## **Editorial**

Glioma invasion: mechanism, modulation and future possibilities V. Amberger-Murphy

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Gliomas are thought to originate from neuroglial cells (e.g. astrocytes) or their progenitors. One of the main biological features of a glioma is the local invasion of its constituent neoplastic cells into the surrounding brain tissue. This invasive behaviour presents a major obstacle to an effective treatment of intrinsic brain tumours. Thus, the transient cell cycle arrest in actively migrating glioma cells protects these cells from the action of cytotoxic drugs and radiation. Moreover, these cells invade into areas of the brain with an intact blood-brain barrier, which makes them inaccessible to systematically administered agents. Therefore, it is very important to understand more about the mechanisms involved in glioma invasion.

The Glioma Invasion Forum (GIF) was formed in 1996; it held its first meeting in spring 1997 in Wuerzburg, Germany, and its members share a common interest in all aspects of invasion and dissemination of gliomas. In this and subsequent issues of Acta Neurochirurgica, a series of reviews are published of the main subjects discussed at the 4<sup>th</sup> International Glioma Invasion Forum. This took place in Ghent, Belgium, in November 2001, financially supported by the Fund for Scientific Research, Flanders.

Discussions during the first meeting in 1997 led to the recognition of the "Go or Grow Hypothesis". This proposed that proliferation and migration of tumour cells are mutually exclusive features and that suppression of active migration might even enhance cell proliferation and vice versa. By 1992, Pilkington had already found that cell surface gangliosides, localised by A2B5 antibody staining, were present only on non-dividing populations within one tumour and that their expression and that of two cell cycle markers, proliferating cell nuclear antigen (PCNA) and bromodeoxyuridine (BudR) were mutually exclusive [8]. Moreover, the addition of simple gangliosides to human glioma cell cultures reduced their rate of proliferation and increased migration and invasion [7]. Giese and co-workers [6] investigated indices of proliferation in malignant glioma cells that were seeded on permissive and non-permissive substrates. They found that migratory cells seeded on permissive substrates were less proliferative than cells seeded on non-permissive substrates and that, on a permissive substrate, the migratory tumour cells at the periphery were less proliferative than the cells in the central region. More recently, studies of the glial precursor marker chondroitin sulphate proteoglycan, NG2, have shown that expression of this cell surface marker is associated with high cell division rates in glioma cells and correlates inversely with invasive potential [3, 4, 5].

These findings, and others discussed in two reviews [1, 2] speak very much in favour of the 'Go or Grow Hypothesis'.

In this issue Rooprai et al. speculate about new approaches to treatment of invasive brain tumours, using six naturally-occurring agents and a heterocyclic drug, to trigger apoptosis and affect the invasive behaviour of brain tumour cells, that they are investigating in their laboratory.

Forthcoming issues deal with other topics – Terzis et al. will consider the molecular approach to the study of brain tumour invasion, focussing on elucidating the interplay of integrins, Fak, Pten and p53. A pre-requisite for valid, informative study of tumour cell invasion is the availability of a suitable model system. The three-dimensional

spheroid model, originally developed in 1971, has since been adapted and refined for studies of brain tumour invasion, and Corcoran et al. explains and discusses several models which are in current use. Levicar et al. will examine the involvement of proteases and their regulation in glioma invasion. Protease activity results from a very complex interplay of protease–protease and protease-inhibitor interactions, influenced by soluble factors and membrane receptors. Soluble factors including growth factors, cytokines and a new glioma repellent factor, are discussed by Mueller et al. These factors cause an autocrine stimulation of the tumour cells and a paracrine activation of the surrounding stroma, resulting in a permissive environment for migrating tumour cells.

The collaborative approach of intensive investigations into the mechanisms underlying invasion and migration, illustrated by these reports, should result in a better understanding of these important mechanisms and promote the development of new, more successful treatment regimens.

## References

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