930

Hydrogel-based tumour microenvironments as models of vascularized Glioblastoma for validation of nanomedicines

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Abstract

The tumour microenvironment (TME) is the main obstacle limiting the efficacy of treatments against aggressive diseases such as glioblastoma (GBM). The high histological complexity, the infiltration by tumour-supporting cells, and the presence of biological barriers such as the blood-brain barrier (BBB) and the rigid extracellular matrix (ECM) hinder the accumulation of molecules and transporters. Reliable *in vitro* systems that recapitulate the complexity of GBM TME are needed to support the design of innovative drugs and carriers able to overcome these barriers.

This work aims to develop a reliable three-dimensional GBM model to investigate the transport of polymer nanoparticles (NPs)-based drug platforms. The model combines different cell actors involved in human GBM, ECM-like biomaterials, and a microfluidic device to reproduce vascularization, to reliably mimics GBM structure and composition.

GBM spheroids were prepared in low adhesion conditions using a combination of GBM cells and GBM-associated Stem Cells, coupled with other cells of the TME, such as microglia and astrocytes, to replicate tumour histology (Fig. 1A). The spheroids were encapsulated in natural (collagen-based) or synthetic (polysaccharide-based) polymer gels with mechanical properties resembling the GBM ECM.

A vascular network was obtained by inserting the GBM spheroids in a commercial microfluidic platform, containing two lateral perfusion channels coated with human brain endothelial cells, from which angiogenic sprouting was induced to vascularize the spheroid (Fig. 1B). Immunostaining confirmed the homogeneous presence of endothelial cells forming tight junctions (Fig. 1C). Moreover, the microvasculature was able to replicate the barrier effect against NPs, resembling our *in vivo* observations.

The model was used to verify the infiltration capacity and viability following treatment with polyurethane NPS loaded with a proteasome inhibitor (Bortezomib, BTZ). The results confirm that the drug can reduce tumour proliferation and infiltration in ECM-like gels, with the effect depending on the cellular composition. NPs-mediated treatment had lower efficacy than the free drug and was able to reduce cytotoxicity on non-tumour cells of TME.

This model represents a promising step in developing a reliable replica of human GBM TME by combining biomaterials and microfluidics. The device could be a valuable tool for the preliminary validation of drugs, nanomedicines, and alternative transporters (e.g., cell-mediated drug delivery).