Novel treatments of malignant brain tumours – experimental models

Half time review seminar, February 23rd 2018

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Background
One of the key problems with malignant brain tumours, such as glioblastoma multiforme, is that despite being able to remove the major bulk of the tumour through surgery and treating the patients with chemotherapy and radiotherapy, we know that tumour cells have already spread throughout the brain. In animal models, this is not often discussed, since the major focus is on survival. We therefore felt that there is a need to design a model where also the satellite tumour cells can be studied. Thus a syngeneic GFP+ model was developed, which can be used in fully immunocompetent animals. This allows for studies of immunological changes, which is highly relevant since the immune response is compromised in the glioblastoma setting. One part of the immune response, the complement system, acts as a functional bridge between innate and adaptive immunity. Still, the role of the complement system has hardly been studied in glioma research.

Material and methods
Homozygous GFP positive Fischer 344 rats were treated with ethylnitrosourea during pregnancy. The offspring developed CNS tumours, one of which was subsequently transplanted to new Fischer 344 recipients, and defined as a cell line (NS1), with an infiltrative growth pattern and perivascular dissemination. This makes it an appropriate model for studying glioblastoma multiforme. The NS1 cell line was then used to further investigate the role of the complement system.
Results
We could demonstrate a significantly increased survival \textit{in vivo} in animals inoculated intracerebrally with glioma cells pre-coated with C1-IA antibodies. Using data from a publicly available database and our own mRNA material from glioblastoma patients, we found an upregulation of C1-IA in human glioblastoma cells. Furthermore, by using immunohistochemistry, we demonstrated the presence of C1-IA on glioma cells \textit{in vitro} both from humans and rats.

Significance
Our findings indicate that overexpression of C1-IA is present in glioblastoma, which makes it a possible target for treatment. Furthermore, we mean that it is important to use a model with fully immune competent rats when immune therapy is studied, and the NS1 model could be such a candidate. Further investigation of the complement system in the glioblastoma setting is needed, we think.

Paper I
Immunocytochemical detection of GFP for sensitive and specific detection of tumor cells in the NS-1 rat glioblastoma model.
Gunnar Skagerberg, Karolina Förnvik, Leif G. Salford and Henrietta Nittby Redebrandt – submitted to Journal of Experimental & Clinical Cancer Research

Paper II
C1-inactivator is upregulated in glioblastoma.
Förnvik K, Maddahi A, Persson O, Osther K, Salford LG, Nittby Redebrandt H.
PLoS One. 2017 Sep 7;12(9):e0183086

Papers not included in the thesis
ITPP Treatment of RG2 Glioblastoma in a Rat Model.
Förnvik K, Zolfaghari S, Salford LG, Redebrandt HN.

Effect of blockade of indolamine 2,3-dioxygenase in conjunction with a single dose of irradiation in rat glioma.
Jonatan Ahlstedt, Karolina Förnvik, Crister Ceberg, Henrietta Redebrandt Nittby
Jacobs Journal of Radiation Oncology 2015, 2(3): 022

A GFP positive glioblastoma cell line NS1 - a new tool for experimental studies.
Henrietta Nittby, Karolina Förnvik, Jonatan Ahlstedt, Crister Ceberg, Peter Ericsson, Bertil R. Persson, Gunnar Skagerberg, Bengt Widegren, Zhongtian Xue, Leif G Salford
Journal of Brain Tumors and Neurooncology 2015, 1:1

Zebularine induces long-term survival of pancreatic islet allotransplants in streptozotocin treated diabetic rats.