Título: COMBINANT ONCOLOGIA I IMMUNOLOGIA: CAP A LA MILLORA DEL TRACTAMENT DEL GLIOBLASTOMA GL261 MITJANÇANT LA IMMUNITAT RELACIONADA AMB EL CÀNCER I EL SEGUIMENT NO INVASIU DE LA RESPOSTA MITJANÇANT MRSI.

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Resumen: Glioblastomas (GB) are invasive brain tumours associated with poor prognosis and limited response to therapy. This thesis focused in improving preclinical GB treatment through cancer-related immunity and Magnetic Resonance Spectroscopic Imaging (MRSI)-based non-invasive response follow-up. The GL261 GB was chosen since it is an immunocompetent preclinical model suitable for studying therapies. Three therapeutic strategies have been tested: a) chemotherapy (Temozolomide, TMZ), administered in an Immune-Enhancing Metronomic Schedule (IMS-TMZ), b) immune checkpoint inhibitor (Programmed cell death protein 1, PD-1 antibody) and c) IMS-anti-PD-1/TMZ combination therapy. Anti-tumour immune responses can be stimulated by therapies targeting different aspects of cell damage. We aimed, on one hand, to induce immunogenic tumour cell damage while sparing replicating immune system cells (with IMS-TMZ). On the other hand, we wanted to counteract the immune suppression within the tumour (anti-PD-1 immunotherapy). IMS-TMZ significantly improved survival in GL261 GB-bearing mice in comparison with standard TMZ treatment, confirming and surpassing results reported by our group. Anti-PD-1 monotherapy was effective when applied at high dose (500/250 μg), although care should be taken since results suggest that differences in tumour volume at immunotherapy starting time can have great impact in its efficacy. As expected, the IMS-anti-PD-1/TMZ

combination therapy showed a great beneficial effect, with much better therapeutic outcome than monotherapies administration. These results support the fact that the host immune system is clearly involved in GB response processes. Previous studies from our group with MRSI-based nosological images pointed that the metabolomic pattern changes could be linked to host immune system local effects onto tumours, acting as a surrogate biomarker of therapy response. Accordingly, we wondered whether the application of this non-invasive MRSI approach in evaluating immunotherapeutic strategies would reflect the same type of metabolomics changes. Thus, the evolution of GL261-tumor bearing mice treated with IMS-TMZ, IMS-anti-PD-1 and IMS-anti-PD-1/TMZ was evaluated using the same MRSI-based nosological images approach. Results confirmed that the IMS-TMZ protocol consistently produced the expected oscillatory changes in the MRSI metabolomics pattern, with a frequency of ca. 6 days. This oscillatory behaviour was also confirmed in mice treated with immunotherapy both in combination with TMZ and as monotherapy, hinting that the observed spectral pattern changes observed during therapy response are shared by different therapeutic strategies, provided the host immune system is elicited and is able to productively attack tumour cells. This opens the way for a translational use of the MRSI-based biomarker for patient-tailored GB therapy, including immunotherapy, for which reliable non-invasive biomarkers are still missing. The participation of immune system is also supported by the rate of cured animals observed in this thesis (range 50 – 100 % depending on the treatment), which also held long-term immune memory against tumour cell re-challenge.
Resistance to TMZ treatment is one of the main reasons for the chemotherapy failure in adjuvant treatment of GB. We investigated the relevance of O6-methylguanine-DNA-methyltransferase (MGMT) and programmed death-ligand 1 (PD-L1) content in chemoresistance, by western-blot (WB) analysis, with special focus on tumours escaping therapy after transient response. Result showed a 3-fold increase in PD-L1 expression in IMS-TMZ relapsing tumours in comparison with control tumours, indicating that PD-L1 can be involved in TMZ resistance for GL261 GB in vivo. Accordingly, anti-PD1 therapy may have potential to ‘rescue’ tumours escaping from TMZ therapy. Appropriate combination of oncology and immunology will pave the way for improving GB treatment and patient outcome.