Targeting tumour-resistant cells in the brain

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An especially aggressive and resilient tumour, the glioblastoma responds poorly to treatment. Researchers at the University of Liège have shown how to increase the vulnerability of radiation-resistant tumour cells that hide in specific areas of the brain.

The word evokes fear and simply speaking it aloud can send a shiver down one's spine: ‘tumour’ This is not always justified, as contrary to a common belief tumours are not necessarily a form of pathological cancer. A tumour is simply an abnormal multiplication of cells within a tissue, resulting from a malfunction in the cell development process. Tumours can be benign or malignant, depending on the type of cells they are composed of. Glioblastomas (GBM), however, are tumours at their most terrifying: the most common and the most aggressive of all central nervous system tumours, the GBM is devastating. Once a diagnosis has been established, very few patients (5%) survive beyond the 3rd year, and half of them fall victim to the tumour within 12 months. What makes GBM even more frightening is that it seems to strike at random. In very rare cases, it occurs in a context of genetic diseases, but in most cases no risk factors can be identified.

Glioblastomas are tumours that affect the glial cells, which are support cells located near neurons in the brain. While the molecular causes of glioblastomas are not (yet) known, the tumours could be the result of mutations occurring inside so-called 'stem cells', which differentiate into neurons and glial cells. Currently, treatment for this pathology consists in a surgical procedure to remove the tumour - when the situation allows it -, followed by radio- and chemotherapy sessions. Still, relapses are almost inevitable. Major progress was made in this
field in 2010, with the identification of four distinct classes of glioblastomas: 'classical', 'neural', 'proneural' and 'mesenchymal'. Each of these has specific characteristics related to the expression of certain proteins or the presence of certain mutations inside the tumour cells. The mesenchymal glioblastoma, for instance, which is the most aggressive and the most resistant to treatment, is characterised by the expression of proteins such as vimentin or N-cadherin, which are not found (or in very small quantities) in the other classes. The advantage of this classification is that it allows to 'predict' how a patient might respond to treatment and to determine how aggressive a glioblastoma is developing in the patient.

A 'haven' that increases the cells' resistance

Relapses are cause by tumour-initiating glioblastoma cells, which resist treatment. A multidisciplinary team from GIGA, led by Nicolas Goffart and supervised by Professor Bernard Rogister, has demonstrated that treatment-resistant cells preferentially migrate to very specific areas of the brain, including the subventricular zone. Far from the heart of the tumour, these cells are not removed during surgery, and they could play an active role in the phenomenon of tumour relapses. But why do they resist radio- and chemotherapy? This is the question Nicolas Goffart and Arnaud Lombard, a post-doctoral fellow and a PhD student at GIGA-Neurosciences' 'Laboratory of Nervous Disorders and Therapy', set out to answer. As a part of their work for a recently-published study in *Neuro-Oncology* (1), they studied the potential role of the subventricular zone of the brain in radiation-resistant tumour-initiating glioblastoma cells, and therefore in tumour relapses. Their investigation revealed that tumour-initiating glioblastoma cells that remain in this zone are more resistant to radiotherapy, as their mesenchymal characteristics are enhanced by a chemokine (CXCL12) that is present in this environment.

When the researchers inhibit the chemokine-mediated pathway, they limit the expression of proteins vimentin and N-cadherin in tumour cells, making them more vulnerable to radiotherapy. These results suggest that an approach combining radiotherapy with inhibitors of the chemokine-mediated pathway is likely to increase the efficiency of current glioblastoma treatments. While this type of tumour remains frightening and resilient, ULg researchers have many ideas and paths to explore in order to defeat it (read also *Cerebral Tumours: combating recurrence*).