Título: IMPROVEMENT OF PROTOCOLS FOR BRAIN CANCER DIAGNOSIS AND THERAPY RESPONSE MONITORING USING MAGNETIC RESONANCE BASED MOLECULAR IMAGING STRATEGIES

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Resumen: Brain tumours account for less than 2% of all primary tumours, but are one of the most lethal cancers when ¿life lost¿ years are considered. Gliomas are the most prevalent type with a median life expectancy below 15 months for the high grade ones, such as glioblastomas (GBM). The most common non-invasive medical technique used for tumour diagnosis and therapy monitoring of brain tumours patients is Magnetic Resonance (MR), in the form of imaging (MRI) and spectroscopy (MRS) or spectroscopic imaging (MRSI). However, due to the ethical restrictions regarding the use of human patients for research study, the improvement of diagnostic and therapy follow-up protocols requires reliable models that mimic human disease. In this regard, mainly murine models are used and can be divided into the genetically engineered model (GEM) of spontaneous tumour development and the engrafted tumour model. In this thesis, a comprehensive MR characterization of two GEM colonies, namely S100ß-v-erbB / inK4a-Arf (+/-) and GFAP-V12 HA-ras B8, was carried out. A low tumour penetrance found (16% and 1%, respectively) together with stochastic onset of GEM tumours, made them impractical for use in therapy response studies. The latter and the scarcity of low/intermediate grade brain tumour preclinical models motivated us to attempt to develop a transplantable glial tumour model of low/intermediate grade by disaggregation of a tumour mass from GEM. This should allow us to obtain an

increased tumour incidence rate in comparison to GEM animals. Gliospheres from a grade III GEM tumour were successfully generated and displayed more than 60% penetrance, when stereotactically injected into the striatum of C57BL/6 mice. However, the application of freezing and cell culture protocols produced a progression to grade IV GBM, which made the developed transplantable model qualify as potential secondary GBM model in mice. Additionally, this transplantable model was widely characterized using MRI/MRS methods, as well as perturbation-enhanced MRSI (PE-MRSI) for a possible application in the future in therapy strategies and development of tumour therapy response detection classifiers. A restricted genetic evaluation of selected murine tumour models (i.e. GL261 tumours, GL261 cell line, GEM and GEM-derived tumours) was carried out using the Sanger method to check for a possible presence of particular driver mutations commonly occurring in gliomas (IDH1, IDH2 and p53). Finally, the work describes the strategy followed for longitudinal therapy studies follow-up and early response/relapse detection in preclinical brain tumours, through molecular imaging methods based in MRSI. GL261 (glioblastoma) tumour bearing mice were treated with temozolomide (TMZ), based on previously established protocols. The expected transient growth arrest (response to therapy) was detected by MRI. Animals subjected to therapy and control animals were followed up by MRSI and pattern recognition techniques (semi-supervised source extraction) were applied. The sources extracted from the region of interest were able to discriminate between GL261 tumours actively proliferating and tumours responding to therapy, based on their metabolome pattern changes recorded by MRSI. Colour-coded nosological images produced throughout and after the course of therapy allowed convenient tracking of response changes and differentiated the intratumoural heterogeneity of response, hinting the growth arrest and relapse, before changes in tumour volume were observed by MRI. The methodology was validated with histopathological analysis and calculation of proliferation and apoptotic rates and mitotic index.