Development of innovative nanocomposite hydrogels for the treatment of Glioblastoma Multiforme

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Glioblastoma multiforme (GBM) is a high recidivism and mortality characterized subtype of gliomas. According to the WHO, it belongs to the Grade IV brain cancers. It is highly invasive and can infiltrate cerebral tissue, therefore, the complete resection of the tumor is difficult. GBM tumor is removed by surgery but it relapses in 90% of cases, 6 to 7 months after treatment due to radiotherapy resistance. Indeed, patients affected with GBM only survive 6 months without treatment whereas with Temozolomide (TMZ) chemotherapy combined with radiotherapy it lengthens their overall survival to 6 additional months [1-7]. TMZ is an alkylating agent, which forms an active metabolite called MTIC in vivo. This latter affects DNA replication, by methylating guanines causing double-strand DNA breaks then cell apoptosis [3]. Another option is the FDA approved Gliadel® wafer that allows the sustainable release of the antineoplasic agent Carmustine® close to the resection cavity. Gliadel® associated to radiotherapy and TMZ increases the overall survival from 1 to 2 years for GBM patients, however this therapy has additional side effects [8-9]. To overcome these hurdles other systems have been investigated like β-Glucan or Silk Fibroin scaffolds imbedding chemoattractants. These systems are designed to concentrate and trap GBM cells into the scaffold in the resection cavity [10-13].
The current project is based on a new injectable nanocomposite hydrogel where a protein is encapsulated in polymeric nanoparticles (NPs). PLGA NPs are prepared via non-toxic and biocompatible solvents [11, 35- 38] and are incorporated into nanocomposite hydrogels to achieve a controlled release of an active 2 compound. Such matrices have been developed in tissue engineering applications such as tissue regeneration [16-32].
The therapeutic protein used is a bone morphogenic protein 4(BMP-4), which is involved in neurogenesis. Herein, a differentiating strategy is applied to lead cancer cells and more precisely cancer stem cells to acquire a less aggressive phenotype that may increase their radiotherapy sensitivity [14-15, 37-38].

Since brain microenvironment is composed of a hyaluronic acid (HA) enriched extracellular matrix (ECM), we expect to develop an injectable, biocompatible, bioadhesive and biodegradable HA scaffold. HA is thus a good candidate since it possesses all those functionalities [16-23].

Finally, the most challenging part of this innovative strategy is the encapsulation of the BMP protein and tuning its delivery in situ. The encapsulation yield and release from hydrogel will be studied in vitro to obtain a proof of concept regarding cytotoxicity and efficiency on NIH3T3 and U87MG cell line and on primary patient cells. During this work, optimization of the formulation process and physico-chemical characterizations such as DLS, rheology, mechanical properties tests and stability studies such as DSC and TGA will be performed [23-30., 39-40]. Bioperformance evaluation of our device on preclinical models is also expected. [44-46].

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