Hotspots in Neuro-Oncology

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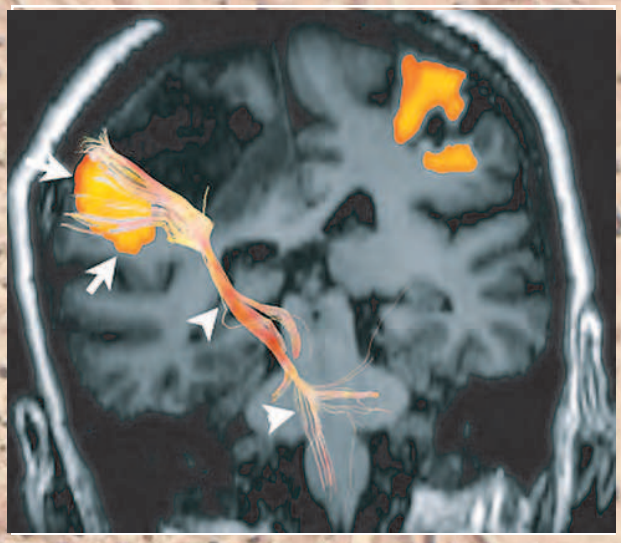

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Hotspots in Neuro-Oncology

Michael Weller

From the Department of Neurology, University Hospital Zurich, Switzerland

Induction of Brain Tumor Stem Cell Apoptosis by FTY720: A Potential Therapeutic Agent for Glioblastoma

Estrada-Bernal A, Palanichamy K, Chaudhury AR, et al. Neuro Oncol 2012; 14: 405–15.

Although their existence has remained somewhat enigmatic, the identification and selective therapeutic elimination of glioma stem cells or initiating cells remains a focus of current research in neuro-oncology. In the April issue, another pharmacological approach to target specifically the stem cell compartment in glioblastoma was proposed. FTY720 is a sphingosine analogue that decreases the levels of G protein-coupled sphingosine-1-phosphate receptors. This drug was approved for the treatment of multiple sclerosis in 2010. It shows high blood-brain barrier permeation and should therefore in principle be capable of targeting glioma cells shielded by the blood-brain barrier. Estrada-Bernal et al report that FTY720 inactivates the ERK/MAP kinase pathway, induces the BH3-only protein Bim and, in terms of cell death induction, does so in synergy with temozolomide. These effects were demonstrated specifically in "brain tumour stem cells". Furthermore, FTY720 inhibited the growth of intracranial xenograft tumours transplanted in nude mice, too. Admittedly, as in multiple sclerosis, it remains somehow unclear how precisely FTY720 is inducing its therapeutic effect. This will probably be the subject of further studies. Yet, given that the drug is already available and tolerated by human patients, it may represent a valid option for clinical evaluation in patients with refractory glioblastoma.

Soluble Factors Secreted by Glioblastoma Cell Lines Facilitate Recruitment, Survival and Expansion of Regulatory T Cells: Implications for Immunotherapy

Crane CA, Ahn BJ, Seunggu J, et al. Neuro Oncol 2012; 14: 584–95.

Immunotherapeutic approaches to glioblastoma experience a revival at present, with multiple smaller vaccination trials ongoing and the epidermal growth factor receptor vIII peptide vaccination entering randomized phase-II and -III trials. Yet, the immune privilege of glioblastoma conferred by an immunosuppressive microenvironment created by these tumours represents a major obstacle for immunotherapy. In the May issue of *Neuro-Oncology*, Crane et al readdress the role of soluble mediators released by glioblastoma cells and specifically examine their effects on regulatory T cells, a major immunosuppressive T cell population. There was an increase in the frequency of regulatory T cells in the tumour tissue as opposed to the periphery in glioblastoma patients. The chemokine CCL22 induced the migration of regulatory T cells more effectively than that of conventional T cells. Yet, interfering with CCL22 signalling at the receptor level did not completely block T cell migration, suggesting that factors other than CCL22 are involved in this process. The authors also found a correlation between tumour burden and regulatory T cell populations in the peripheral blood, reinforcing the idea (that has never been proven) that immunotherapy will work better in glioblastoma patients with minimal residual disease. This study illustrates once more how glioblastomas maintain their micromilieu in an immunosuppressed state and shows that the balance between immunosuppressive and immunostimulatory signals must be altered to facilitate tumour cell recognition and attack by the immune system.

Treatment-Related Myelodysplasia in Patients with Primary Brain Tumors

Baehring JM, Marks PW. Neuro Oncol 2012; 14: 529–40.

The life expectancy of many glioma patients, notably suffering from non-glioblastoma gliomas, is probably increasing, due to improved techniques in neurosurgery and radiotherapy as well as an increasing repertoire of medical treatments, and also improved post-treatment surveillance and symptomatic treatment. At the same time, more patients are treated with alkylating-agent chemotherapy up-front whereas radiotherapy is delayed. Therefore, as outlined in a comprehensive overview by Baehring and Marks in the May issue, treatment-related myelodysplastic syndrome (t-MDS) and treatment-related acute myelogenous leukemia (t-AML) require attention during long-term follow-up. In that regard, the EORTC study 22033, which compares radiotherapy with protracted dose-dense temozolomide in patients with low-grade gliomas, will be particularly helpful for estimating the risk of such complications. So far, the risk for t-MDS and t-AML remains low among glioma patients, but the occasional practice of maintaining patients on alkylating-agent chemotherapy for more than a year or even until progression should be discouraged until appropriate data indicate a survival benefit from such prolonged chemotherapy regimens.

Correspondence to:
Michael Weller, MD
Department of Neurology, University Hospital Zurich
Frauenklinikstrasse 26
8091 Zurich, Switzerland
e-mail: michael.weller@usz.ch