. 2). Expression of laminin-8 appears to predict a shorter time to recurrence for GBMs than expression of laminin-9. 'In GBMs, laminin-8 might be associated with neovascularization and might thus contribute to tumour aggression,' suggests Ljubimova. She predicts that overexpression of laminin-8 in GBM, together with other factors that promote tumour growth, might be an important prognostic factor – and a potential target of glioma therapy. 'If we slow down the tumour growth or process of neovascularization by blocking the α-4-laminin gene, or its product, we would be able to extend patient survival times,' she says.

### Future studies

Ljubimova and colleagues are now working intensively to develop *in vitro* cell culture systems and *in vivo* preclinical studies to locate specific molecular targets for drug therapy. 'New drugs might be some way in the future, but at least we now have a way forward,' she says.

### References


1 Ljubimova, J.Y. *et al.* (2001) Overexpression of α-4 chain-containing laminins in human glial tumors identified by gene microarray analysis. *Cancer Res.* 61, 5601–5610

2 Seghal, A. (1998) Molecular changes during the genesis of human gliomas. *Semin. Surg. Oncol.* 14, 3–12

3 Colognato, H. and Yurchenco, P.D. (2000) Form and function: the laminin family of heterodimers. *Dev. Dyn.* 218, 213–234

4 Libby, R.T. *et al.* (2000) Laminin expression in adult and developing retinas. *J. Neurosci.* 20, 6517–6528