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Understanding Neural-cancer Interactions and Invasiveness in Glioblastoma

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Abstract
Neural-cancer interactions involve the complex interplay between the nervous system and cancer cells, influencing tumour initiation, progression, and metastasis. In gliomas, these interactions mostly entail the secretion of paracrine growth factors, and electrochemical communication mediated by synapses between neurons and glioma cells. Understanding such interactions is vital for developing new therapeutic strategies against cancer aimed at modulating neuron-to-tumour communication. For this purpose, we have used *in vivo* mouse models of glioblastoma (GB) and established *in vitro* assays to study neural-cancer interactions, including the co-culture of cancer cells with either hiPSC-derived glutamatergic neurons or GABAergic interneurons, as well as 3D cultures of tumour spheres and fetal spheroids. The co-culture of hiPSC-derived neurons and cancer cells, including GB cells, was established both as a contact and non-contact assay, allowing to study the relevance of neural-cancer interactions for cancer cell proliferation and migration. While 3D spheroids generally replicate the organization and complexity i of tissues effectively, our 3D invasion assay between organ spheroids and tumour spheres enabled us to specifically examine tumour invasion. This is exemplified by GB tumour spheres that exhibit reduced invasiveness of 3D brain spheroids upon repression of *EGFR* regulatory sequences. Additionally, the co-culture systems enabled us to profile the transcriptome and chromatin accessibility of GB cells upon neural activity stimulation. GB cells in contact with either glutamatergic neurons or GABAergic interneurons exhibit differential gene expression and chromatin accessibility profiles. This provides new insights into the regulatory networks mediating neuron-to-glioma communication and highlights the relevance of GABAergic signalling in GB pathogenesis. This integrated approach holds promise for furthering our understanding of neural-cancer interactions, offering potential candidates to target neural pathways involved in tumour progression.

Keywords: 3D culture systems, glioblastoma, cancer neuroscience, neurogliomal synapses GABAergic interneurons, glutamatergic neurons, synaptic signalling, chromatin profiling, chromatin accessibility, gene expression, gene regulation.

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