SEVE BALLESTEROS FOUNDATION-CNIO BRAIN TUMOUR JUNIOR GROUP

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OVERVIEW

Malignant gliomas (astrocytomas, oligodendrogliomas and oligoastrocytomas) are the most frequent form of brain tumours and Glioblastoma Multiforme (GBM), a grade IV astrocytoma, is the most lethal tumour of the central nervous system in the adult. Standard GBM therapy consists of tumour resection and postsurgical treatment with chemotherapy and ionising radiation (IR). Although there have been improvements in surgical and imaging techniques, available treatments for GBMs are still inefficient, most likely due to intrinsic resistance to the current therapeutic modalities and high cellular heterogeneity.

In our laboratory, we use a combination of genomic analysis, mouse models and primary tumour cell cultures, with the main goal of identifying the molecular mechanisms that could provide the basis for novel treatments for GBM patients.

"The main focus of our Group is to uncover the genetic alterations present in GBM patients that are responsible for the aggressiveness and the poor treatment response of this tumour type."

RESEARCH HIGHLIGHTS

Next generation glioma mouse models

A decade of studies has underlined the complexity of the glioma genome, however, the functional significance of the vast majority of the genetic alterations remains elusive. Understanding the genetic events that lead to glioma formation and the mechanisms of resistance to therapy will be instrumental for the development of new treatment modalities for gliomas. To accurately reproduce the high genetic heterogeneity observed in glioma patients, we would have to recreate not just a handful of genetic alterations, but possibly dozens. The advent of the CRISPR/Cas genome editing technology has now made it possible to target almost any candidate cancer gene in the *in vivo* setting. We are actively working to develop the 'next-generation' glioma mouse models that more faithfully recapitulate *in vivo* the complexity of the GBM genome, with a particular interest in tumour suppressor genes and complex gene rearrangements.

Overcoming therapy resistance in GBM

The standard therapies for GBM patients, IR and temozolomide (TMZ), generate double-stranded DNA breaks (DSDBs), the most deleterious form of DNA damage. The DSDBs are then responsible for the initiation of the DNA Damage Response (DDR) and, consequently, the activation of DNA repair pathways and cell-cycle checkpoints. DDR signalling is a very intricate pathway and many of its elements can be altered in a given tumour patient, offering both challenges and opportunities from a treatment perspective. The most frequent resistance mechanism to TMZ treatment is the expression of the DNA-repair gene O^6-methylguanine DNA methyltransferase (MGMT), however, other resistance mechanisms have still to be identified.

Through a variety of genetic approaches (Haploid cells transposone mutagenesis, gRNA and shRNA screenings) we have identified the main signalling pathways that mediate resistance to TMZ. We are currently performing a series of synthetic lethality screenings in order to bypass these mechanisms of resistance. ■

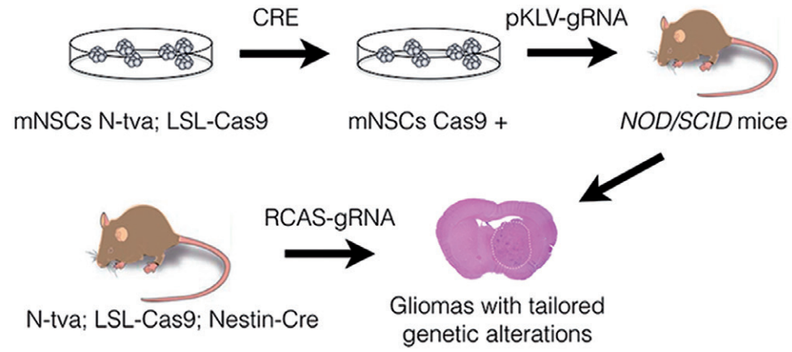

Figure Schematic representation of the RCAS-CRISPR-Cas9 system to generate gliomas with tailored genetic alterations.

PUBLICATIONS

- Bowman R, Wang Q, Carro A, Verhaak RGW, Squatrito M (2016). GlioVis data portal for visualization and analysis of brain tumor expression datasets. *Neuro-Oncology*. PMID: 28031383.
- de Lucas AG*, Schuhmacher AJ*, Oteo M, Romero E, Cámara JA, de Martino A, Arroyo AG, Morcillo MÁ, Squatrito M#, Martinez-Torrecuadrada J#, Mulero F# (2016). Targeting MT1-MMP as an immunoPET-based strategy for imaging gliomas. *PloS One* 11, e0158634. *Co-first author, #corresponding author

AWARDS AND RECOGNITION

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