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Cell of origin affects malignancy and drug sensitivity of brain tumors

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Patients with glioblastoma have very poor prognosis since there are no effective therapies. In a study published in *Cell Reports*, researchers at Uppsala University have discovered a correlation between the cell type from which the tumour originates and the growth and drug sensitivity of the tumour. More knowledge about the mechanisms behind this correlation could be important for developing more effective drugs against subgroups of glioblastoma.

Glioblastoma is the most common form of primary brain tumour in adults and is essentially lethal. Presently, the development of more effective therapies is hampered by the large degree of tumour heterogeneity, both between different patients and in a single tumour. The heterogeneity between different tumours is partly due to the fact that the tumour can originate from different kinds of brain cells. The tumour's cell of origin can be either an immature neural stem cell or a more differentiated glial cell.

To develop improved therapies for glioblastoma, more knowledge is needed about how the cell of origin affects the characteristics of the cancer cells. Such studies must initially be performed in mice since it is not possible to identify the cell of origin in patient material. In the present study the researchers used several clinically relevant glioblastoma models in mice and found that tumours that originated from immature neural stem cells developed faster than tumours that originated from more differentiated glial cells.

"We discovered that several important characteristics of the cancer cells could be linked to the tumour's cell of origin. Immature neural stem cells gave rise to glioblastomas that grew faster and were more malignant than those that originated from glial cells. Tumours from neural stem cells also contained more glioblastoma stem cells, cells that are believed to give rise to tumour recurrence after therapy," says Lene Uhrbom, senior lecturer at the Department of Immunology, Genetics and Pathology and lead author of the study.

To determine how the cell of origin affected the characteristics of glioblastoma cells, the researchers analysed how the activity of a large number of genes differed between tumours with different origins. They were able to identify a 'gene signature' of almost 200 genes.

"When we compared the gene signature activity of glioblastoma cells from around 60 patients we found that a large number of patients could be divided into subgroups that showed a correlation between gene activity, tumour cell characteristics and cell of origin similar to the one we had seen in the mice study. This indicated that the cell of origin also has a direct influence on the characteristics of human tumours," says Uhrbom.

One feature of the tumour cells that the researchers were particularly interested in was their sensitivity to cancer drugs, and here too they found a correlation with the cell of origin. Glioblastoma cells from patients that could be linked by the gene signature analysis with an immature origin generally showed a higher sensitivity to cancer drugs than glioblastoma cells that were associated with a more differentiated cell of origin.

"We show that the cell of origin is important for the malignancy and drug sensitivity of glioblastoma cells, and that the findings can also be applied to glioblastoma cells from patients. We hope the gene signature

we identified can provide the basis for an improved classification of glioblastoma patients and for identifying new targets for therapy," says Uhrbom.

More information: Jiang, Yiwen et al.: "Glioblastoma cell malignancy and drug sensitivity are affected by the cell of origin", *Cell Reports*, DOI: 10.1016/j.celrep.2017.01.003

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