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The cell of origin in childhood brain tumors affects susceptibility to therapy

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Children that are diagnosed with the severe the brain tumour malignant glioma often have a very poor prognosis. Knowledge about how pediatric malignant glioma arises and develops is still limited. New findings from Uppsala University show that in mice glioma development and glioma cell properties are affected by both age and the cell type from which the tumour has arisen. The tumour cell of origin was also important for the susceptibility of the tumour cells towards cancer drugs.

The study is published in the journal *Cancer Research*.

The brain is composed mainly of two types of cells; neurons and supportive cells called glial cells. Glioma are brain tumours that are similar to glial cells and in adults malignant glioma is the most common form of primary brain tumour. In children malignant glioma is relatively rare, but, as for adults, the prognosis is very poor, and of all childhood cancers malignant glioma is among the most lethal.

Malignant glioma in children is much less studied than in adults and to improve the possibilities to find efficient drugs more knowledge and relevant disease models are needed. Also, most studies in the field have been focused on the genetics of the disease and there is a lack of knowledge about in which cell type the tumour has originated and how this particular cell type affects the properties of the tumour. This is exactly what the researchers have investigated in the present study where they have used mouse models of glioma and have found that malignant glioma originating from different cell types behave differently.

The researchers induced glioma tumours from both undifferentiated stem cells, that can give rise to both neurons and glial cells, and from oligodendrocyte precursor cells (OPC), that are more differentiated and can only give rise to glial cells.

'It turned out that tumours originating from stem cells were both more frequent and more aggressive as compared to those that originated from OPC. A very interesting finding was that tumour cells that had originated from undifferentiated stem cells were more susceptible to a range of cancer drugs,' says Lene Uhrbom who has led the study at the Department of Immunology, Genetics and Pathology.

The researchers also compared how the tumours developed in young mice as compared to adult mice and found that both age and cell of origin are important for tumour development. Furthermore, they could show that their tumour models in young mice were highly similar to a subgroup of malignant glioma in children.

'We have developed new models that are relevant for studies of childhood malignant glioma. There is a lack of such models and we believe that these can become very useful in further studies to uncover the underpinnings of this devastating disease. Our finding that the cell of origin could influence the response to treatment also shows that is important to identify clinically relevant subgroups of childhood malignant glioma, to be able to design the most efficient therapy for each patient. Our next challenge will be to find out how different cells of origin for glioma gives rise to these differences and to identify new targets for therapy,' says Lene Uhrbom.

More information: S. Sreedharan et al, Mouse models of pediatric supratentorial high-grade glioma reveal how cell of origin influences tumor development and phenotype, *Cancer Research* (2016). DOI: 10.1158/0008-5472.CAN-16-2482

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