SEVE BALLESTROS FOUNDATION-CNIO BRAIN TUMOUR JUNIOR GROUP

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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 unreparable (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 TMZ resistance. Moreover, we have discovered that chromosomal rearrangements of the O-6-methylguanine-DNA methyltransferase (MGMT) lead 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).