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New treatment for brain tumors: Sensitization of multi-resistant glioblastoma clones

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Research area:

Cancer/Oncology

Brief description

Gliobastoma multiforme is the most malignant primary brain tumor.
The cancer cells vary between more treatment-resistant and more treatment-sensitive cell-states. Current studies aim to uncover forces that drives these changes in treatment resistance and make all cells vulnerable to therapy.

Aim

Sensitization of multi-resistant glioblastoma multiforme clones towards conventional and new promising therapies.

Background

Gliobastoma multiforme (GBM) is the most malignant primary brain tumor and treatment is essentially lacking. As most solid tumors GBM is heterogenous and the tumor cells vary in therapy response and molecular characteristics. We hypothesize that the chances for curative treatment would greatly improve if this diversity could be diminished, that is if all cells could be made vulnerable to a certain therapy.
By raising cell cultures from single tumor cells originating from the same patient tumor (clones) we partly capture this variation and have linked drug and radiation resistance to a cell state of mesenchymal (MES) character (Segerman et al., Cell Reports, 2016 , http://www.cell.com/cell-reports/fulltext/S2211-1247(16)31629-1). Importantly, this cell state appears epigenetically regulated and reversible. We find that the cancer cells seem to naturally, but at low speed, slide back and forth between more treatment-resistant and more treatment-sensitive modes or cell-states.

Project plan

Current studies aim to uncover forces that drives the change in treatment resistance/cell state. The general approach is to by various means stimulate and/or antagonize pathways that appear to be more active in sensitive and resistant clones, respectively. We then monitor for changes in drug response. Natural ligands, drugs and possibly genetic techniques are used. Follow up studies to link phenotypic and molecular changes is part of the project, to identify markers coupled to drug response.
Preliminary results indicate that combinatory treatments will be needed to sensitize resistant clones and reverse the MES-like cell state.

The studies concern GBM but this type of general, epigenetically regulated, resistance mechanism, is seen in diverse malignancies and the concept if successful might well be applicable on other tumor types.

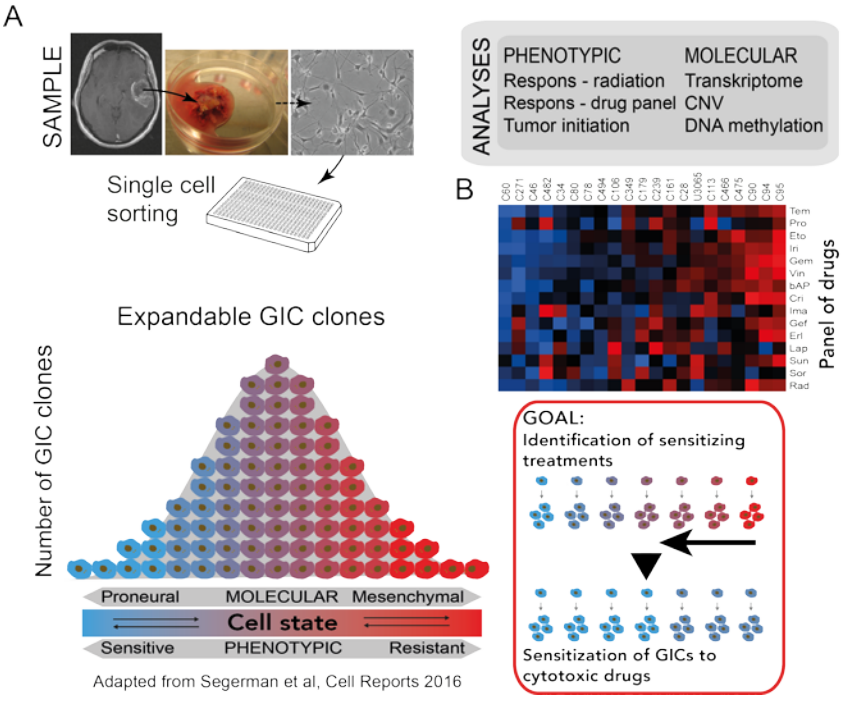

Figure 1: A. Clones were expanded from glioma surgical samples under stem cell conditions and characterized phenotypically and molecularly in parallell. B. Heat map of the drug- and radiation response pattern of individual U3065 clones (vertical) towards a panel of drugs and radiation (Rad) (horizontally). Note the presence of multi-therapy resistant and sensitive clones. Red=resistance, Blue=sensitivity

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