Tumour Treating Fields (TTFields) and DNA damage response (DDR) inhibitors enhance glioma cell death through chemo-/radiosensitisation

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Aims: High grade gliomas are the most common primary brain cancer malignancies with ~300,000 global diagnoses each year with glioblastomas (WHO grade IV) conferring the worst prognoses. This arises from their treatment resistance, rationalised by the presence of glioma stem cell-like (GSC) tumour sub-regions and high intratumoural spatio-heterogeneity. TTFields are clinically approved alternating electric fields of intermediate frequency that exert anti-mitotic effects and invoke downregulation of the DDR. Therefore, TTFields alongside clinically developed, and blood brain barrier (BBB) penetrating DDR inhibitors (DDRi) could boost cell death and overcome treatment resistance through chemo-/radiosensitisation.

Methods: Primary GSC cell lines were derived from surgically resected and clinically defined tumour core and invasive edge regions and grown in more biologically relevant 3D-printed Alvetex™ scaffolds, offering highly clinically relevant models. Cells were then pre-treated with DDRi, subjected to chemo-/radiotherapy and then incubated under TTFields (200 kHz, 72 hrs) with their survival measured by clonogenic assays after 3 weeks. Immunofluorescence and western blot analysis were used to analyse the combination treatment effects on the DDR.

Results: In multiple 3D-grown core/edge GSC models, western blot analyses revealed that the DDR was altered by TTFields and clonogenic survival assays revealed that TTFields alongside DDRi led to significant chemo-/radiosensitisation.

Conclusions: TTFields alongside DDRi effectively enhances cell death by significant treatment sensitisation effects in clinically relevant 3D GSCs which exhibit extensive intra and intertumoral spatio-heterogeneity. Given that all the DDRi used are BBB penetrable and are either clinically approved or in clinical trials, TTFields could additionally compliment these treatment regimens in gliomas to boost their efficacy.