SEVE BALLESTEROS FOUNDATION-CNIO BRAIN TUMOUR JUNIOR GROUP

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OVERVIEW

Glioblastoma (GBM) is the most common and lethal primary central nervous system tumour in adults. Despite the recent advances in treatment modalities, GBM patients generally respond poorly to all therapeutic approaches and prognosis remains dismal. Radiation and chemo-resistance are characteristic of various cancer types, however it is not clear if this therapy resistance is a consequence of tumour progression or if it is intrinsically associated with the genetic events that lead to tumour formation in the first place. Gaining insights into the pathways that determine this poor treatment response will be instrumental for the development of new therapeutic modalities.

In our laboratory, we use a variety of approaches – both genetic and small molecule drug screenings – coupled with *in vivo* GBM mouse models in order to identify genes involved in therapy resistance of gliomas. We reason that these studies will help to define new therapeutic targets for the treatment of brain tumours.

"The current most effective treatment for GBM patients is a combination of radiotherapy and alkylating agents. Increasing the sensitivity of the tumour cells to these therapies will possibly extend the survival of the patients."

Post-Doctoral Fellow
Miguel Jiménez (since June)

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Carolina Almeida, Alvaro Curiel (until July), Veronica Matía

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'Titulado Superior (Advanced Degree)

RESEARCH HIGHLIGHTS

Novel therapeutic approaches for therapy-resistant malignant brain tumours

The standard therapies for GBM patients, IR and Temozolomide (TMZ), generate double-strand DNA breaks (DSBs), which are the most deleterious form of DNA damage. The DSBs are then responsible for the initiation of the DNA Damage Response (DDR) and consequently the activation of DNA repair pathways and cell-cycle checkpoints. We have previously presented evidence that alterations in key DNA repair and checkpoint proteins can modulate the GBM treatment response.

The 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. Loss of components of a specific DNA repair pathway might be balanced by the increased activity of other components or pathways. Upregulated DNA repair pathways could lead to resistance to radiotherapy and DNA-damaging chemotherapy, therefore inhibitors of these pathways could potentially increase the sensitivity of the cells to these therapies. By contrast, pathways that are lost represent weaknesses in the DNA repair ability of the tumour cell and they could be exploited by choosing a suitable chemotherapy to induce unrepairable (more toxic) DNA damage. It is estimated that the efficacy of radiotherapy and chemotherapy would be improved if tumour cells could be rendered more sensitive without altering the sensitivity of normal tissues.

Through different functional genetic studies, we have observed that defects in components of the Mismatch Repair (MMR) system are significantly associated with resistance to TMZ. Moreover, we have discovered that chromosomal rearrangements of the O-6-methylguanine-DNA methyltransferase (MGMT) lead to overexpression of MGMT and contribute to TMZ resistance, both in high-grade and low-grade gliomas. Most importantly, we have identified another alkylating agent that is able to overcome these resistance mechanisms and that has a synergistic effect when used in combination with TMZ (FIGURE). ■

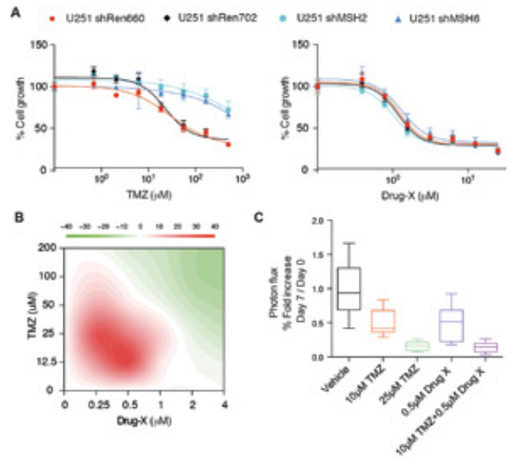

Figure Overcoming TMZ resistance. (**A**) Silencing of MMR component (MSH2 and MSH6) leads to resistance to TMZ (*left*) but not to the novel alkylating drug (*right*). (**B-C**) TMZ and Drug-X have synergistic effects both *in vitro* (**B**) and on brain-tumour slices cultured *ex-vivo* (**C**).

PUBLICATIONS

- Zhao N, Sebastiano V, Moshkina N, Mena N, Hultquist J, Jimenez-Morales D, Ma Y, Rialdi A, Albrecht R, Fenouil R, Sánchez-Aparicio MT, Ayllon J, Ravisankar S, Haddad B, Ho JSY, Low D, Jin J, Yurchenko V, Prinjha RK, Tarakhovsky A, Squatrito M, Pinto D, Allette K, Byun M, Smith ML, Sebra R, Guccione E, Tumpey T, Krogan N, Greenbaum B, van Bakel H, García-Sastre A, Marazzi I (2018). Influenza virus infection causes global RNAPII termination defects. *Nat Struct Mol Biol* 25, 885-893.
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