A tumorsphere model of glioblastoma multiforme with intratumoral heterogeneity for quantitative analysis of cellular migration and drug response

Glioblastoma multiforme (GBM) is the most common and malignant type of primary brain tumor and is characterized by its sudden onset and invasive growth into the brain parenchyma. The invasive tumor cells evade conventional treatments and are thought to be responsible for the ubiquitous tumor regrowth. Understanding the behavior of these invasive tumor cells and their response to therapeutic agents could help improve patient outcome. In this study, we present a GBM tumorsphere migration model with high biological complexity to study migrating GBM cells in a quantitative and qualitative manner. We demonstrated that the in vitro migration model could be used to investigate both inhibition and stimulation of cell migration with oxaliplatin and GBM-derived extracellular vesicles, respectively. The intercellular heterogeneity within the GBM tumorspheres was examined by immunofluorescent staining of nestin/vimentin and GFAP, which showed nestin and vimentin being highly expressed in the periphery of tumorspheres and GFAP mostly in cells in the tumorsphere core. We further showed that this phenotypic gradient was present in vivo after implanting dissociated GBM tumorspheres, with the cells migrating away from the tumor being nestin-positive and GFAP-negative. These results indicate that GBM tumorsphere migration models, such as the one presented here, could provide a more detailed insight into GBM cell biology and prove highly relevant as a pre-clinical platform for drug screening and assessing drug response in the treatment of GBM.