Glioblastoma growth

The invasive nature of glioblastoma is problematic in a radical surgery approach and can be responsible for tumor recurrence. In order to create new therapeutic strategies, it is imperative to have a better understanding of the mechanisms behind tumor growth and invasion. The continuous cross-talk between glioma stem cells (GSCs) and the tumor microenvironment (TME) contributes to disease progression, which renders research in this field difficult and challenging. The main aim of the review was to assess the different possible mechanisms that could explain resistance to treatment promoted by TME and GSCs in glioblastoma, including the role of M2 macrophages, micro RNAs (MicroRNAs), and long non-coding RNAs (lncRNAs) from exosomes from the TME. A systematic review of the literature on the role of the TME in developing and promoting radioresistance and chemoresistance of GBM was performed according to PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines. A dedicated literature review search was also performed on the immunotherapeutic agents against the immune TME. We identified 367 papers using the reported keywords. The final qualitative analysis was conducted on 25 studies. A growing amount of evidence in the current literature supports the role of M2 macrophages and non-coding RNAs in promoting the mechanisms of chemo and radioresistance. A better insight into how GBM cells interact with TME is an essential step towards comprehending the mechanisms that give rise to resistance to standard treatment, which can help to pave the way for the development of novel therapeutic strategies for GBM patients [1)].

Knowledge of growth rates and underlying growth dynamics is useful for understanding basic tumor biology, developing realistic tumor models, and planning treatment logistics.

By using repeated pretreatment contrast-enhanced T1-weighted MRI scans from 106 patients (aged 26-83 years), we studied the growth dynamics of untreated glioblastomas in vivo. Growth rates were calculated as specific growth rates and equivalent volume doubling times. The fit of different possible growth models was assessed using maximum likelihood estimations.

RESULTS: There were large variations in growth rates between patients. The median specific growth rate of the tumors was 1.4% per day, and the equivalent volume doubling time was 49.6 days. Exploring 3 different tumor growth models showed similar statistical fit for a Gompertzian growth model and a linear radial growth model and worse fit for an exponential growth model. However, large tumors had significantly lower growth rates than smaller tumors, supporting the assumption that glioblastomas reach a plateau phase and thus exhibit Gompertzian growth.

Based on the fast growth rate of glioblastoma shown in this study, it is evident that poor treatment logistics will influence tumor size before surgery and can cause significant regrowth before adjuvant treatment. Since there is a known association between tumor volume, extent of surgical resection, and response to adjuvant therapy, it is likely that waiting times play a role in patient outcomes [2)].

Generating MR-derived growth pattern models for glioblastoma multiforme (Glioblastoma) has been an attractive approach in neuro-oncology, suggesting a distinct pattern of lesion spread with a tendency in growing along the white matter (WM) fibre direction for the invasive component. However, the direction of growth is not much studied in vivo. In this study, we sought to study the dominant directions of tumour expansion/shrinkage pre-treatment. We examined fifty-six

Glioblastomas at two time-points: at radiological diagnosis and as part of the pre-operative planning, both with contrast-enhanced T1-weighted MRIs. The tumour volumes were semi-automatically segmented. A non-linear registration resulting in a deformation field characterizing the changes between the two time points was used together with the segmented tumours to determine the dominant directions of tumour change. To compute the degree of alignment between tumour growth vectors and WM fibres, an angle map was calculated. Our results demonstrate that tumours tend to grow predominantly along the WM, as evidenced by the dominant vector population with the maximum alignments. Our findings represent a step forward in investigating the hypothesis that tumour cells tend to migrate preferentially along the WM [3].

1)
Agosti E, Panciani PP, Zeppieri M, De Maria L, Pasqualetti F, Tel A, Zanin L, Fontanella MM, Ius T. Tumor Microenvironment and Glioblastoma Cell Interplay as Promoters of Therapeutic Resistance. Biology (Basel). 2023 May 18;12(5):736. doi: 10.3390/biology12050736. PMID: 37237548; PMCID: PMC10215375.
2)
Stensjøen AL, Solheim O, Kvistad KA, Håberg AK, Salvesen Ø, Berntsen EM. Growth dynamics of untreated glioblastomas in vivo. Neuro Oncol. 2015 Oct;17(10):1402-11. doi: 10.1093/neuonc/nov029. Epub 2015 Mar 10. PubMed PMID: 25758748; PubMed Central PMCID: PMC4578579.
3)
Esmaeili M, Stensjøen AL, Berntsen EM, Solheim O, Reinertsen I. The Direction of Tumour Growth in Glioblastoma Patients. Sci Rep. 2018 Jan 19;8(1):1199. doi: 10.1038/s41598-018-19420-z. PubMed PMID: 29352231.