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Optimization of Bioreactor Cultures of Glioblastoma Cells Immobilized in Alginate Microfibers

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Glioblastoma is the most common and aggressive malignant brain tumor in adults. Existing treatment choices that include surgery, radiation and chemotherapy are not successful in long-term survival, while development of new anticancer drugs is being held back by the lack of adequate model systems for anticancer drug testing. Namely, in traditionally used two-dimensional (2D) monolayer cancer cell cultures the native cell morphology, polarity and interactions between both cells and cells and extracellular components are either changed or absent, while studies on animals often produce misleading results due to interspecies differences. Hence, there is a pressing need for new glioblastoma model systems that provide more in vivo-like environment for investigation and development of new anticancer drugs. The aim of this work was to develop a biomimetic 3D environment for cultivation of glioblastoma cells based on alginate microfibers as cell carriers and perfusion bioreactors. Previous studies have shown that static cultures of cervical cancer cells SiHa immobilized in alginate microfibers may be diffusion limited while perfusion, which enhanced mass transport, has induced negative effects on human embryonic teratocarcinoma cells NTERA-2 in superficial zones of alginate microbeads by hydrodynamic shear stresses. Thus, in the present study, the specific focus was on optimization of cell concentration within microfibers and regimes of cultivation to achieve beneficial effects of fluid flow in perfusion bioreactors. A series of experiments were conducted in which the concentration of rat glioma cells C6 was varied between 2 and 8×10^6 cell cm^{-3} at several flowrates and regimes of static and perfusion culture periods. Mixed results were obtained implying that efficient mass transport has a higher effect in microfiber cultures at lower cell concentrations (*i.e.* $\sim 2 \times 10^6$ cell cm^{-3}). In specific, medium flow at the superficial velocity of $100 \mu\text{m s}^{-1}$ induced considerable cell proliferation as compared to control static cultures, which maintained the initial cell numbers. Mathematical modelling indicated that the convective transport of substances with low diffusion coefficients ($\sim 10^{-19} \text{m}^2 \text{s}^{-1}$) may have induced the observed positive effects. Still, exact relations of cultivation conditions and cell responses in terms of viability, proliferation and metabolic activity should be further investigated.